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*APPLICATION NUMBER:*

**206756Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	April 16, 2015
<b>From</b>	Anthony G. Durmowicz, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA # Supplement#</b>	NDA 206756
<b>Applicant</b>	Boehringer-Ingelheim
<b>Date of Submission</b>	May 22, 2014
<b>PDUFA Goal Date</b>	May 22, 2015
<b>Proprietary Name / Established (USAN) names</b>	Stiolto Respimat/tiotropium and olodaterol inhalation spray
<b>Dosage forms / Strength</b>	Inhalation Spray/2.5 mcg tiotropium, 2.5 mcg olodaterol/actuation (one dose is 2 actuations)
<b>Proposed Indication(s)</b>	...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
<b>Recommended:</b>	Approval

## 1. Introduction

On May 22, 2014, Boehringer Ingelheim (BI) submitted a 505(b)(2) New Drug Application (NDA 206-756) for tiotropium and olodaterol inhalation spray (Tio/Olo), proposed at a dose of 5 mcg/5 mcg for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The proposed tradename is Stiolto Respimat. Tio/Olo is a combination inhalation product comprised of an antimuscarinic agent and a long-acting beta-agonist (LABA). Tiotropium is currently marketed in 2 different presentations by BI to relieve airflow obstruction in patients with COPD, as the Spiriva HandiHaler, approved January 30, 2004 and as Spiriva Respimat, more recently approved on July 31, 2014. The olodaterol component was also recently approved as Striverdi Respimat to relieve airflow obstruction in patients with COPD on September 24, 2014. To support the 5 mcg/5 mcg once daily dose for the proposed indication, BI relied on the development programs for the individual component programs as well as a combination product clinical program that included two replicate 52-week safety and efficacy trials that assessed the single drug components at doses of 2.5 mcg and 5 mcg for tiotropium and 5 mcg for olodaterol in order to establish the contribution of the monocomponents to the combination and the combination at 2 doses, Tio 2.5 mcg/Olo 5 mcg, and Tio 5 mcg/Olo 5 mcg. This CDTL review summarizes the development program for Tio/Olo. Since both Tio and Olo have been approved as individual products using the Respimat inhalation spray dosing platform, the review will focus primarily on the data that support the benefit of the Tio/Olo combination over the individual components.

## 2. Background

Several drug classes are available for the treatment of COPD. These include beta-adrenergic agonists, combination products containing long-acting beta-adrenergic agonists and corticosteroids, anticholinergic agents, combination products containing anticholinergic and beta-adrenergic agonists, methylxanthines, and phosphodiesterase-4 (PDE4) inhibitors. LABAs currently marketed in the US for the treatment of COPD include salmeterol, formoterol, arformoterol, indacaterol, and vilanterol. Salmeterol and formoterol are marketed individually and in combination with inhaled corticosteroids (fluticasone propionate and mometasone furoate, respectively). Salmeterol, formoterol, and arformoterol are dosed twice daily and indacaterol is dosed once-daily.

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

Inhaled anticholinergics are widely used in the US and worldwide. In the US, a short-acting anticholinergic, ipratropium bromide, has been approved as a bronchodilator for patients with

COPD since 1986. Other longer acting antimuscarinics marketed in the US include tiotropium bromide (Spiriva Handihaler/Spiriva Respimat), aclidinium bromide (Tudorza Pressair), and umeclidinium bromide approved as a single entity (Incruse Ellipta) or in combination with the LABA vilanterol (Breo Ellipta). Common anticholinergic adverse effects include dry mouth, constipation, and urinary retention.

The issue of cardiovascular safety and stroke risk in COPD patients who receive inhaled antimuscarinics has been a topic of interest in recent years. Following is a discussion of the potential systemic safety signals that were identified for tiotropium after approval of Spiriva HandiHaler.

Initial safety concerns came to light in November 2007, when BI voluntarily submitted a document to the Agency that described a potential stroke safety signal with tiotropium observed from pooled safety data from 29 controlled clinical trials, 25 with Spiriva HandiHaler and 4 with Spiriva Respimat, which reflected 13,544 patients contributing 4572 person years of exposure to tiotropium. Based upon BI's analysis, there was a numerical increase in the risk ratio for stroke of 1.37 (95% CI: 0.73, 2.56) with use of tiotropium. It was in this context that BI submitted the original NDA for Spiriva Respimat in November 2007. Review of clinical data from the clinical program for this new Tio formulation showed that there was a numerical increase in deaths favoring placebo in the two 48-week clinical trials. In addition to the death imbalance noted in the clinical program for Spiriva Respimat, the above concerns regarding stroke and cardiovascular safety that had been raised for tiotropium resulted in a Complete Response that was issued on September 16, 2008.

