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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name	Tiotropium/Olodaterol Inhalation Spray
(Proposed) Trade Name	
Therapeutic Class	LABA/anticholinergic
Applicant	Boehringer-Ingelheim
Formulation(s)	Inhalation Spray
Dosing Regimen	5mcg/5mcg
Indication(s)	The long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema
Intended Population(s)	Adult COPD population

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action, from a clinical prospective, is Approval of the fixed dose combination (FDC) of tiotropium and olodaterol inhalation spray (T+O) at a dose of 5/5mcg 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 demonstration of replicate evidence of efficacy as a bronchodilator, along with an acceptable safety profile, warrants the recommendation of Approval.

1.2 Risk Benefit Assessment

The proposed indication for T+O 5/5mcg once daily is the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

The core phase 3 COPD development program consisted of two replicate 52-week safety and efficacy trials (1237.5 and 1237.6), (b) (4)
 and one 6-week treatment period crossover 24-hour spirometry trial (1237.20).

The two replicate 52-week COPD trials were used as primary support of efficacy. These trials included 5-treatment arms which were as follows: olodaterol (Olo) 5mcg, tiotropium (Tio) 2.5mcg, Tio 5mcg, T+O 2.5/5mcg, and T+O 5/5mcg. There were no placebo arms in these trials as there was sufficient evidence to support the efficacy of both Olo 5mcg and Tio 5mcg compared to placebo (see NDA 203108 and 021936). As such, demonstration of efficacy of the T+O FDC over their constituent monoproducts was sufficient to support efficacy. The primary endpoints of these trials were trough forced expiratory volume in 1 second (FEV1) and FEV1 AUC (0-3hours) response at week 24. For both primary endpoints, both FDC doses demonstrated statistically significant improvements compared to both the constituent monotherapy products, demonstrating that both the Tio and Olo components of the FDC contributed to the treatment effect. The treatment effect was also numerically larger when comparing T+O 5/5 to the 2.5/5mcg dose. Efficacy was further supported by the secondary spirometric endpoints in these trials, which included trough FEV1 response and FEV1 AUC (0-3 hours) throughout the treatment period. Throughout the treatment period, for both parameters, the FDC doses demonstrated a larger treatment effect compared to both constituent monotherapy products. Moreover, there was also consistent numerical separation between the two 5/5mcg and 2.5/5mcg FDC doses. These trials also

measure serial spirometry for 24-hours post dosing at week 24. The results demonstrated that at all time points, both FDC doses had a larger treatment effect compared to their constituent monotherapy products. Additionally, there was clear dose separation over the 24-hour interval when comparing T+O 2.5/5 to 5/5mcg. The results from the 24-hour spirometry trial (1237.20) were also generally consistent with the serial spirometry data from the 52-week trials in that both doses of the FDC demonstrated a larger treatment effect compared to their constituent monotherapy products. However, in contrast, there was no clear dose separation between the two FDC doses.



Based on the available data, both doses of the T+O FDC appear to have a significant effect on bronchodilation compared to their constituent monotherapy products. The 5/5mcg dose also appears to have a numerical benefit above the 2.5/5mcg dose, which supports selection of the T+O 5/5mcg dose. Overall, these data support efficacy of T+O 5/5mcg. (b) (4)

The safety information for T+O comes primarily from the 52-week COPD trials. The 52-week trials included a total of 5162 patients. Of these, 1029 received T+O 5/5mcg and 1030 received T+O 2.5/5mcg. While there was no placebo comparison, as the safety of both Tio 5mcg and Olo 5mcg have previously been established (see NDA 203108 and 021936), comparisons of the FDC to their constituent monoproduct was sufficient to evaluate safety. The percentages of patients who died were fairly similar across treatment groups and when comparing both FDC doses to their respective monoproducts. The observed causes of death were consistent with the trial population. The most common cause of death was COPD. This was true for the adjudicated and non-adjudicated analysis of death. Non-fatal serious adverse events (SAE) were also generally similar between treatment groups. The types of SAEs were fairly typical for the study population. An adjudicated analysis of SAEs was also performed to determine if hospitalizations, intubations, and deaths were respiratory-, cardiovascular-,

