CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203108Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 19, 2014
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 203108
Applicant	Boehringer-Ingelheim
Date of Submission	June 2, 2014
PDUFA Goal Date	August 2, 2014
Proprietary Name / Established (USAN) names	Striverdi Respimat/olodaterol inhalation spray
Dosage forms / Strength	Inhalation Spray/2.5 mcg/actuation
Proposed Indication(s)	…for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
Recommended:	Approval

Reference ID: 3596074

1. Introduction

Boehringer Ingelheim (BI) initially submitted a 505(b)(1) new drug application for use of Striverdi Respimat (olodaterol inhalation spray "for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD" on May 14, 2012. Upon review, from a clinical standpoint, Striverdi Respimat at a dose of 5 mcg (2 actuations) once daily demonstrated substantial efficacy and an acceptable safety profile as a long-acting bronchodilator for treatment of patients with COPD. Efficacy and safety were also felt to be demonstrated by the Pulmonary Allergy Advisory Committee (PADAC), who voted 15 yes, 1 no, and 1 abstention when asked whether to approve for marketing. However, manufacturing and testing facilities associated with the drug substance and drug product did not have an acceptable GMP recommendation from the Office of Compliance, which precluded approval and a Complete Response action was taken on March 14, 2013. As the clinical determination of the efficacy and safety of Striverdi Respimat has already been made, this review will briefly summarize the salient points of the Striverdi Respimat program. For a more detailed discussion of the program, please see the previous Division Director review by Dr. Badrul Chowdhury, CDTL review by Dr. Theresa Michelle, and the primary clinical review by Dr. Robert Lim.

2. Background

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, indacaterol, and vilanterol. Some of these are marketed as single ingredient products and others as combination products with inhaled corticosteroids. 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. This has been discussed at various FDA Advisory Committee meetings and has led to publications expressing concerns on safety. Unlike patients with asthma, patients with COPD do not appear to carry a similar signal of worsening disease; however, 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 for COPD. For a more in depth discussion of the safety issues surrounding LABA-containing products, refer to the CDTL and Division summary reviews from the original NDA submission.

The Agency and BI had milestone meetings typical of development of a new molecular entity and 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 Phase 3 COPD phases. In a subsequent meeting, the Agency recommended evaluating dose and dose regimen in patients with asthma.

3. Chemistry, Manufacture, and Controls

The product, Striverdi Respimat Inhalation Spray, is composed of a Striverdi Respimat cartridge and a 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 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 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. The 2 jets of solution collide and create an aerosol that emits from the mouthpiece that the patient inhales. 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. Although the Respimat device is somewhat more complex than standard MDIs and DPIs, based on experience with that Combivent Respimat, there do not appear to be significant problems or issues regarding patients being able to use the device correctly.

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 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 now have an acceptable GMP recommendation from Office of Compliance allowing a recommendation for Approval from the CMC team.

4. Nonclinical Pharmacology/Toxicology

BI submitted results from a full preclinical program to the Agency. Pivotal inhalation toxicity studies were conducted in rats for up to 26 weeks and in dogs for up to 52 weeks. Target organs of toxicity for the rats and dogs (skeletal muscle, increased heart rate, ventricular premature beats, and liver glycogen accumulation) are known class effects of beta-agonist drugs. 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 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. As such, the relevance of these findings to humans is unknown.

5. Clinical Pharmacology/Biopharmaceutics

The program clinical pharmacology 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. Inhaled olodaterol has approximately 30% bioavailability resulting from pulmonary absorption; as 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. 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. There are no outstanding clinical pharmacology issues and the recommendation from the clinical pharmacology team is Approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Dose Selection

As the safety concerns of LABAS are felt to be dose-related, dose selection is a critical element of LABA programs. Even though this is a COPD program, because patients with asthma have greater airway response to bronchodilators, for this program, dose ranging studies were conducted in both asthma and COPD patients. Study 1222.5, a parallel arm, multiple-dose ranging study in 405 patients with COPD in which patients were randomized to receive one of four doses of olodaterol (2, 5, 10, or 20 mcg) once daily for 4 weeks, was a principle dose ranging study. Patients were required to have an FEV1 ≥30% and <80% predicted. As can be seen in Table 1 taken from Dr. Michelle's previous CDTL review, the results demonstrated a clear dose ordering from 2 to 20mcg, with a decrease in incremental benefit

Reference ID: 3596074

with increasing dose. Based on the findings of this and other studies, two olodaterol doses were selected for evaluation in the phase 3 program, 5 mcg and 10 mcg.

Table 1: COPD dose-ranging (Study 1222.5). Primary Endpoint. Trough FEV1 response at 4 weeks.

Treatment	N (total=405)	Trough FEV1 [L] Response (SE)	Difference from placebo (SE)
Placebo	79	-0.014 (0.021)	
Olo 2 mcg	81	0.046 (0.021)	0.061 (0.027)
Olo 5 mcg	80	0.082 (0.021)	0.097 (0.027)
Olo 10 mcg	86	0.109 (0.021)	0.123 (0.026)
Olo 20 mcg	79	0.118 (0.021)	0.132 (0.027)

All p-values <0.05 compared to placebo

Phase 3 Clinical Program

Bronchodilation

Bronchodilation was assessed in 4, 48-week, Phase 3 clinical trials of almost identical 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. Specifically, patients with asthma were excluded. These studies allowed standard of care background therapy with short-acting beta-agonists, inhaled corticosteroids, oral corticosteroids, anticholinergics, and methylxanthines in all treatment groups. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, ECGs, and Holter monitoring in a subset of patients.

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 troughFEV1. Results at weeks 24 and 48 were generally comparable to results at week 12.

Table 2. 48-week COPD studies; ΔFEV1 trough and ΔFEV1 AUC0-3 hr at week 12 (co-primary efficacy end points)

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)

Reference ID: 3596074

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)

Exercise Endurance

BI proposed 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 3). Results of the two studies submitted during the first review cycle showed statistically significant differences between olodaterol and placebo for these measures (Table 3). However, the increases in exercise time were relatively small, 40-50 seconds (12-14%) above the average baseline (354 seconds to 370 seconds). Presently, there is not a recognized minimal clinically important difference (MCID) for exercise testing. There also has not been any correlation demonstrated defining the magnitude of increase in exercise tolerance that corresponds to improvement in activities of daily living. In addition, exercise testing was performed approximately 2 hours post-dose, which corresponds to the time at which the bronchodilator effect of olodaterol has reached its peak. As such, it is not known if the benefit with olodaterol would persist later in the dosing period. For these reasons, it was determined the data submitted were inadequate to support a novel claim for patients with COPD.

Table 3. Exercise endurance studies (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 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. Although such a risk of worsening disease has not been shown in COPD, marketing an unnecessary and unreasonably high dose has safety concerns for COPD patients as well. BI conduced adequate dose ranging and dose regimen studies and selected 5 mcg and 10 mcg once daily doses for the pivotal confirmatory studies. Of the two doses, BI is proposed to market the lower 5 mcg dose because there was no

Reference ID: 3596074

separation between the two doses. From a safety perspective, the Division agreed with that strategy.

Database
The size of the safety database for olodaterol was reasonable. 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. Forty eight week parallel group studies included a total of 3104 patients, of whom 1759 patients were exposed to olodaterol 5 mcg or 10 mcg.