In order to address the potential death and stroke risk with Tio, in November 2008, BI submitted the results of a 4-year, placebo-controlled, parallel group trial with Spiriva HandiHaler in approximately 6000 patients with moderate-severe COPD called "Understanding Potential Long-term Impacts on Function with Tiotropium" or UPLIFT. While primarily an efficacy study, UPLIFT also provided a substantial amount of controlled long-term safety data for Spiriva HandiHaler as it doubled the existing safety database. Overall, the results showed that Spiriva HandiHaler did not increase the risk of overall death, MI, or stroke compared to placebo. The data were presented at a Pulmonary Allergy Advisory Committee (PADAC) meeting on November 19, 2009, at which time the panel agreed that the death, MI, and stroke issue with the Spiriva HandiHaler had been addressed. During the PADAC meeting, the Agency also presented information on the death imbalance noted in the other Tio program (Spiriva Respimat). Since they were different drug products with potentially different pharmacodynamic effects, the committee recommended that additional safety data for Spiriva Respimat be collected. As a result BI conducted the large, prospective safety trial in 17,135 patients with COPD (Tiotropium Safety and Performance in Respimat trial; TIOSPIR) to compare Spiriva Respimat at doses of 2.5 mcg and 5 mcg with Spiriva HandiHaler at the approved dose of 18 mcg, which the Agency had concluded did not have an increased risk of stroke, MI, or death. The results showed that both doses of Spiriva Respimat were non-inferior (NI margin 1.25) to Spiriva HandiHaler for all-cause mortality. Since the results of the previous study for the HandiHaler (UPLIFT) had not shown a safety signal of death or stroke with Spiriva HandiHaler, and Spiriva Respimat was non-inferior to the HandiHaler for all-

cause mortality, it was concluded that the safety issue for the Spiriva Respimat had also been addressed. Spiriva Respimat was subsequently approved in the US on July 31, 2014.

### 3. Chemistry, Manufacture, and Controls

This application is recommended for approval from the CMC perspective providing that an acceptable recommendation is available from the Office of Compliance (OC). The status for all drug master files (DMFs) supporting this application is also adequate.

Stiolto® Respimat® (Tio/Olo) Inhalation Spray is a drug-device combination product consisting of a plastic/aluminum cartridge containing sterile aqueous formulation of tiotropium bromide and olodaterol hydrochloride, and a Respimat delivery device developed by BI (Figure 1).

The drug substance tiotropium bromide is approved for treatment of COPD as a dry powder inhaler, Spiriva HandiHaler, and in a liquid formulation as Spiriva Respimat Inhalation Spray. The drug substance olodaterol hydrochloride is approved for treatment of COPD in a liquid formulation as Striverdi Respimat Inhalation Spray. The Respimat device itself is currently cleared as an integral part of three inhalation products for treatment of COPD: Combivent Respimat (ipratropium bromide/albuterol) Inhalation Spray, Spiriva Respimat (tiotropium bromide) Inhalation Spray, and Striverdi Respimat (olodaterol) Inhalation Spray.

The proposed fix dose combination (FDC) was developed on the basis of the already existing mono products noted above, Spiriva Respimat and Striverdi Respimat with the formulation highly similar to that for Spiriva Respimat in that the proposed drug product formulation is an aqueous based, sterile solution contained in a sealed cartridge containing (b) (4) % of tiotropium, (b) (4) % of benzalkonium chloride, (b) (4) % of olodaterol, (b) (4) % of sodium edetate and hydrochloric acid (b) (4)

The Respimat inhaler produces an aerosol by mechanical means; there is no propellant. Prior to first use, the patient inserts the cartridge into the inhaler and a piercing of the sterile cartridge occurs during this time. After priming, each actuation delivers from the mouthpiece 2.5 mcg of tiotropium and 2.5 mcg of olodaterol in (b) (4) µL spray volume. The proposed dose is comprised of two actuations, i.e., 5.0 mcg of tiotropium and 5.0 mcg of olodaterol delivered in (b) (4) µL volume, with metered volume of (b) (4) µL. The Respimat device contains an actuation counter. The commercial device delivers 60 actuations (30 doses) after priming and it locks to prevent further use. Also, there is a physician sample version which delivers 28 actuations (14 doses) after priming. During development of the Tio/Olo combination inhalation spray, BI fully characterized dose performance in accordance with the Guidance for Industry on Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – Chemistry, Manufacturing and Controls Documentation (July 2002). Spray content uniformity for the combination products was evaluated in comparison to the monotherapy products as well particle size distribution by laser diffraction and by the andersen cascade impactor. These data support the in vitro comparability of the dose delivered for both tiotropium and olodaterol whether administered by the combination drug product or the corresponding monotherapy product.