cerebrovascular-, or other- related. Overall, this analysis did not demonstrate any large differences between treatment groups or when comparing either FDC dose to its monoprodukt. An analysis of major cardiac events (MACE) was also conducted. This analysis demonstrated no imbalances. The sponsor's MACE analysis was also complemented by a cardiovascular assessment based on grouped terms [Standard MedDRA Queries (SMQs) and Applicant defined groupings]. The percentage of patients with events were generally similar across treatment groups and when comparing the FDC doses to their constituent monotherapy products.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

The proposed product is a fixed-dose long-acting anticholinergic and long-acting beta agonist (LABA) combination inhalation spray delivered via the Respimat device. The fixed dose combination (FDC) contains tiotropium bromide as the anticholinergic and olodaterol hydrochloride as the LABA and is packaged in an aluminum cartridge. The cartridge is packaged with the Respimat device and delivers either 28 or 60 actuations [2.5/2.5mcg (tiotropium/olodaterol) per actuation]. The proposed dose for COPD is 5/5mcg (2 actuations) once daily. Figure 1 depicts the Respimat device.

Figure 1. Respimat device with cartridge inserted (right) and cartridge alone (left).



Source: Quality Overall Summary; figure 1; pg7

To use the tiotropium plus olodaterol (T+O) FDC product, the patient initially removes the transparent base on the Respimat device and inserts the cartridge containing the formulation. The clear base is replaced and the patient turns the base until a 'click' is heard, then primes the device by spraying until a mist is observed and then another 3 times into the air. To administer a dose, the cap is then opened and the patient seals his lips around the mouthpiece. During inhalation, the patient presses the trigger button while continuing to inhale.

The Respimat device and cartridge are approved in the United States for use with the Combivent Respimat (albuterol/ipratropium) (NDA 21-747; approved October 7, 2011), Striverdi Respimat (olodaterol) (NDA 203,108; approved July 31, 2014), and Spiriva Respimat (tiotropium)(NDA 21,936; approved September 24, 2014).

2.2 Tables of Currently Available Treatments for Proposed Indications

There are several classes of drug currently used to treat patients with COPD (Table 1). These include bronchodilator products (short and long acting beta-2 adrenergic agonists); anticholinergic agents such as ipratropium, tiotropium, acclidinium and umeclidinium; and combinations of inhaled corticosteroids and anticholinergics and long-acting beta-2 agonists and anticholinergics. Some anticholinergics, combinations of inhaled corticosteroids and beta-2 agonists, and PDE-4 inhibitors are approved for reducing exacerbations of COPD.

Table 1. Approved treatments for COPD

Class		Generic Name	Brand Name
Beta ₂ -adrenergic agonists	Short-acting (SABA)*	Albuterol sulfate	Accuneb, ProAir HFA, Proventil HFA, Ventolin HFA
		Levalbuterol tartrate	Xopenex HFA
		Pirbuterol	Maxair autoinhaler
		Terbutaline sulfate	
	Long-acting (LABA)	Salmeterol	Serevent Diskus
		Formoterol	Foradil Aerolizer
		Arformoterol	Brovana
		Formoterol Solution	Perforomist
		Indacaterol maleate	Arcapta Neohaler
Anti-cholinergics	Short-acting	Ipratropium bromide	Atrovent HFA
	Long-acting	Tiotropium bromide	Spiriva Handihaler, Spiriva Respimat
		Acidinium bromide	Tudorza Pressair
		Umeclidium bromide	Incruse Ellipta
Combination	SABA/anti-cholinergic	Albuterol/Ipratropium Albuterol/Ipratropium	Combivent Combivent Respimat
	Corticosteroid/LABA	Fluticasone/Salmeterol	Advair Diskus
Budesonide/Formoterol		Symbicort	
Fluticasone/Vilanterol		Breo Ellipta	
	LABA/anticholinergic	Vilanterol/umeclidinium	Anoro Ellipta
Xanthines		Theophylline	Multiple
Phosphodiesterase Inhibitors	PDE4 Inhibitor	Roflumilast	Daliresp