Safety Summary
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.

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 comparator groups, respectively. There were 4 cases of small cell lung carcinoma, all in the olodaterol 10 mcg group. However, 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, the Division did not feel this was likely a real 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, and formoterol groups, respectively. Consistent with other safety findings, nonfatal MACE events were generally balanced. Analysis of common adverse events, ECGs, and laboratory parameters and common adverse events also did not show any specific findings of concern.

The submitted safety 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.

9. Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on January 29, 2013. The committee voted 15-yes, 1-no, and 1 abstain that there was substantial evidence of efficacy, and also voted 15-yes, 1-no, and 1 abstain that the safety of olodaterol was acceptable. The committee voted 15-yes, 1-no, and 1 abstain that olodaterol should be approved for marketing. Regarding a non-voting question requesting the discussion of the

Reference ID: 3596074

evidence to support an exercise endurance claim, most panel members noted that more information was needed to understand optimal exercise trial design for COPD and clinically important exercise improvement and endpoints.

10. Pediatrics

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 the disease does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

- 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.

- DSI audits information: 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. All studies were conducted in accordance with accepted ethical standards.

12. Labeling

- Proprietary Name: BI initially submitted (b) (4) as the original proposed proprietary name. The DMEPA rejected this proposed name because t (b) (4) BI subsequently submitted Striverdi Respimat as the proposed proprietary name, which was accepted by the DMEPA.
- Physician Labeling: The label was reviewed by various disciplines within DPARP, the Office of Medical Policy Programs (OMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were made to reflect the data accurately and better communicate the findings to healthcare providers. The labeling language in the Clinical Trials section related to exercise endurance was not allowed due to lack of efficacy demonstrated for this label claim (see section 7 above). Asthma-related class 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.
- Carton and Immediate Container Label: These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

- Patient Labeling and Medication Guide: Olodaterol will carry an asthma-related safety warning that will be part of the Medication Guide.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for this NDA is for 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, including chronic bronchitis and emphysema, at a dose of 5 mcg once daily. Manufacturing and testing facilities deficiencies that precluded approval during the first review cycle have been corrected and now have an acceptable GMP recommendation from the Office of Compliance.

- 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. The submitted safety data do not show any unique safety findings with olodaterol compared to other inhaled LABA products approved for treatment of patients with COPD. From an efficacy standpoint, the clinical program showed that olodaterol at 5 mcg once-daily dose provided statistically significant replicate bronchodilator effect with effect.

1. Recommendation for Post-marketing Risk Management Activities

Olodaterol will carry an asthma-related safety warning that will be part of the Medication Guide. No additional post-marketing risk management activities are recommended beyond standard pharmacovigilance methods.

2. Recommendation for other Post-marketing Study Commitments

None

3. Recommended Comments to Applicant

No additional comments are recommended to be conveyed.

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/s/

ANTHONY G DURMOWICZ
07/19/2014

Cross-Discipline Team Leader Review

Date	January 31, 2013
From	Theresa M. Michele, MD
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 203,108
Applicant	Boehringer-Ingelheim Pharmaceuticals, Inc.
Date of Submission	May 14, 2012
PDUFA Goal Date	March 14, 2012
Proprietary Name / Established (USAN) names	Striverdi Respimat/ olodaterol
Dosage forms / Strength	inhalation solution / 5 mcg once daily
Proposed Indication(s)	Long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema
Recommended:	Approval

1 INTRODUCTION

Boehringer Ingelheim (BI) Pharmaceuticals, Inc. submitted a 505 (b)(1) new drug application (NDA 203,108) on May 14, 2012 for the use of Striverdi Respimat (olodaterol inhalation solution) as a once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema. The indication for olodaterol is standard for bronchodilator products in COPD. Initially, BI was also seeking claims for increased exercise tolerance, increased inspiratory capacity (IC) at rest and during exercise, reduced lung hyperinflation based on decreased functional residual capacity (FRC) and improved quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ). Based on FDA comments in the 74-day letter and the Advisory Committee briefing document, BI withdrew claims for IC at rest, FRC, and SGRQ. If approved, olodaterol would represent the first medication in COPD with an exercise claim. As such, regulatory policy regarding the development pathway required for such a claim is still evolving.

BI performed an extensive development program for olodaterol consisting of seven dose ranging/dose regimen trials (3 in COPD and 4 in asthma), four 48-week trials, and six 6-week trials, two of which were focused on exercise. All of the trials included both a 5 mcg and a 10 mcg olodaterol dose, providing additional dose ranging data from Phase 3. The

Reference ID: 3253418

majority of the trials permitted usual care background therapy including long-acting anti-muscarinic agents (tiotropium), but excluded the use of LABAs.

The PDUFA due date for this application is March 14, 2013. This memorandum provides an overview of the NDA submission, including a discussion of the Advisory Committee meeting. Because the AC occurred late in the review cycle—just two days prior to the date of this review—the results of the meeting have not yet been fully vetted within the Division. As such, conclusions are preliminary and potentially subject to change based on further discussion.

2 BACKGROUND

2.1 Related drugs: issues with long-acting beta agonists (LABA)

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

Olodaterol is a new molecular entity that belongs to the class called beta-adrenergic agonists. Due to its longer duration of action, olodaterol belongs to the subclass called long-acting beta-adrenergic agonists (LABA). 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. These are marketed either as single ingredient products or as combination products with inhaled corticosteroids. All are dosed either once daily or twice daily, and all are marketed at one dose level.

Inhaled beta-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-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 a safe use

[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 Professional drug label for Serevent (salmeterol xinafoate), Foradil (formoterol fumarate), Advair (fluticasone propionate and salmeterol), Symbicort (budesonide and formoterol fumarate), and Dulera (mometasone furoate and formoterol fumarate). Rockville, MD: U.S. National Library of Medicine (http://dailymed nlm nih.gov/dailymed/about.cfm).

Reference ID: 3253418

strategy outlined by the FDA.[10] 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 exacerbations compared to the approved lower dose.[11] Unlike use of LABAs in patients with asthma, use of LABAs in patients with COPD does 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 for COPD. The dose and dosing frequency are the same for asthma as for COPD for all marketed LABAs approved for both indications in the United States.

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 for LABAs, such as salmeterol (Serevent Diskus) 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 LABAs were conducted in patients with asthma, and the same 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 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.

2.2. Regulatory history

The regulatory history of olodaterol is fairly straightforward, with milestone meetings typical of a first-cycle NDA submission. In the End of Phase 2 meeting, the Agency agreed that the 5 and 10 mcg doses were reasonable to carry forward into Phase 3, although

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[6] Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008; and Pulmonary-Allergy Drugs Advisory Committee Meeting, December 12, 2011.
[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] 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.

Reference ID: 3253418

additional trials were required to establish the dosing interval. In a subsequent meeting, FDA recommended evaluating dose and dose regimen in patients with asthma.