Of note is that during development two strengths for Stiolto Respimat (Tio/Olo) Inhalation Spray (1.25 µg / 2.5 µg and 2.5 µg / 2.5 µg per actuation) were developed and used in Phase 3 clinical trials. BI has provided CMC documentation for both in the NDA, however only the 2.5 µg / 2.5 mcg product/actuation is proposed for marketing. The CMC data pertaining to the 1.25 mcg/2.5 mcg strength were reviewed and are considered adequate to support the comparability of the in vitro dose performance for the two strengths (including the in vitro dose proportionality) for the purpose of use in clinical program.

**Figure 1: Stiolto Respimat**



#### **4. Nonclinical Pharmacology/Toxicology**

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

## 5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology team's recommendation for the application is approval.

The general clinical pharmacology and biopharmaceutics considerations for tiotropium bromide were addressed in the tiotropium (Spiriva HandiHaler and Respimat) applications (NDAs 21395/21936) approved on January 30 1994 and July 31, 2014, respectively, and in the olodaterol (Striverdi Respimat) application (NDA 203108) approved on September 24, 2014.

The clinical pharmacology aspects of tiotropium and olodaterol as monotherapies, including nominal dose and the once daily dosing regimen have been adequately investigated and supported in the respective monotherapy development programs, and have been reviewed (see reviews for NDA 021936 for tiotropium by Dr. Yunzhao Ren and for NDA 203108 for olodaterol by Dr. Ping Ji).

For the current combination clinical pharmacology program included a Tio/Olo drug drug interaction study to ensure the systemic exposure of the drug components was bioequivalent. In the study, patients with COPD received either the fixed dose combination (FDC) (Tio 5 mcg/Olo 10 mcg, Olo 10 mcg (Reference 1) or Tio 5 mcg (Reference 2) once daily all via the Respimat device for 21 days. Steady-state exposure, AUC, and C<sub>max</sub> were assessed as the relevant clinical pharmacology variables. Results of the study demonstrated there was no significant drug drug interaction in that systemic exposure to Tio and Olo after inhalation of the FDC was not substantially different to the exposure after inhalation of Tio or Olo monotherapies (Test/Reference ratios of the PK parameters between the FDC and olodaterol monotherapy or tiotropium monotherapy were between 90–98%).

Regarding cardiovascular pharmacodynamic effects, thorough QT studies have been conducted for the Tio and Olo monocomponents. For Tio, the results did not show significant QT prolongation while for Olo, consistent with beta-2 agonists, dose-dependent individual subject corrected QT interval prolongation (QTcI) was observed with the maximum mean (one-sided 95% upper confidence bound) difference in QTcI from placebo after baseline correction being 2.5 (5.6) ms, 6.1 (9.2) ms, 7.5 (10.7) ms, and 8.5 (11.6) ms following doses of 10, 20, 30, and 50 mcg, respectively. To evaluate cardiovascular pharmacodynamics for the FDC, ECG assessments were performed post-dose on days 1, 85, 169, and 365 in approximately 5162 patients with COPD in 2 randomized, double-blind 52-week phase 3 clinical trials. In a pooled analysis the number of subjects with changes from baseline-corrected QT interval of >30 msec (using both the Bazett (QTcB) and Fredericia (QTcF), corrections) was not different for the Tio 5 mcg/Olo 5 mcg FDC group compared to Tio 5 mcg or Olo 5 mcg treatment groups.

## 6. Clinical Microbiology

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

## 7. Clinical/Statistical- Efficacy

BI conducted a clinical program to support the safety and efficacy for the Tio 5 mcg/Olo 5 mcg FDC program. The key clinical studies relevant to regulatory decision making are shown Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the section 8.

**Table 1 Clinical studies relevant to regulatory decision making**

Study No.	Description	Subjects	Design	Dose (qD)	Duration	Endpoints
1237.5 1237.6	P3 Safety and Efficacy	5162 (total) COPD pts ≥40 yrs	R, DB, AC, MC, PG	Tio/Olo 2.5/5 mcg Tio/Olo 5/5 mcg Tio 2.5 mcg Tio 5 mcg Olo 5 mcg	52 weeks	FEV1 AUC (0-3) Trough FEV1 SGRQ
1237.20*	24-hour spirometry	219 COPD pts ≥ 40 years	R, DB, PC, XO	Tio/Olo 2.5/5 mcg Tio/Olo 5/5 mcg Tio 2.5 mcg Tio 5 mcg Olo 5 mcg Placebo	6 weeks	FEV1 AUC (0-24)

(b) (4)

\*Trial 1237.20 was conducted to assess serial spirometry over the 24h dosing interval. As serial spirometry was also assess in the Phase 3 pivotal trials that are the basis for support for the efficacy and safety of the FDC, the results for Trial 1237.20 are somewhat redundant and will not be addressed further in this review.