*not specifically approved for COPD

2.3 Availability of Proposed Active Ingredient in the United States

Both monocomponents of the T+O are available in the United States. Tiotropium is available in a dry powder inhaler and as an inhalation spray in the Respimat device.. Olodaterol is available as an inhalation spray in the Respimat device under the tradename Striverdi Respimat. All three products are indicated for COPD. However, only the Spiriva Handihaler and Spiriva Respimat products carry an indication for exacerbation reduction.

2.4 Important Safety Issues With Consideration to Related Drugs

Anticholinergic safety concerns:

Class effects of anticholinergic agents include worsening of narrow angle glaucoma and worsening of urinary retention.

The Agency has also historically been concerned with the cardiovascular safety of anticholinergic agents. The concerns have been discussed extensively both in the

medical literature and in open public forums^{1,2,3}. Additionally, a pooled analysis of 29 studies conducted by the Applicant in 2007 suggested an increased risk of stroke with tiotropium bromide.⁴ As a result of these concerns, the Agency released Early Communications on March 18, 2008 and October 7, 2008 about the ongoing safety review of tiotropium marketed as Spiriva Handihaler (SHH). Following the Early Communication, BI submitted data from a 6,000 patient, 4-year study with the SHH [Understanding Potential Long-term Impacts on Function with Tiotropium trial (UPLIFT⁵, trial 205.235)] which was analyzed by the Agency and discussed at a Pulmonary Allergy Drug Advisory Committee (PADAC) in November of 2009. As a result, in January 2010 the Agency provided a Follow-Up⁶ to the previous Early Communications regarding the safety of tiotropium marketed as the SHH. In this update, the Agency communicated its conclusion that the available data, including results from UPLIFT do not support an association between the use of SHH (tiotropium) and an increased risk for stroke, heart attack, or death from a cardiovascular cause. A summary of the Agency's conclusions regarding the safety of tiotropium may also be found in the medical literature⁷.

There have also been safety concerns specific to tiotropium inhalation spray via the Respimat device (tiotropium Respimat), one of the monotherapy components for the proposed T+O FDC. In the initial NDA review cycle, tiotropium Respimat was given a Complete Response (CR) due to mortality differences observed in both 48-week exacerbation trials. To address this safety concern, BI ultimately performed a trial titled Tiotropium Safety and Performance in Respimat (TIOSPIR), which was a multicenter, multinational, randomized, double-blind, double dummy parallel group trial whose primary endpoint was all-cause mortality for tiotropium Respimat vs. SHH. All patients were followed until the end of the trial for vital status, regardless of whether trial medication was discontinued. The total patient year exposure to tiotropium Respimat 5mcg was 11,343 years. The hazard ratio for all-cause mortality of tiotropium Respimat 5mcg to SHH was 0.957. The 95% confidence interval was (0.837, 1.094), which beat the pre-specified non-inferiority margin of 1.25. As such, non-inferiority of tiotropium Respimat 5mcg to SHH was clearly demonstrated in terms of all-cause mortality. These results were discussed at a PADAC (August 14, 2014). The majority of the PADAC concluded that the TIOSPIR trial adequately address the safety concerns raised in the 48-week exacerbation trials (vote: yes=9, no=4) and that tiotropium Respimat should be

1 November 2009 FDA Pulmonary-Allergy Drugs Advisory Committee Meeting.

2 Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2008; 300:1439-50.

3 Lee TA, Pickard S, Au DH et al. Risk of Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease. *Annals of Internal Medicine* 2008;149:380-390.

4 FDA Early Communication about an Ongoing Safety Review of Tiotropium.
[Http://www.fda.gov/cder/drug/early_comm/tiotropium.htm](http://www.fda.gov/cder/drug/early_comm/tiotropium.htm)

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

6 Follow-Up to the October 2008 Updated Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler), January 14, 2010. Available at:
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm197429.htm>

7 Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium – the FDA's conclusions. *NEJM* 2010;363(12):1097-9.

approved (vote: yes=10, no=3). Based on PADAC discussion and FDA review, it was determined that tiotropium Respimat was safe and effective in COPD at a dose of 5mcg once daily.