3 CMC/DEVICE

The product Striverdi Respimat includes a Striverdi (olodaterol inhalation solution) cartridge and a Respimat inhaler. Olodaterol inhalation solution is an aqueous solution with a concentration of 2.5 mcg olodaterol per spray, which is equivalent to 2.7 mcg of olodaterol hydrochloride. The proposed dose is two sprays once daily for a total dose of 5 mcg olodaterol. The solution contains the excipients benzalkonium chloride, edentate disodium and citric acid. The Respimat inhaler has a yellow protective cap, a main part with mouthpiece and dose release button into which the patient inserts the Striverdi cartridge prior to first use, and a clear base part with a piercing element in the base. A dose indicator is also visible through the clear base. To deliver a dose, the patient loads an actuation by mechanically turning the base of the device until it clicks, closes his/her lips around the mouthpiece and presses the dose release button while taking a slow, deep breath. A second actuation is taken in the same way to complete the dose.

The Respimat device delivers a mist aerosol using a spring activated mechanism with no propellants. One cartridge is used per inhaler. The Respimat device is relatively new to the United States market, with one product, Combivent Respimat (ipratropium bromide and albuterol) Inhalation Spray, approved for marketing in October 2011. BI conducted patient handling studies using the Respimat device, and the device was reviewed by CDRH under NDA 21,936 (tiotropium; Spiriva Respimat). NDA 21,936 received a Complete Response in 2008 due to a potential mortality signal. (b) (4)

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(b) (4)

Reference ID: 3253418

(b) (4)

As of the date of this review, the recommendation from the Chemistry reviewer, Dr. Craig Bertha, is approvable pending a satisfactory recommendation from the microbiology team and adequate facilities inspection from the Office of Compliance.

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 following target organs of toxicity were identified in rats (with organ-specific findings in parentheses): 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). The following target organs of toxicity were identified in dogs (with organ-specific findings in parentheses): 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). In general, findings in rats and dogs 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.

The recommendation from the Pharmacology/Toxicology reviewer, Dr. Carol Rivera-Lopez, is approval. There are no outstanding toxicology issues or comments to the sponsor.

Reference ID: 3253418

5 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

BI submitted results from a comprehensive clinical pharmacology program to the Agency. 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 are 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 recommendation from the Clinical Pharmacology and Biopharmaceutics review team is approval. There are no outstanding clinical pharmacology issues or comments to the sponsor.

6 CLINICAL MICROBIOLOGY

As of the date of this review, the recommendation from the microbiology reviewer is pending the sponsor's response to an information request. In order to recommend approval, additional information is needed regarding the (b) (4) for the container-closure system.

7 CLINICAL AND STATISTICAL—EFFICACY

7.1 Overview of the clinical program

Some characteristics of the relevant clinical trials are shown in Table 1. The design and conduct of these trials are briefly described below, followed by efficacy and safety findings. The trials are shown in Table 1 in three groupings – dose ranging/regimen COPD and asthma trials, 48-week COPD trials, and 6-week COPD trials.

Reference ID: 3253418

Table 1. Relevant clinical studies with olodaterol

Study	Objective	Design	Population	Olodaterol Dose	Treatment Duration	Primary Endpoint
Phase 2 –COPD Dose Ranging						
1222.3	Dose range, PK	R, DB, PC, CO	COPD patients ≥40 years old N=36	Olo 2 mcg x1 Olo 5 mcg x1 Olo 10 mcg x1 Olo 20 mcg x1 Pbo x 1	single dose	Trough FEV1
1222.5	Dose range	R, DB, PC, MC	COPD patients ≥40 years N=405	Olo 2 mcg qD Olo 5 mcg qD Olo 10 mcg qD Olo 20 mcg qD Pbo	4 weeks	Trough FEV1
1222.26	Dosing regimen	R, DB,CO, MC	COPD patients ≥40 years N=47	Olo 10 mcg qD Olo 5 mcg BID Olo 5 mcg qD Olo 2 mcg BID	3 weeks	FEV1 $AUC_{(0-12)}$ FEV1 $AUC_{(12-24)}$
Phase 2-Asthma Dose Ranging						
1222.4	Dose range	R,DB,PC CO, MC	Asthma ≥18 years N=31	Olo 2 mcg x1 Olo 5 mcg x1 Olo 10 mcg x1 Olo 20 mcg x1 Pbo x 1	Single dose	PC20
1222.6	Dose range	R, DB, PC, MC	Asthma ≥18 years N=296	Olo 2 mcg qD Olo 5 mcg qD Olo 10 mcg qD Olo 20 mcg qD Pbo	4 weeks	Trough FEV1
1222.27	Dose range	R, DB, PC, AC, CO, MC	Asthma 18-70 years N=198	Olo 2 mcg qD Olo 5 mcg qD Olo 10 mcg qD Olo 20 mcg qD For 12 mcg BID Pbo	4 weeks	FEV1 $AUC_{(0-24)}$
1222.29	Dosing regimen	R, DB, PC, CO, MC	Asthma 18-70 years N=180	Olo 10 mcg qD Olo 5 mcg BID Olo 5 mcg qD Olo 2.5 mcg BID Pbo	3 weeks	FEV1 $AUC_{(0-24)}$
Phase 3- 48 week COPD Pivotal Trials						
1222.11	Safety, Efficacy, PK	R, DB, PC, MC	COPD ≥40 years N=624	Olo 5 mcg qD Olo 10 mcg qD	48 weeks	FEV1 $AUC_{(0-3)}$ Trough FEV1 at day 85
1222.12	Safety, Efficacy, PK	R, DB, PC, MC	COPD ≥40 years N=642	Olo 5 mcg qD Olo 10 mcg qD	48 weeks	FEV1 $AUC_{(0-3)}$ Trough FEV1 at day 85
1222.13	Safety, Efficacy, PK	R, DB, PC, MC	COPD ≥40 years N=904	Olo 5 mcg qD Olo 10 mcg qD For 12 mcg BID	48 weeks	FEV1 $AUC_{(0-3)}$ Trough FEV1 at day 169

Reference ID: 3253418

1222.14	Safety, Efficacy, PK	R, DB, PC, MC	COPD ≥40 years N=934	Olo 5 mcg qD Olo 10 mcg qD For 12 mcg BID	48 weeks	FEV1 $AUC_{(0-3)}$ Trough FEV1 at day 169
Phase 3- Six week COPD Trials						
1222.24	24 hour FEV1 time profile	R, DB, PC, AC, CO, MC	COPD ≥40 years N=99	Olo 5 mcg qD Olo 10 mcg qD For 12 mcg BID Pbo	6 weeks	FEV1 $AUC_{(0-12)}$ FEV1 $AUC_{(12-24)}$
1222.25	24 hour FEV1 time profile	R, DB, PC, AC, CO, MC	COPD ≥40 years N=100	Olo 5 mcg qD Olo 10 mcg qD For 12 mcg BID Pbo	6 weeks	FEV1 $AUC_{(0-12)}$ FEV1 $AUC_{(12-24)}$
1222.39	24 hour FEV1 time profile	R, DB, PC, AC, CO, MC	COPD ≥40 years N=108	Olo 5 mcg qD Olo 10 mcg qD Tio 18 mcg qD Pbo	6 weeks	FEV1 $AUC_{(0-12)}$ FEV1 $AUC_{(12-24)}$
1222.40	24 hour FEV1 time profile	R, DB, PC, AC, CO, MC	COPD ≥40 years N=122	Olo 5 mcg qD Olo 10 mcg qD Tio 18 mcg qD Pbo	6 weeks	FEV1 $AUC_{(0-12)}$ FEV1 $AUC_{(12-24)}$
1222.37	Exercise endurance	R, DB, PC, CO, MC	COPD ≥40 years N=151	Olo 5 mcg qD Olo 10 mcg qD Pbo	6 weeks	Endurance time IC FRC
1222.38	Exercise endurance	R, DB, PC, CO, MC	COPD ≥40 years N=151	Olo 5 mcg qD Olo 10 mcg qD Pbo	6 weeks	Endurance time IC FRC