### *Dose Selection*

Dose selection for the Tio/Olo Respimat was primarily based on trials for the individual components, tiotropium bromide and olodaterol approved at doses on 5 mcg once daily as Spiriva Respimat and Striverdi Respimat, respectively.

Dose selection was also supported by two randomized, double-blind, active-controlled, 4-week trials. For trial 1237.18 in 233 patients with COPD, 3 Tio doses (1.25, 2.5, and 5 mcg) were given in combination with Olo 5 mcg or 10 mcg and were evaluated compared to Olo 5 mcg monotherapy. Results demonstrated improvement in trough FEV1 for the combination when compared to olodaterol alone. The differences in trough FEV1 for the Tio/Olo doses of 1.25/5, 2.5/5, and 5/5 mcg once daily from Olo 5 mcg were 0.054 L (85% CI 0.016, 0.092), 0.065 L (0.027, 0.103), and 0.084 L (0.046, 0.122), respectively. In the second trial (1237.4) in 360 patients with COPD, 3 Olo doses (2 mcg, 5 mcg, and 10 mcg) were given in combination with Tio 5 mcg and were evaluated compared to Tio 5 mcg monotherapy. The difference in trough FEV1 for the Tio/Olo doses of 5/2, 5/5, and 5/10 mcg once daily from Tio 5 mcg were 0.024 L (85% CI -2.9, 0.076), 0.033 L (-0.019, 0.085), and 0.057 L (0.004, 0.11), respectively. Results of these trials supported the evaluation of once daily doses of Tio 2.5 mcg/Olo 5 mcg and Tio 5 mcg/Olo 5 mcg in the phase 3 trials.

### **Efficacy Study Design**

*Trials 1237.5 and 1237.6*

Trials 1237.5 and 1237.6 were identical randomized, double-blind, placebo controlled and parallel group design 52 week trials in patients with moderate-to-severe COPD that formed the basis for the establishment of efficacy for the Tio/Olo FDC product. The trials enrolled patients with a diagnosis of moderate to severe COPD, with the following pertinent entry criteria: a) 40 years of age and older; b) FEV1 < 80% predicted; and c) current or ex-smokers with a smoking history of > 10 years. Background therapy with short-acting beta-agonists, inhaled corticosteroids, oral corticosteroids, and methylxanthines were permitted in all treatment groups, however, LABA) and long-acting antimuscarinics were prohibited. Pertinent exclusion criteria included a recent history of myocardial infarction within one year, unstable or life-threatening cardiac arrhythmia, oxygen use > 1 hr/day, and use of oral steroids > 10 mg/day.

The co-primary endpoints for the trials were trough FEV1 response and FEV1 AUC<sub>0-3h</sub> response at week 24. Secondary endpoints for individual trials included FEV1 AUC<sub>0-3h</sub> response at days 1, 85 and 365, trough FEV1 response on days 15, 43, 85, 169, and 365, FVC AUC<sub>0-3h</sub> response at day 1, 85, 169, and 365, and trough FVC response at days 15, 43, 85, 170, and 365. Relevant secondary endpoints for pooled analyses included FEV1 AUC<sub>0-12h</sub> and <sub>0-24h</sub> response at 24 weeks, SGRQ total score, and COPD exacerbations. A COPD exacerbation was defined as “a complex of lower respiratory events/symptoms (increase of new onset) related to the underlying COPD, with a duration of three days or more, requiring a change in treatment” where a “complex of lower respiratory events/symptoms” meant at least two of the following: shortness of breath, increased sputum production, occurrence of purulent sputum, cough, wheezing, or chest tightness and where “a required change in treatment” included a prescription of antibiotics and/or systemic steroids and/or significant change for prescribed respiratory medication (bronchodilators including theophyllines)

Safety assessments generally included recording of adverse events, vital signs, physical examinations, clinical laboratory measures, and ECG.



## **Efficacy Results**

### *Trials 1237.5 and 1237.6*

#### *Bronchodilator Effect*

The co-primary efficacy assessments for both studies 1237.5 and 1237.6 were based on the analyses of FEV1 AUC<sub>0-3h</sub> response and trough FEV1 response assessed after 24 weeks of treatment. According to the pre-specified hierarchical testing sequence, the primary endpoint comparisons for Tio 5 mcg/Olo 5 mcg were tested first across endpoints and the comparisons for Tio 2.5 mcg/Olo 5 mcg were tested thereafter. Table 2 below shows the nominal effects of each treatment in each study while Table 3 contains the statistical comparison between the Tio/Olo/ FDC and their respective individual components. In all hypothesis tests, the Tio/Olo FDCs were superior to the respective individual components for both primary endpoints in both trials.