LABA safety concerns:

Class effects of LABAs include hypokalemia, hyperglycemia, and cardiovascular effects (i.e., increases in pulse rate, blood pressure, ECG changes of unclear clinical significance, and symptoms).

Drugs belonging to the LABA pharmacologic class are inhaled medications used in both the treatment of asthma and of COPD. LABAs are associated with an increased risk of severe exacerbation of asthma symptoms, leading to hospitalizations, as well as death in some patients using LABAs for the treatment of asthma.⁸ FDA announced in February 2010⁹ that they would require manufacturers to revise their drug labels to include updated guidelines for the use of LABA in asthma, and in April 2011¹⁰ announced that they would require manufacturers of LABAs to conduct five randomized, double-blind, controlled clinical trials comparing the addition of LABAs to inhaled corticosteroids versus inhaled corticosteroids alone. These risks identified for LABAs are believed to be restricted to the asthma population and have not been observed in COPD.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The monotherapy components of the propose FDC were approved on July 31, 2014 and September 24, 2014, for olodaterol Respimat 5mcg (NDA 201,388) and tiotropium Respimat 5mcg (NDA 021,936), respectively.

Prior to submission of this NDA, this product was developed under IND 76,397. Relevant regulatory interactions are summarized below:

End-of-Phase 2 meeting (August 4, 2011). The major discussion points were as follows:

- Agreement on primary endpoints for pivotal trials (trials 1237.5 and 1237.6)

⁸FDA Drug Safety Communication: Drug labels now contain updated recommendations on the appropriate use of long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs), June 2, 2010. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm>; accessed August 3, 2013.

⁹FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs), February 18, 2010. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm>; accessed August 3, 2013.

¹⁰FDA Drug Safety Communication: FDA requires post-market safety trials for Long-Acting Beta-Agonists, April 15, 2011. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm251512.htm>; accessed August 3, 2013.

- Agreement that no placebo comparator was required provided that the monotherapies were approvable or approved
- Agreement that a QT study was not needed for the FDC
- Recommendation that the pivotal trials include 24-hour spirometry in a subset of patients.

2.6 Other Relevant Background Information

none

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was appropriately indexed and complete to permit review. DSI audits were not requested.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in each clinical study report.

3.3 Financial Disclosures

See appendix 9.4 Financial Disclosure Review Template

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The recommendation from the CMC review team is for Approval, pending inspection. The proposed drug product is a fixed dose combination of olodaterol hydrochloride and tiotropium bromide for inhalation. An aqueous solution of olodaterol hydrochloride and tiotropium bromide is delivered via the Respimat device. The aqueous solution contains (b) (4) of tiotropium bromide and (b) (4) of olodaterol hydrochloride and is packaged in a plastic container within an aluminum cartridge. This cartridge is packaged with the Respimat device, which delivers 60 actuations (2.5mcg of tiotropium and olodaterol per actuation) after priming. The proposed dose for COPD is 5mcg both

for tiotropium and olodaterol (2 actuations) once daily. Details of the CMC review can be found in Dr. Eugenia Nashed's review.

4.2 Clinical Microbiology

The preliminary recommendation from the microbiology review team is Approval. Details of the Clinical Microbiology review can be found in Dr. Jessica Cole's review.

4.3 Preclinical Pharmacology/Toxicology

The recommendation from the pre-clinical review is Approval. Details of the Pharmacology/Toxicology review can be found in Dr. Andrew Goodwin's review.

Both approved monoproduct development programs included comprehensive pre-clinical development programs. In the T+O submission, the Applicant also performed additionally pre-clinical studies using the combination and no new safety concerns were revealed.

4.4 Clinical Pharmacology

The recommendation from the Clinical Pharmacology team is Approval. Details of the Clinical Pharmacology review can be found in Dr. Ritesh Jain's review.