Olo=olodaterol, Tio=tiotropium, For=formoterol, R=randomized, DB=double-blind, PC=placebo controlled, AC=active controlled, CO=cross-over, MC=multicenter, PK=pharmacokinetics, FEV1=force expiratory volume in 1 second, IC=inspiratory capacity, FRC=forced residual capacity, AUC=area under the curve, qD= once daily, BID=twice daily, Pbo=placebo, PC20=provocative concentration of methacholine required to cause a 20% fall in FEV1 from baseline
Source: FDA created table

In subsequent sections, design and conduct of the trials are described following the order the trials appear in Table 1. Efficacy findings and safety findings are described later in this section after description of the design and conduct of the trials.

Design and conduct of the trials

Dose ranging and dose regimen trials

Trials in COPD (1222.3, 1222.5, and 1222.26)

Trial 1222.3 was a randomized, double-blind, placebo controlled, 5-way cross-over, dose-ranging trial with an open label extension in 36 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). The treatment arms included placebo, olodaterol 2 mcg, olodaterol 5 mcg, olodaterol 10 mcg, and olodaterol 20 mcg. In order to collect more PK data, an olodaterol 40 mcg group was added as an open label extension. In each treatment period, patients received one dose of trial medication followed by pulmonary function testing (PFTs). Between treatment periods, there was a 14-day washout period. The primary endpoint was FEV1 24 hours after a single dose of

olodaterol. Secondary endpoints included FEV1 AUC(0-3 hr), FEV1 AUC(0-12 hr), FEV1 AUC(0-24 hr), and FEV1 AUC(12-24 hr).

Trial 1222.5 was a randomized, double-blind placebo controlled, parallel group, multiple-dose, dose-ranging trial in 405 patients with COPD. Patients were required to have an FEV1 ≥30% and <80% predicted. Patients were randomized to receive one of four doses of olodaterol (2, 5, 10, or 20 mcg) once daily for 4 weeks. Patients performed PFTs at baseline and after 1, 2, and 4 weeks of treatment. The primary endpoint was trough FEV1 after 4 weeks of treatment. Secondary endpoints included trough FEV1 after 1 and 2 weeks of treatment, FEV1 AUC(0-3 hr) after the first dose, after 1, 2 and 4 weeks, and FEV1 AUC(0-6 hr) after 4 weeks.

Trial 1222.26 was double-blind, randomized, 4-way crossover, dose regimen trial in 47 patients with moderate to severe stable COPD. The objective of this trial was to determine optimum dosing interval (qD versus BID). Each treatment period lasted 3 weeks with no washout period between. The doses of olodaterol were 2 mcg BID, 5 mcg BID, 5 mcg qD, and 10 mcg qD. PFTs were performed at baseline (prior to any test article) and at the end of each 3 week treatment period. There was no placebo group as patients were compared to their own baseline. The co-primary endpoints were change from baseline in FEV1 AUC(0-12 hr) and FEV1 AUC(12-24 hr). Secondary endpoints included change from baseline in FEV1 AUC(0-24 hr) and trough FEV1 after 3 weeks of treatment.

Trials in asthma (1222.4, 1222.6, 1222.27, and 1222.29)

Trial 1222.4 was a randomized, double-blind, placebo controlled, 5-way cross-over, single dose, dose-ranging trial in 31 patients with intermittent asthma. Patients were randomized to receive a sequence of single doses of placebo, and olodaterol 2 mcg, 5 mcg, 10 mcg and 20 mcg. Each treatment was separated by 14-21 days. Following administration of trial 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. Of note, this is not a standard endpoint for dose-ranging trials; therefore, results should be interpreted with caution. Secondary endpoints included Log_2(PC20 FEV1) at 0.5, 4, 8, and 32 hours post-treatment.

Trial 1222.6 was a 4-week multi-center, randomized, double-blind, placebo controlled, parallel group, multiple dose, dose-ranging trial in 296 patients with asthma (FEV1≥60% and <90% predicted). Patients were randomized to receive either placebo or olodaterol at doses of 2, 5, 10, or 20 mcg once daily. During the double-blind phase, patients had weekly study visits. The primary endpoint was trough FEV1 after 4 weeks of treatment. The key secondary endpoint was peak expiratory flow rate after 4 weeks of treatment.

Trial 1222.27 was a 16 week, multi-center, randomized, double-blind, placebo and active controlled, double dummy, 4-period incomplete block, multiple dose, dose-ranging trial in 198 patients with asthma who were on ICS and were still symptomatic. Patients were randomized to receive a sequence of 4 out of a possible 6 treatments (olodaterol 2, 5, 10, 20 mcg qD, placebo, and formoterol 12 mcg BID). Each treatment period was 4 weeks. There was no washout between treatment periods. PFTs were conducted at baseline (prior to any treatment) and at the end of each 4 week treatment period. The primary endpoint was FEV1

Reference ID: 3253418

AUC(0-24 hr) after each 4 week treatment period. Secondary endpoints included trough FEV1, FEV1 AUC(0-12 hr), and FEV1 AUC(12-24 hr).

Trial 1222.29 was a 17 week, multi-center, randomized, double-blind, placebo controlled, dose-regimen trial including two parallel 3-way crossovers in 180 patients with moderate to severe persistent asthma. Following the screening period, patients were randomized to receive a treatment sequence consisting of 3 week treatment periods with olodaterol 2.5 mcg BID, 5 mcg qD, and placebo; or olodaterol 5 mcg BID, 10 mcg qD, and placebo. There were a total of 12 possible treatment sequences. Between each 3 week treatment period, there was a 2 week washout period. The primary endpoint was FEV1 AUC(0-24 hr) after 3 weeks of treatment. The key secondary endpoints were FEV1 AUC(0-12 hr) and FEV1 AUC(12-24 hr) after 3 weeks of treatment.

48-week trials

Trials 1222.11 and 1222.12 were identical in design. These trials were 48-week, multi-center, randomized, double-blind, placebo controlled, parallel group trials to assess the safety and efficacy of two doses of olodaterol (5 mcg qD and 10 mcg qD) in approximately 600 patients with COPD. Patients had FEV1 of <80% predicted, with an FEV1/FVC ratio of <70% predicted and were current smokers, or had at least a 10 pack year smoking history. Patients with asthma were excluded. The trials included 11 study visits. Consistent with standard of care, background therapy with short-acting beta-agonists, inhaled corticosteroids, oral corticosteroids, anticholinergics (including tiotropium), and methylxanthines were permitted in all treatment groups. The co-primary endpoints for these trials were trough FEV1 response and FEV1 AUC(0-3 hr) response at week 12. There were a number of secondary endpoints, including a variety of spirometry measures, rescue medication use, and exacerbation endpoints.