**Table 2. Mean trough FEV1 and FEV1 AUC<sub>0-3h</sub> response at week 24.**

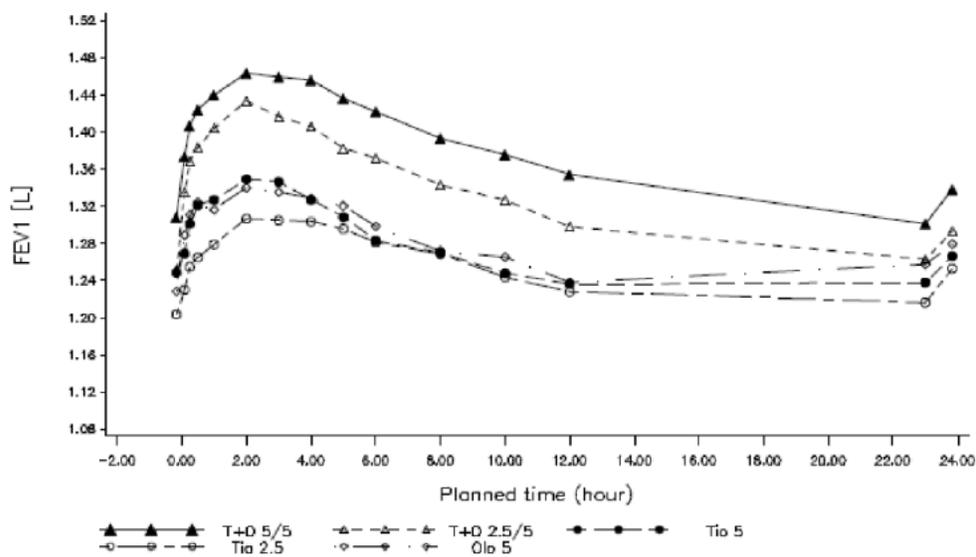
Treatment	Trial 1237.5		Trial 1237.6	
	Trough FEV1	FEV1 AUC (0-3)	Trough FEV1	FEV1 AUC (0-3)
Olo 5	0.054	0.133	0.057	0.136
Tio 2.5	0.083	0.148	0.062	0.125
Tio 5	0.065	0.139	0.096	0.165
Tio+Olo 2.5/5	0.111	0.241	0.125	0.256
Tio+Olo 5/5	0.136	0.256	0.145	0.268

**Table 3. Treatment comparisons for FEV1 AUC<sub>0-3h</sub> and trough FEV1 response after 24 weeks.**

Treatment	Trial 1237.5		Trial 1237.6	
	Trough FEV1 (95% CI)	FEV1 AUC (0-3) (95% CI)	Trough FEV1 (95% CI)	FEV1 AUC (0-3) (95% CI)
Tio+Olo 2.5/5				
Δ from Olo 5 (L)	0.058 (0.034, 0.081)	0.109 (0.086, 0.132)	0.067 (0.042, 0.092)	0.121 (0.096, 0.145)
Δ from Tio 2.5 (L)	0.029 (0.005, 0.052)	0.093 (0.070, 0.116)	0.062 (0.037, 0.087)	0.131 (0.106, 0.155)
Tio+Olo 5/5				
Δ from Olo 5 (L)	0.082 (0.059, 0.106)	0.123 (0.100, 0.146)	0.088 (0.063, 0.113)	0.132 (0.108, 0.157)
Δ from Tio 5 (L)	0.071 (0.047, 0.094)	0.117 (0.094, 0.140)	0.050 (0.024, 0.075)	0.103 (0.078, 0.127)

To provide further characterization of the bronchodilatory profile of the Tio/Olo FDC serial spirometry was conducted in a subgroup of patients in both Trials 1237.5 and 1237.6 5 on study day 169. Although assessments were taken at only 2 time points over the second half of the dosing interval, both FDCs demonstrated increased bronchodilator efficacy compared with the monotherapies (Figure 2).