4.4.1 Mechanism of Action

Tiotropium is a long-acting muscarinic antagonist (anticholinergic). In the airways, it exhibits pharmacological effects through inhibition of M3-receptors at the smooth muscle leading to bronchodilation.

Olodaterol is a long-acting beta agonist, and acts by binding and activating beta-2-adrenergic receptors in the lungs, predominantly in bronchial smooth muscle, to promote bronchodilation.

4.4.2 Pharmacodynamics

Traditionally, approval for an inhaled FDC for COPD follows approval of the constituent monocomponents and the dosing for the FDC is taken from the monocomponent programs. In the case of T+O, at the time the NDA was submitted, neither tiotropium Respimat nor olodaterol Respimat were approved but were under review. However, shortly after NDA submission, both monocomponents were approved at a dose of 5mcg once daily. The dose-ranging programs for the monoproducts were comprehensive and fully supportive of the doses carried to the pivotal phase 3 trials, where the 5mcg once daily dose for both tiotropium and olodaterol were confirmed to be optimal. The dose-ranging trials for the monoproducts will not be reviewed here as they were previously

reviewed under NDAs 021,936 and 203,108 for tiotropium Respimat and olodaterol Respimat, respectively. Because there was no approved dose for the monocomponents when the T+O development program was initiated, the Applicant also included dose-ranging trials for the FDC. These trials were consistent with the results from the monocomponent development programs and support the two FDC doses carried into the phase 3 trials (T+O 2.5/5mcg and 5/5mcg qD). The dose ranging trials for the FDC are summarized in Table 2

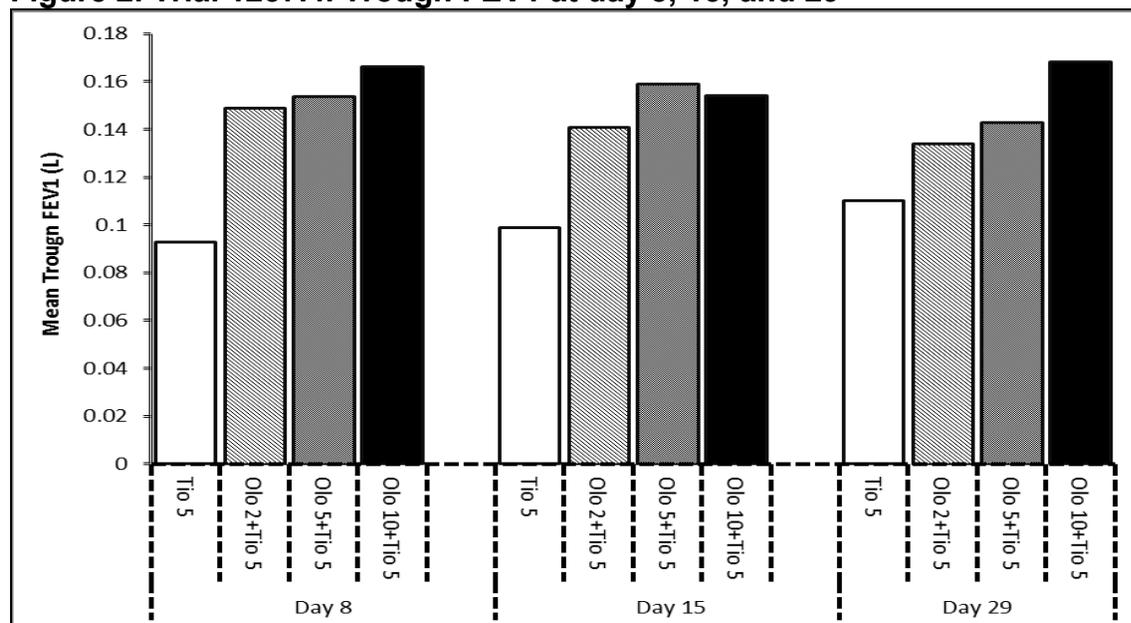
Table 2. Phase dose-ranging trials for combination product