Trials 1222.13 and 1222.14 were also identical in design. The trials were similar in design to 1222.11 and 1222.12 except for the addition of an active comparator arm and inclusion of additional endpoints related to dyspnea and quality of life. These trials were 48-week, multi-center, randomized, double-blind, placebo controlled, parallel group trials to assess the safety and efficacy of two doses of olodaterol (5 mcg qD and 10 mcg qD) in approximately 900 patients with COPD. These trials also included an active comparator arm, formoterol 12 mcg twice daily, in a blinded double-dummy fashion. Patients had FEV1 of <80% predicted, with an FEV1/FVC ratio of <70% predicted and were current smokers, or had at least a 10 pack year smoking history. Patients with asthma were excluded. The trials included 11 study visits. Consistent with standard of care, background therapy with short-acting beta-agonists, inhaled corticosteroids, oral corticosteroids, anticholinergics (including tiotropium), and methylxanthines were permitted in all treatment groups. The co-primary endpoints for these trials were trough FEV1 response, FEV1 AUC(0-3 hr) response, and Mahler Transitional Dyspnea Index (TDI) at week 24. Key secondary endpoints were total St. George's Respiratory Questionnaire (SGRQ) after 24 weeks of treatment (olodaterol versus placebo), trough FEV1 response after 24 weeks of treatment (olodaterol versus formoterol), and FEV1 AUC(0-3 hr) response after 24 weeks of treatment (olodaterol versus formoterol).

Reference ID: 3253418

6-week trials

FEV1 profile trials (1222.24, 1222.25, 1222.39, and 1222.40)

Trials 1222.24 and 1222.25 were identical trials meant to characterize the 24-hour FEV time profile of olodaterol. These were randomized, double-blind, double-dummy, placebo controlled, 4-way cross-over trials to characterize the 24-hour FEV1 time profiles of olodaterol (5 mcg and 10 mcg once daily) and formoterol (12 mcg BID) in approximately 100 COPD patients with FEV1≤80% predicted. Trials 1222.39 and 1222.40 were similar except that they included a tiotropium (HandiHaler 18 mcg qD) active comparator instead of formoterol. Each of the four treatment periods lasted 6 weeks, and periods were separated by a 2 or 3 week washout period. After each six 6 week treatment period, 24 hour post-dose spirometry was performed. Spirometry was performed 30 minutes pre-dose, and at 0.5, 1, 2, 3, 4, 6, 8, 10, 11, 11:50, 12:30, 13, 14, 22, 23, and 23:50 hours post-dose. The 12:30, 13, and 14 hour time points were not included in trials 1222.39 and 1222.40. Two weeks after the last treatment period, the patients were seen for their final follow-up visit. In trials 1222.25 and 1222.26, patients were permitted to continue long-acting muscarinic antagonists (LAMAs); however, LABAs were prohibited. In Trials 1222.39 and 1222.40, both LABAs and LAMAs were prohibited.

Exercise trials (1222.37 and 1222.38)

Trials 1222.37 and 1222.38 were identical in design. They were multi-center, multi-national, randomized, double-blind, 3-way cross-over trials in approximately 150 moderate to severe COPD patients with an exercise endurance time of less than 25 minutes at baseline. The three 6 week treatment arms included placebo, olodaterol 5 mcg, and olodaterol 10 mcg. Between each treatment period there was a 2 week washout period. Patients were allowed to take ICS, methylxanthines, and short acting anticholinergics during the trial. However, LABAs and tiotropium were not permitted. The primary endpoint was exercise endurance time during constant rate cycle ergometry to symptom limitation at 75% maximal work capacity after 6 weeks of treatment. Key secondary endpoints were inspiratory capacity at isotime (defined as the endurance time of constant work rate exercise of shortest duration) at 75% maximal work capacity and intensity of breathing discomfort as measured by the Borg Scale at isotime.

Efficacy Findings

The clinical program showed that olodaterol at 5 and 10 mcg once-daily doses provided statistically significant bronchodilatory effects in patients with COPD with replicate findings for these doses. Olodaterol 5 and 10 mcg also demonstrated statistically significant improvement in exercise endurance time and inspiratory capacity at isotime during exercise. Some pertinent efficacy results, specifically FEV1 results and exercise results are presented in subsequent sections, with some comments.

Reference ID: 3253418

7.2 Dose and dose regimen

Total daily dose

As discussed in the Background section, dose ranging in asthma patients is important because the population is more responsive to bronchodilators and can show a greater separation of doses compared to patients with COPD. Given this, the discussion of the dose-ranging results will focus on the results of the multiple dose, asthma dose-ranging trials followed by the COPD data.

The single dose, dose-ranging trial in asthma (1222.4) demonstrated clear dose ordering from 2 to 20 mcg; however, the endpoint was based on methacholine challenge testing rather than FEV1, which limits interpretability of the trial. Trial 1222.6, which was a 4-week dose ranging trial in asthma, demonstrated an unclear effect of olodaterol that is inconsistent with other olodaterol trials. BI repeated this trial, adding a formoterol comparator arm (Trial 1222.27), again showing a clear dose response although the incremental benefit decreased with increasing dose. See Table 2. Based on this trial, the 20 mcg dose did not appear to demonstrate benefit over the 10 mcg dose, suggesting that the 20 mcg dose is near the top of the dose response curve. In addition, the 2 mcg dose appeared to be suboptimal as it showed a substantially smaller response compared to the active comparator, formoterol. The 5 mcg dose of olodaterol provided similar response as formoterol.

Table 2: Asthma dose-ranging (1222.27). Primary endpoint. FEV1 AUC(0-24 hr) response after 4 weeks of treatment

Treatment	N (total =198)	FEV1 AUC(0-24) [L] Response (SE)	Difference from placebo (SE)
Placebo	122	-0.004 (0.025)	
Olo 2 mcg	119	0.135 (0.025)	0.140 (0.022)
Olo 5 mcg	126	0.178 (0.025)	0.182 (0.021)
Olo 10 mcg	121	0.201 (0.025)	0.205 (0.022)
Olo 20 mcg	119	0.225 (0.025)	0.229 (0.022)
For 12mcg BID	122	0.164 (0.025)	0.169 (0.022)

p-values all <0.0001 for Olo compared to placebo
Source: Trial 1222.27 CSR; Table 11.4.1.1:1; pp93

The assessment of dose in COPD demonstrated similar results to the asthma trials. The single dose, dose-ranging trial in COPD (1222.3) showed clear dose ordering from 2 to 20 mcg, with a decrease in incremental benefit with increasing dose. This was consistently demonstrated in the 4 week multiple dose ranging trial in COPD (Trial 1222.5). See Table 3.

Reference ID: 3253418

Table 3. COPD dose-ranging (1222.5). Primary Endpoint. Trough FEV1 response after 4 weeks.

Treatment	N (total=405)	Trough FEV1 [L] Response (SE)	Difference from placebo (SE)
Placebo	79	-0.014 (0.021)	
Olo 2 mcg	81	0.046 (0.021)	0.061 (0.027)
Olo 5 mcg	80	0.082 (0.021)	0.097 (0.027)
Olo 10 mcg	86	0.109 (0.021)	0.123 (0.026)
Olo 20 mcg	79	0.118 (0.021)	0.132 (0.027)

All p-values <0.05 compared to placebo
Source: Trial 1222.5 CSR; Table 11.4.1.1:1; pp81

The results from the dose ranging trials in patients with asthma and COPD provide support for the two doses BI selected for evaluation in the phase 3 program, 5 mcg and 10 mcg. Inclusion of more than one dose in the phase 3 program provides additional dose response information for both efficacy and safety and further informs dose selection. Further evaluation of dose in Phase 3 is discussed under bronchodilator effects.