**Figure 2. Serial adjusted mean FEV1 over 24 hours after 24 weeks (Trials 1237.5 and 1237.6 combined)**



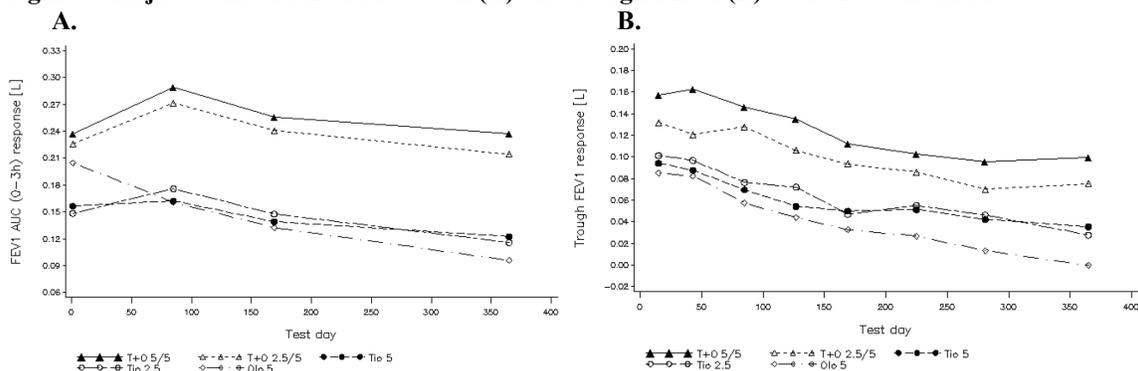
### Secondary Endpoints

BI analyzed many secondary endpoints for Trials 1237.5 and 1237.6, both individually and pooled, the analyses of which were not corrected for multiplicity. Below are results for selected relevant endpoints.

#### Comparison of Tio/Olo 5/5 mcg and 2.5/5 mcg combinations

Adjusted mean FEV1 AUC<sub>0-3h</sub> and trough FEV1 responses over the 52 week treatment periods of trials 1237.5 and 1237.6 were evaluated as a secondary endpoint to assess for differences in response between the 2 Tio/Olo FDC doses, Tio 5 mcg/Olo 5 mcg and Tio 2.5 mcg/Olo 5 mcg as well as to observe for any changes in effect over a 52 week period. As can be seen visually, the Tio 5 mcg/Olo 5 mcg FDC consistently demonstrates improved FEV1 AUC<sub>0-3h</sub> and trough FEV1 responses compared to the Tio 2.5 mcg/Olo 5 mcg FDC. The difference when measured at 24 weeks was statistically significant in Trial 1237.5. The results are similar for Trial 1237.6.

**Figure 3. Adjusted mean FEV1 AUC<sub>0-3h</sub> (A) and trough FEV1 (B) over 52 weeks-Trial 5**



#### FEV1 AUC<sub>0-12h</sub> and FEV1 AUC<sub>0-24h</sub> responses at week 24

The adjusted mean responses and comparisons of each FDC to monotherapies for FEV1 AUC<sub>0-12h</sub> and FEV1 AUC<sub>0-24h</sub> responses at 24 weeks were evaluated in the subset of patients who had serial spirometry assessments. As would be expected based on the results of the co-primary endpoints, the differences between the Tio/Olo FDCs and the respective individual components for both measurements were all statistically significant.