Study	Objective	Design	Population	Treatment arms	Primary endpoint
1237.4	Dose-ranging	R, DB, PG 4-week	COPD ≥40 years	Tio+Olo 5/2mcg Tio+Olo 5/5 mcg Tio+Olo 5/10 mcg Tio 5 mcg 5mcg	Trough FEV1@4wk
1237.9	Dose-ranging	R, DB, XO 4-week	COPD ≥40 years	Tio+Olo 5/2mcg Tio+Olo 5/5 mcg	Trough FEV1@4wk
1237.18	Dose-ranging	R, DB, XO 4-week	COPD ≥40 years	Tio+Olo 1.25/5mcg Tio+Olo 2.5/5 mcg Tio+Olo 5/5 mcg Tio+Olo 1.25/10mcg Tio+Olo 2.5/10 mcg Tio+Olo 5/10 mcg Olo 5mcg Olo 10mcg	Trough FEV1@4wk

Trial 1237.4

Trial 1237.4 was a 4-week randomized, double-blind, parallel group trial in COPD patients evaluating the olodaterol dose in the T+O FDC. In this trial, the olodaterol doses ranged from 2-5mcg once daily with the tiotropium dose held constant at 5mcg once daily. This trial also included a tiotropium 5mcg only treatment arm as the active comparator. The trough FEV1 results of this trial are summarized in Figure 2.

Figure 2. Trial 1237.4. Trough FEV1 at day 8, 15, and 29



Source: Adapted from Clinical Pharmacology Review Figure 1.

In two of the three assessed time points (day 8 and 29), as the olodaterol dose increased, there appeared to be small incremental increases in trough FEV1 above tiotropium 5mcg alone. At week 2 (day 15), there was no incremental benefit of the 10mcg olodaterol dose over the 5mcg dose. These data, taken with the data from the olodaterol monoproduct development program, are supportive of the phase 3 olodaterol dose (5mcg) used in the FDC program.

Adverse events were less frequent in the T+O 5/5mcg treatment group (29%) compared to the other treatment groups (33-34%).

Trial 1237.9

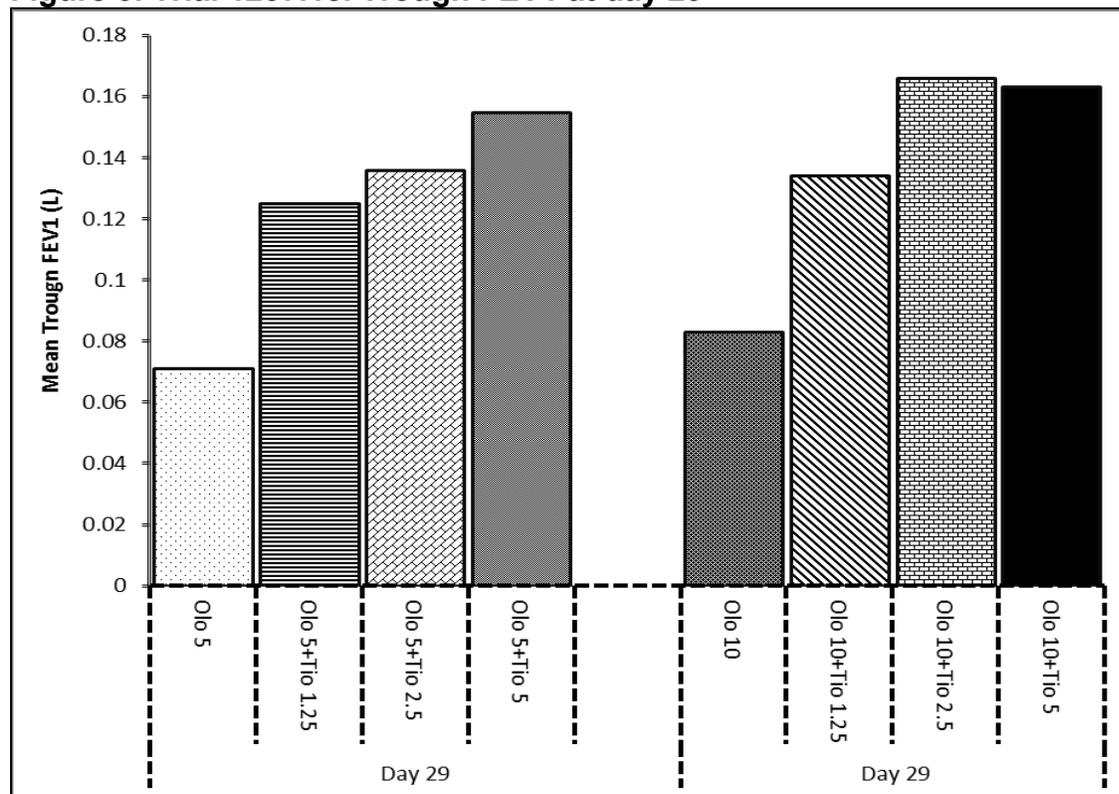
Trial 1237.9 was a 4-week treatment period randomized, double-blind, cross-over trial in COPD patients evaluating the comparing the T+O doses of 5/2 and 5/5 mcg once daily. There was a 2-week washout period between treatment periods. There was no monotherapy arm in this trial. After 2 weeks of treatment, the change from baseline in trough FEV1 for T+O 5/5 dose was numerically larger than for the 5/2mcg dose. At week 4, the treatment effect was similar between groups. At neither time point were the doses statistically significantly different. The percentage of patients with any adverse event was marginally higher during the T+O 5/2 treatment period compared to the 5/5 treatment period (44% versus 38%) as were AEs leading to discontinuation (3.6% versus 1.4%).