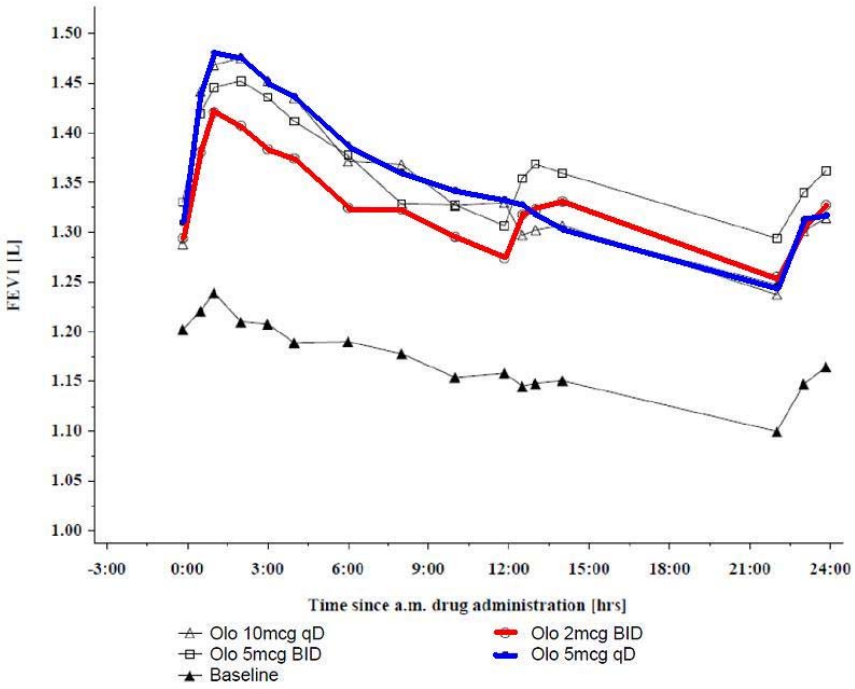
Dose regimen

BI completed two dose regimen trials for olodaterol, one in asthma (1222.29) and one in COPD (1222.26). The asthma trial demonstrated small benefits for twice daily dosing over once daily dosing, but the small benefit in the second half of the 24-hour dosing interval was not sufficient to argue in favor of twice daily dosing, especially since the BID regimen did not result in decreased overall total daily dose. In contrast to the asthma data, the COPD trial did not demonstrate a benefit of twice daily dosing over once daily dosing for the 5 mcg dose, even when similar total daily doses were compared. See

Figure 1.

Reference ID: 3253418

Figure 1: COPD dose regimen (1222.26). FEV1 at individual timepoints after 3 weeks of treatment



Source: modified from Trial 1222.26 CSR; Figure 11.4.1:1;pg72

Based on the evaluation of dosing regimen, once daily dosing for olodaterol is supported.

7.3 Efficacy

7.3.1 Bronchodilator effects

The results for the co-primary efficacy variables for the 48-week trials using the protocol-specified analysis are shown in Table 4. The primary endpoint of Trials 1222.13 and 1222.14 was at 24 weeks, not 12 weeks, but data are all shown at 12 weeks for ease of comparison. The results of the 48-week trials showed that olodaterol 5 and 10 mcg were statistically significant compared to placebo for the co-primary endpoints with the exception of Trial 1222.12 in which the 5 mcg olodaterol group was not significant for trough FEV1. Results at 12 weeks were generally comparable with results at 24 and 48 weeks. In addition, secondary spirometric endpoints were generally consistent with the primary endpoint results.

Reference ID: 3253418

Table 4. 48-week trials: Change from baseline FEV_1 AUC_{0-3hr} (liters) and trough FEV1 at week 12

Trial	Treatment	N	AUC (0-3hr)	AUC(0-3 hr) Response (95% CI)	tFEV1	tFEV1 Response (95% CI)
1222.11	Placebo	188	0.002		-0.032	
	Olo 5mcg	192	0.167	0.164 (0.120, 0.209)	0.052	0.084 (0.040, 0.129)
	Olo 10mcg	192	0.157	0.155 (0.111, 0.199)	0.048	0.080 (0.037, 0.124)
1222.12	Placebo	197	0.021		0.005	
	Olo 5mcg	196	0.155	0.134 (0.090, 0.177)	0.038	0.033 (-0.013, 0.080)
	Olo 10mcg	201	0.151	0.130 (0.087, 0.172)	0.049	0.045 (-0.001, 0.090)
1222.13	Placebo	187	-0.003		-0.027	
	Olo 5mcg	208	0.176	0.178 (0.137, 0.219)	0.056	0.083 (0.043, 0.123)
	Olo 10mcg	207	0.167	0.170 (0.129, 0.211)	0.048	0.075 (0.035, 0.114)
	For 12mcg	200	0.182	0.185 (0.144, 0.226)	0.033	0.059 (0.019, 0.100)
1222.14	Placebo	212	-0.008		-0.041	
	Olo 5mcg	220	0.138	0.145 (0.108, 0.182)	0.018	0.059 (0.022, 0.095)
	Olo 10mcg	219	0.167	0.175 (0.138, 0.212)	0.052	0.093 (0.057, 0.130)
	For 12mcg	217	0.163	0.170 (0.133, 0.208)	0.024	0.065 (0.028, 0.101)

Source: FEV1 2012 08 02.sas and Subgr FEV1 AUC 2012 12 01.sas

A comparison of the two dose groups is important to evaluate the dose response with regards to efficacy. As shown in Table 4, the results for the 5 and 10 mcg group were similar, and BI has chosen to propose the 5 mcg dose of olodaterol for marketing approval.

In general, the observed treatment effect for olodaterol is somewhat lower than that observed in most registration trials for other long-acting bronchodilators; however, in all of the olodaterol trials, patients were permitted to be on COPD background medications except for LABAs, which was not the case in other COPD development programs. In Trials 1222.13 and 1222.14, formoterol 12 mcg BID was included as an active comparator arm. The treatment effect of olodaterol in these trials was generally comparable to the observed treatment effect with formoterol. In addition, a somewhat larger treatment effect comparable to tiotropium was observed in the 6-week trials 1222.39 and 1222.40 in which LAMA background therapy was not permitted.

The analysis model also had an impact on effect size. The initial protocol-specified analysis of spirometric endpoints for Trials 1222.11 and 1222.12 included treatment-by-tiotropium stratum interaction terms in the mixed effects model. In a post-hoc analysis, the sponsor removed these terms from the model due to differences in the size of the tiotropium and non-tiotropium strata resulting in increased variability. The post-hoc analysis used in Trials 1222.11 and 1222.12 was the same as primary analysis pre-specified in Trials 1222.13 and 1222.14 (i.e. treatment-by-tiotropium stratum interaction removed). Using the sponsor's post-hoc analysis, all 4 trials showed a statistically significant benefit of olodaterol 5 mcg over placebo for both trough FEV1 and FEV1 AUC(0-3 hr), with differences from placebo ranging from 0.047-0.091L for trough FEV1 and 0.145-0.178L for FEV1(AUC 0-3 hr) at 12 weeks.