#### St. Georges Respiratory Questionnaire (SGRQ)

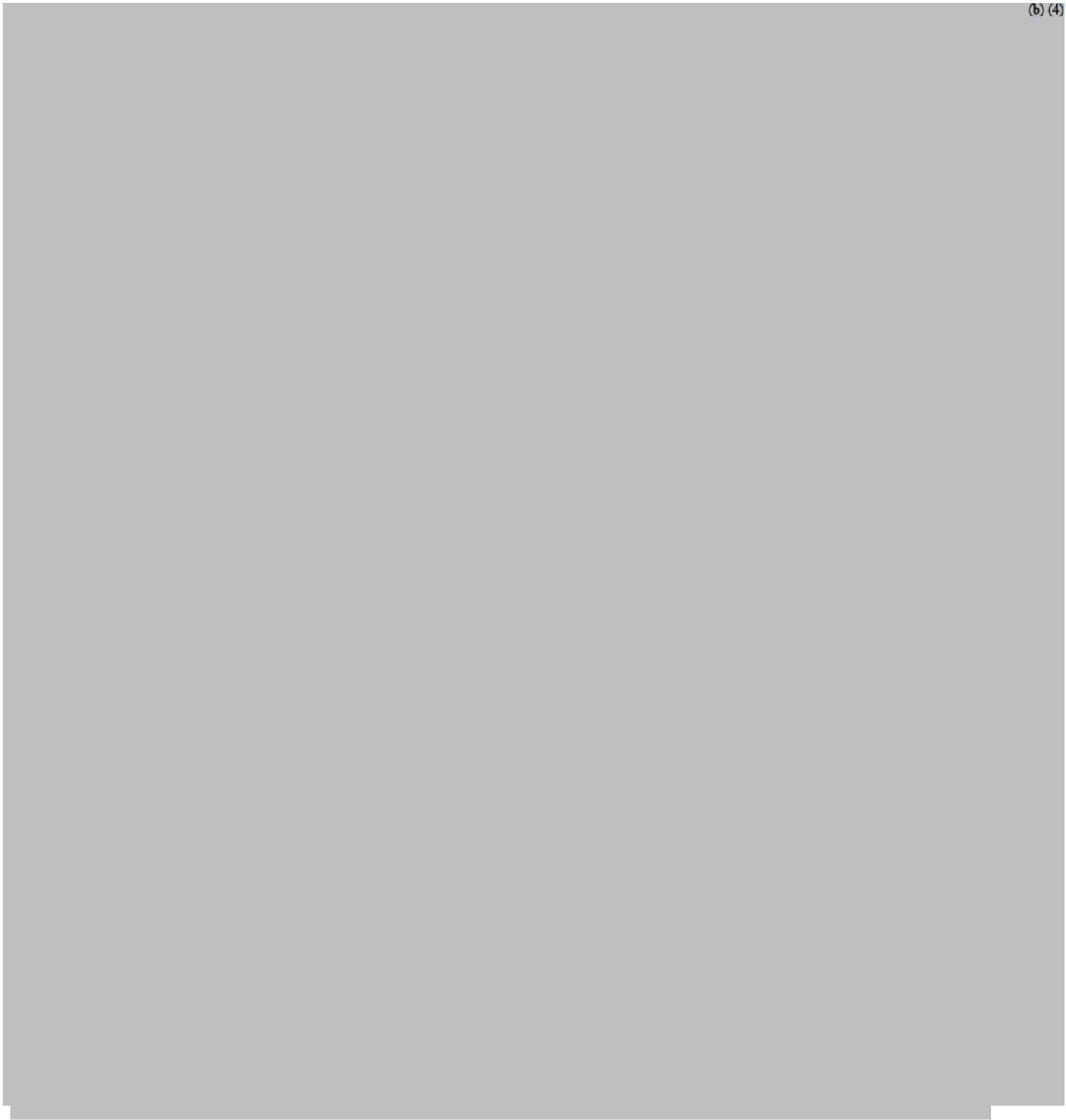
The protocols for Trials 1237.5 and 1237.6 also included an additional primary endpoint to address their EMA submission of SGRQ total score at day 169 using data pooled from both trials. When comparing the FDC to its monocomponents, neither FDC dose demonstrated a difference greater than the MCID (-4), although for the Tio 5 mcg/Olo 5 mcg, the difference when compared to Tio 5 mcg and Olo 5 mcg was statistically significant (-1.2 points (p=0.0252) and -1.7 points, p=0.0022), respectively).

#### COPD exacerbations

Exacerbation related endpoints were analyzed for the pooled Trial 1237.5 and 1237.6 data set. These endpoints included time to first exacerbation, time to first moderate to severe

exacerbation, number of exacerbations/patient year, and number of moderate to severe exacerbations. For these exacerbation endpoints, there were no statistical differences when comparing the FDC to their monocomponents, except when comparing T+O 2.5/5 to Tio 2.5. These data do not support an additional benefit of the proposed dose of Tio 5 mcg/Olo 5 mcg FDC over the monocomponents in terms of exacerbations.

Morning and even peak flows and rescue medication use were also included as additional endpoints. In general, morning and evening peak flows averaged weekly were higher in the FDC groups and rescue medication use lower in the FDC groups compared to their monocomponents.



## 8. Safety

As the general safety and cardiovascular safety of tiotropium at doses relevant for this program have been assessed extensively in the 2 tiotropium (Spiriva HandiHaler and Spiriva Respimat) clinical programs that included 2 large safety studies, UPLIFT and TIOSPIR, referred to above, the focus of the safety determination for the Tio 5 mcg/Olo 5 mcg proposed Respimat FDC will be on whether there appears to be any new or increased safety signals for the FDC over the Tio and Olo monocomponents.

The overall the size of the database, with added safety data from the clinical programs conducted for the monocomponent Tio and Olo products was adequate to assess the relative safety of the Tio/Olo FDC. The safety determination for Tio 5 mcg/Olo 5 mcg comes primarily from the 52-week COPD trials. The 52-week trials included a total of 5162 patients. Of these, 1029 received the proposed dose of Tio 5 mcg/Olo 5 mcg. There was no placebo comparison, as the relative safety of both Tio 5 mcg and Olo 5 mcg have previously been established (see NDA 203108 and 021936) and medical practice dictates that relatively severe COPD patients should receive appropriate COPD treatment within the structure of a clinical trial.

Mean exposure across all treatment groups was similar and ranged from 326-344 days.

In the 52-week COPD trials there were a total of 75 deaths during the on-treatment period. The system organ class most commonly associated with deaths were respiratory, thoracic, and mediastinal (0.4%); cardiac disorders (0.4%), and neoplasms benign, malignant, and unspecified (0.3%). The most common causes of death were COPD (0.2%), cardiac arrest (0.1%), and death (0.1%). The causes of death were similar between treatment groups with no dose responses or concerning imbalances.