Trial 1237.18

Trial 1237.18 was a 4-week randomized, double-blind, parallel group trial in COPD patients evaluating multiple doses of tiotropium in conjunction with olodaterol in free

combination. In this trial, tiotropium doses of 1.25-5 mcg once daily were given with either olodaterol 5 or 10mcg. This trial also included olodaterol 5 and 10mcg as active comparators. The washout period between treatment periods was 3-weeks. Results for trough FEV1 are summarized in Figure 3.

Figure 3. Trial 1237.18. Trough FEV1 at day 29



Source: Adapted from Clinical Pharmacology Review Figure 2.

Statistically significant increases in trough FEV1 response were seen for all tiotropium doses in free combination with olodaterol 5mcg and 10mcg when compared to olodaterol alone. With increased doses of tiotropium, there were, in general, incremental increases in FEV1 response. The percentage of patients with adverse events ranged from 29-39%. It is also worth noting that when comparing T+O free dose combination dose of 5/10 and 5/5, the trough FEV1 response is numerically similar. Adverse events were most commonly seen in the T+O 1.25/5 free dose combination (39%) and least frequently in the T+O 1.25/10 free dose combination (29%).

In summary, data from these dose-ranging trials demonstrated dose-related increases in trough FEV1 that appeared to plateau at the 5mcg dose for both tiotropium and olodaterol when given in combination. Based on these results, and the data from the monocomponent programs, the Applicant carried the 2.5/5 and 5/5 T+O once daily doses to phase 3.

4.4.3 Pharmacokinetics

The clinical pharmacology (CP) of the tiotropium and olodaterol was comprehensively evaluated in the monocomponent programs. The CP of the monocomponents was previously reviewed (see CP reviews of NDAs 203108 and 021936) and will not be discussed in this review. This application did include additional CP trials evaluating the PK/PD of the two drugs in fixed and free combination. These trials demonstrated that systemic exposure (peak and steady state) to the monocomponents was similar when given in combination or alone and that there were no notable PK interactions when combined. Given the lack of interaction and the previously completed comprehensive CP programs for the monocomponents, no specific studies were performed to assess ADME properties, influence of extrinsic or intrinsic factors on systemic exposure, or effects on QT interval.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3. Reviewed Trials