Reference ID: 3253418

7.3.2 Effects on exercise

BI seeks claims related to exercise tolerance, inspiratory capacity, and hyperinflation, which were evaluated in the 6 week exercise trials (1222.37 and 1222.38). These are novel claims without an established regulatory pathway; thus, there are many questions regarding appropriate design of the trials and interpretation of results. For example, with regards to the design of the trials, 6 weeks may be too short of a treatment duration to establish a treatment effect, since pivotal trials of bronchodilator efficacy are required to be longer. In addition, exercise testing was performed approximately 2 hours post-dosing (expected peak drug effect), and it is unclear if a benefit would have been maintained for the entire dosing period.

The results of the exercise trials show that olodaterol 5 mcg increased cycle ergometry exercise endurance time after 6 weeks of treatment from 42-52 seconds (12-14%) as shown in Table 5. There was no dose response between the 5 and 10 mcg dose groups. Similarly, olodaterol treatment resulted in a statistically significant increase in inspiratory capacity at isotime compared to placebo. See Table 5.

Table 5. Trials 1222.37 and 1222.38; Exercise Endurance time [seconds] and Inspiratory Capacity [Liters] after 6 weeks of treatment

Treatment	Endurance time [s]	Endurance time Treatment/Placebo (95% CI)	IC end exercise [L]	IC Treatment Difference [L] (95% CI)
1222.37				
Placebo	369.8		1.887	
Olo 5mcg	421.6	1.14 (1.065, 1.221)	2.067	0.180 (0.107, 0.252)
Olo 10mcg	420.7	1.14 (1.062, 1.219)	2.024	0.137 (0.064, 0.210)
1222.38				
Placebo	354.3		2.158	
Olo 5mcg	396.3	1.12 (1.043, 1.199)	2.236	0.078 (0.010, 0.146)
Olo 10mcg	391.5	1.10 (1.030, 1.184)	2.330	0.172 (0.105, 0.240)

Source: Endure 2012 08 21.sas; IC Isotime 2012 08 21.sas

Functional residual capacity (FRC) was one of many other secondary endpoints; the analysis is considered exploratory because this endpoint was not included in the analysis hierarchy to control type 1 error. There was a decrease in FRC compared to placebo at $p<0.05$ for both treatment groups at 1 hour post dosing but not at 30 minutes post dosing.

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 101-153 seconds (34%)[12,13]. 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

[12] 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.
[13] 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.

Reference ID: 3253418

MCID is likewise unknown. In theory, increases in inspiratory capacity imply a decrease in dynamic hyperinflation during exercise.

7.3.3 Efficacy conclusions

The spirometry data from the 48-week trials demonstrate a clear bronchodilator effect for olodaterol over placebo plus standard of care, with a benefit on FEV1 over the first 3 hours after dosing and at the end of the dosing interval (trough). Dose ranging and dose regimen trials in both asthma and COPD are supportive of the sponsor's decision to take both the 5 and 10 mcg once daily doses into Phase 3. The 48 week trials demonstrate no benefit of the 10 mcg dose over the 5 mcg dose and support the sponsor's proposed dose of 5 mcg.

While the two replicative 6 week exercise trials demonstrated a statistically significant benefit on exercise duration and inspiratory capacity, it is unclear if this represents a true clinical benefit. Additional data demonstrating long-term benefit and benefit across the dosing interval will likely be necessary for a claim, although this remains under discussion by the project team. In addition, since the MCID for these endpoints is unknown, a clinical anchor associating the degree of benefit on exercise with some other clinically-meaningful endpoint would also be helpful in interpretation.

8 SAFETY

8.1 Safety in COPD

The safety assessment of olodaterol is based primarily on the 48-week trials shown in Table 1. Findings in the shorter-term trials were consistent with the safety profile observed in the 48-week trials. Including all phases of development, a total of 4312 patients were exposed to at least one dose of olodaterol monotherapy. Of these, 3353 were COPD patients. Of the COPD patients, 3142 received olodaterol 5 or 10 mcg once daily in Phase 3 parallel group or crossover trials. The 48-week trials included a total of 3104 patients. Of these patients, 1,759 patients were exposed to olodaterol at a dose of 5 or 10 mcg. Given that the lower 5 mcg dose is proposed for marketing, it is important to also consider data from the 10 mcg dose as supportive evidence of safety.

As part of the safety analysis, the sponsor evaluated deaths, serious adverse events (SAEs), adverse events (AEs), and also conducted specific analyses of Major Adverse Cardiac Events (MACE) endpoints and respiratory adverse events. Deaths and SAEs were all adjudicated by independent committees. In addition, the sponsor also collected vital status information out to 337 + 14 days (50 weeks) for patients who discontinued from the trials. Overall, vital status data are available for 98% of all patients randomized in the 48-week trials.

Reference ID: 3253418

Deaths and Serious Adverse Events (SAEs)[14] occurred in the COPD program as would be expected in the relatively older and sicker patient population studied. In the 48-week trials, there were a total of 53 on-treatment deaths, which were generally balanced between treatment groups [13 (1.5%) placebo, 13 (1.5%) olodaterol 5mcg, 17 (1.9%), olodaterol 10mcg, and 10 (2.2%) formoterol]. Deaths were reported both as determined by the investigators and as determined by the adjudication committee. According to the investigators, the most frequent causes of death were COPD exacerbation, respiratory failure, and pneumonia; the most frequent causes of death as determined by the mortality adjudication committee were COPD exacerbation, sudden cardiac death, unknown, and lung cancer. Numbers of each individual event were too small to draw any definitive conclusions regarding safety signals. Including vital status information, there were 23 (2.6%), 19 (2.2%), 21 (2.4%), and 13 (2.8%) deaths in the placebo, olodaterol 5 mcg, olodaterol 10 mcg, and formoterol treatment groups, respectively. Given that there was substantial differential discontinuation in the placebo group in the 48-week trials, vital status information is useful to account for potential bias due to a healthy survivor effect in the placebo group.

In the 48-week trials there were 499 patients with on-treatment SAEs (fatal and non-fatal) that were generally balanced across treatment groups. As expected in the moderate to severe COPD patient population, the most frequent SAEs were COPD exacerbation and pneumonia. There was a small imbalance in the olodaterol 10 mcg group compared to placebo for neoplasms primarily driven by 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. However, given the small numbers, long lead time for lung neoplasms, and lack of similar findings in animal carcinogenicity studies, it is not clear that this is a safety signal. Pneumonia was also relatively increased in the olodaterol 10 mcg group compared to placebo with 13 (1.5%), 14 (1.6%), 22 (2.5%), and 7(1.5%) in the placebo, olodaterol 5 mcg, olodaterol 10 mcg, and formoterol groups, respectively. The imbalance persists for adjudicated cases of pneumonia. Again, numbers are small and not corrected for exposure. These relative imbalances did not occur in the olodaterol 5 mcg dose group.