All deaths were also reviewed by a mortality adjudication committee (MAC). Overall, the MAC analysis was consistent with primary analysis of death in that no clinically significant imbalances were identified when comparing treatment groups.

Fifteen and one half per cent of patients (798) reported SAEs in the 52 week trials, 1237.5 and 1237.6. SAEs were most commonly reported in the respiratory, thoracic, and mediastinal SOC (6.7%); followed by the infections and infestations SOC (2.8%) and were balanced across treatment groups. The most common SAEs by preferred term were by far COPD (5.7%) and pneumonia (1.3%).

In the 52-week trials, of the 5162 patients who were treated with study drug, 419 discontinued due to on-treatment adverse events. The most common reason for discontinuation was worsening of COPD; this was more common in the monotherapy arms supporting the benefit of the FDC over the monocomponents.

Due to historical safety concern regarding cardiovascular AEs associated with antimuscarinics and LABAs, these events were of special interest. There were no consistent differences between treatment groups for cardiovascular-related AEs including those termed as ischemic heart disease, cerebrovascular disorders, arrhythmia, and, cardiac failure, myocardial infarction, hemorrhagic or ischemic cerebrovascular conditions.

### ***Summary of Safety***

The safety data support the use of the proposed Tio 5 mcg/Olo 5 mcg FDC inhalation spray for relief of airflow obstruction in patients with COPD. The number and causes of deaths and non-fatal serious adverse events were similar between FDC and the Tio and Olo monocomponent treatment groups. The adjudicated analysis of SAEs performed to determine if hospitalizations, intubations, and deaths were related to specific respiratory, cardiovascular, cerebrovascular causes did not demonstrate clinically significant differences between treatment groups or when comparing either FDC dose to its monoproduct. A MACE analysis also did not demonstrated any imbalances.

## **9. Advisory Committee Meeting**

Since both individual drugs are marketed as approved drug products for maintenance treatments for patients with COPD and the clinical program for the tiotropium/olodaterol combination product did not raise any concerns regarding efficacy or safety, a PADAC meeting was not necessary for this application.

## **10. Pediatrics**

BI is requesting an indication for treatment of patients with COPD only. Since COPD is a disease that occurs only in adults, specific pediatric studies would not be required that relate to this action specific to COPD. PeRC had previously agreed that for such COPD applications a full waiver should be granted because studies the disease does not exist in pediatric patients.

## **11. Other Relevant Regulatory Issues**

- **Financial Disclosure:** The applicant submitted acceptable financial disclosure statements certifying that no debarred individuals were used in the conduct of the trials included in this NDA. For trials 1237.5 and 1237.6, there were a total of 5 investigators with significant payments of other sorts. Given that both trials were large randomized, double-blinded, controlled trials and each investigator was only responsible for enrolling a small number of patients, it was determined to that this financial disclosure information did not significantly affect the conduct of the trials.
- **DSI audits** were not conducted as both monocomponents are already approved products and the data were consistent with what is expected of for bronchodilator products for COPD. No ethical issues were present. All trials were conducted in accordance with accepted ethical standards.

## 12. Labeling

- Proprietary Name: The name Stiolto Respimat was judged acceptable
- Physician Labeling: The label was reviewed by various disciplines within DPARP, the Office of Medical Policy Programs (OMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were made to reflect the data accurately and better communicate the findings to healthcare providers. The labeling language in the Warnings and Precautions and Clinical Trials sections were edited to include the information relevant for an antimuscarinic/beta-agonist combination for COPD. Final labeling discussions are ongoing at the time of finalization of this review.
- Carton and Immediate Container Label: These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for this NDA is for approval of Stiolto Respimat (tiotropium/olodaterol inhalation spray) at a dose of 5 mcg/5 mcg 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.

- Risk Benefit Assessment

The overall risk-benefit assessment supports approval of Stiolto Respimat (tiotropium/olodaterol inhalation spray) at a dose of 5 mcg/5 mcg once daily for the long-term, once-daily maintenance treatment of airflow obstruction in patients with COPD. The submitted safety data are consistent with that seen for similar products and do not show any unique safety signals for an antimuscarinic/beta agonist combination product for COPD. From an efficacy standpoint, the clinical program demonstrated that the 5 mcg/5 mcg once daily dose provided a statistically significant bronchodilator effect and the additive effect of the individual drug components to the bronchodilatory effect of the combination.

### 1. Recommendation for Post-marketing Risk Management Activities

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

### 2. Recommendation for other Post-marketing Study Commitments

None

### 3. Recommended Comments to Applicant

No additional comments are recommended to be conveyed.

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/s/  
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ANTHONY G DURMOWICZ  
04/16/2015