In the COPD studies, the adverse event profile was typical for COPD patients with respiratory disorders and infectious disorders being most common. Adverse events leading to discontinuations and commonly reported adverse events did not raise any specific or unique safety concerns for olodaterol in COPD patients. Adverse events relating to beta-adrenergic effects, such as those in the cardiovascular system and cerebrovascular system, did not occur more frequently in the olodaterol groups. An adjudicated analysis of major adverse cardiac events (MACE) did not reveal any concerns. Fatal MACE events

[14] 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.

Reference ID: 3253418

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

8.2 Safety in asthma

Because of the safety issues with LABAs in patients with asthma, it is important to review the safety data from the asthma studies with regards to serious asthma exacerbations, hospitalizations, intubations, and deaths. BI has short term data with olodaterol in approximately 700 patients with asthma. No asthma related deaths occurred in the asthma dose ranging trials and there was no increase in asthma-related SAEs for either the 5 mcg or 10 mcg dose of olodaterol, raising no safety concerns for asthma-related events with the proposed 5 mcg dose of olodaterol.

8.3 Safety conclusions

The size and duration of the safety database for olodaterol are appropriate for a COPD program. Overall, the adverse event profile is consistent with known LABA class effects of and with the COPD patient population. The sponsor did appropriate analyses to evaluate for serious respiratory and cardiovascular related events as well as an adjudicated analysis of deaths with vital status follow up to account for potential differential discontinuation. The asthma data, while limited, demonstrates no increase in asthma-related SAEs. In addition, it is reassuring that the sponsor has conducted an extensive dose ranging program for olodaterol, ultimately choosing the lower of the two doses taken forward into Phase 3, since many of the LABA class safety issues are known to be dose related.

9 ADVISORY COMMITTEE MEETING

On January 29, 2013, FDA held a meeting of the Pulmonary-Allergy Drugs Advisory Committee to discuss the adequacy of the efficacy and safety data submitted by BI to support the approval of olodaterol inhalation solution at a dose of 5 mcg every day (once-daily), for the long term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema. The major issues discussed at the PADAC meeting were: a) whether the bronchodilator benefit observed in the setting of background therapy represents a clinically meaningful difference, b) whether or not the exercise claims are supported, and c) the safety of olodaterol.

The committee voted almost unanimously in favor of olodaterol bronchodilator efficacy, safety, and approval. The vote was 15 yes, 1 no, and 1 abstention for all three voting questions. 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 raised was the occurrence of 4 cases of non-small cell lung carcinoma in the olodaterol 10 mcg group compared to placebo. Members noted that while this may have been a random occurrence, appropriate post-marketing surveillance is warranted.

The committee observed that exercise tolerance is an important endpoint for patients, and many members expressed support for inclusion of exercise endpoints in pharmaceutical

Reference ID: 3253418

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.

10 PEDIATRICS

Boehringer-Ingelheim is requesting a claim for Striverdi Respimat for COPD only and is not requesting a claim for asthma. Since COPD is a disease that occurs only in adults, FDA granted a pediatric waiver for this application. The product label will clearly state that indacaterol is not indicated for children. No pediatric trials were conducted.

11 OTHER RELEVANT REGULATORY ISSUES

11.1 Ethics and data integrity

For the pivotal 48-week trials submitted in this application, there was only one investigator who reported payments in excess of $25,000, which was for grant funding and attendance at 3 meetings. Given the large size of the Phase 3 program, it is highly unlikely that data from this site could have influenced the results.

For this application, the Division of Scientific Investigations (DSI) was consulted to conduct site inspections. Sites from three of the four 48-week trials were audited [Trials 1222.11 (two US sites), 1222.12 (one US site), and 1222.13 (one site in Argentina)]. In addition, the sponsor site in Raritan, New Jersey was audited. The auditor did not have significant findings at the three US sites or at the sponsor's site in New Jersey. A Form FDA 489 with Voluntary Action Indicated was issued to the site in Argentina due to 7 patients who received study drug outside of the Interactive Voice Response System for at least one visit and to study drug medication returns that could not be located for 6 patients. FDA biostatisticians reanalyzed the results from Trial 1222.13 removing the patients from this site from the analysis, which did not affect the overall results of the trial.

11.2 Risk Evaluation and Mitigation Strategy (REMS)

BI submitted a Risk Evaluation and Mitigation Strategy (REMS) for Striverdi Respimat consisting of a communication plan regarding LABA safety (asthma related death). The communication plan includes a Dear Health Care Professional Letter, information posted on a website, and letters of notification to professional societies. This is consistent with other bronchodilators in the LABA class.

Because the information regarding LABA safety and asthma-related death has been widely distributed to physicians with demonstrated uptake of the information into clinical practice, no REMS is required for Striverdi Respimat. A Medication Guide, which is not part of the REMS, along with a boxed warning regarding asthma-related death will be required for this product.

Reference ID: 3253418

12 LABELING

Due to the Advisory Committee meeting late in the cycle, some issues that directly impact the clinical sections of labeling are pending at the time of this review. Therefore, the Division has adopted an alternative approach to labeling discussions. At the time of this review, labeling comments on the non-clinical sections have been sent to the sponsor. A labeling teleconference with the sponsor is pending. The sponsor has proposed a boxed warning for asthma-related death and other warnings and precautions that are consistent with approved LABA class labeling. A Medication Guide will also be included, consistent with LABA class labeling.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed proprietary name. DMEPA found the proposed proprietary name, Striverdi Respimat, acceptable for this product based on the product characteristics and safety profile. The sponsor withdrew the originally proposed name, (b) (4) BI has submitted revised labeling, including carton and container labeling, with the new name Striverdi Respimat.

13 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

13.1 Recommended regulatory action

The recommended regulatory action for this application is approval provided there is successful resolution of the outstanding microbiology issue and successful facilities inspection.

13.2 Risk benefit assessment

Replicate findings of statistically significant differences between olodaterol 5 mcg once-daily and placebo were shown in 3 of 4 trials in COPD patients for the primary efficacy endpoint of 24-hour post-dose trough FEV1 after 12 (Trial 1222.12) and 24 weeks (Trials 1222.13 and 1222.14) of treatment, and for various secondary measures of efficacy. The bronchodilator effect should be interpreted in the setting of background therapy. The sponsor conducted extensive dose ranging with olodaterol, including taking two doses forward into Phase 3. The sponsor proposes the lower of these two doses, 5 mcg once daily, for marketing, which is appropriate given that there is no apparent benefit of the higher 10 mcg dose over the 5 mcg dose. There were no major identified safety concerns with COPD patients. No asthma-related deaths or increase in asthma related adverse events were apparent in asthma dose-ranging trials. Based on the safety and efficacy data, the risk-benefit profile of olodaterol 5 mcg once daily for the treatment of bronchospasm associated with COPD appears favorable.

Reference ID: 3253418

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

Striverdi Respimat will carry standard class labeling for LABA agents. The review team does not recommend a REMS for LABA safety issues because physicians have already been made aware of these class issues. See Section 11.2.

13.4 Recommendation for other post-marketing requirements and commitments

There are no recommendations for further postmarketing requirements or commitments at the time of this review.

13.5 Recommended comments to applicant

As of the date of this review, there are no recommended comments to the applicant.

Reference ID: 3253418

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/s/

THERESA M MICHELE
01/31/2013