Study	Objective	Design	Population	Treatment arms	Primary endpoints
1237.5 1237.6	Safety. Efficacy	Replicate, R, DB, AC, MC, PG 52-week	COPD ≥40 years N=5162 (total)	Tio+Olo 2.5/5 mcg Tio+Olo 5/5 mcg Tio 2.5 mcg Tio 5 mcg Olo 5 mcg	FEV1 AUC (0-3) Trough FEV1@24wk SGRQ pooled 12-hour PFTs @24 wk in a subset
1237.20	24-hour spirometry curve	R, DB, PC, XO 6-week treatment period	COPD ≥ 40 years N=219	Tio+Olo 2.5/5 mcg Tio+Olo 5/5 mcg Tio 2.5 mcg Tio 5 mcg Olo 5 mcg	FEV1 AUC (0-24) @6weeks

(b) (4)

5.2 Review Strategy

This clinical review focuses on the replicate phase 3 fifty-two week trials (1237.5 and 1237.6) as primary evidence of efficacy. Reviews of the (b) (4) 24-hour spirometry trial (1237.20) are also included as the Applicant has proposed label claims based on these. The efficacy results from the 52-week trials are presented in section 6 Review of Efficacy. The efficacy results from the other trials are included in section 6.1.6. Combined safety data from the 52-week trials are presented in section 7 Review of Safety. (b) (4)

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Trial 1237.5 (COPD)

Administrative Information

- **Study title:** A randomized, double-blind, parallel group study to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol (T+O) fixed dose combination (2.5 µg/5 µg; 5µg /5µg) (delivered by the Respimat Inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD)
- **Study dates:** 9/15/2011-9/19/2013
- **Study sites:** multinational (25 countries)
- **Study report date:** 4/10/2014

Objectives/Rationale

- To assess the long-term efficacy and safety of T+O (2.5/5mcg and 5/5mcg) compared to monoproduct therapy in patients with COPD

Study Design and Conduct

Overview

This was a multi-center, randomized, double-blind placebo-controlled, 52-week parallel group trial to assess the safety and efficacy of two doses of T+O (2.5/5mcg qD and 5/5mcg qD) for the treatment of COPD. These COPD patients were ≥ 40 years old, had an FEV1 of $< 80\%$ predicted and were current smokers, or had at least a 10 pack year smoking history. Asthmatics were excluded. The trial had a total of 11 visits. Consistent with standard of care, background therapy with short-acting beta-agonists, inhaled corticosteroids, oral corticosteroids, and methylxanthines were permitted in all treatment

groups. However, long-acting beta-agonists (LABA) and long-acting anticholinergics were prohibited (except for trial medication).

Consent was obtained from patients at visit 0, and patients were informed of restricted medications. At the screening visit (visit 1, week -2), baseline information was collected. Baseline spirometry was also performed. Eligible patients then began a 2-week run-in period. Prior to the end of the run-in period, a subset of patients received baseline 24-hour Holter monitoring (approximately 75/arm). At visit 2, patients were randomized into the 52-week double-blind treatment portion of the trial. During the double-blind treatment period, patients were instructed to record peak expiratory flow rate (PEFR), symptoms, study medication use, and rescue medication use in their eDiaries. After the randomization visit, there were 9 additional clinic visits (weeks 2, 6, 12, 18, 24, 32, 40, 46, and 52). The co-primary efficacy endpoints were assessed at 24 weeks (days 169 and 170); the remainder of the trial was primarily for collection of safety data. PFTs were performed at each clinic visit. At the week 24 visit, a subset of patients received additional post-dose PFTs to characterize the 12-hour FEV1 curve. After the final visit at week 52, there was a solicited vital status follow-up phone call at day 385 for all patients including those who prematurely discontinued from the trial. The trial schedule and assessments are summarized in Table 4.

Table 4. Trial 1237.5. Assessment Schedule

	Screening			Treatment Period										FU		
	0	1	2*	2	3	4	5	6	7	7*	8	9	TC ³		10	11
Visit Number																
Week		-2	-1 ¹⁷	0	2	6	12	18	24	V7	32	40	46	EOT	52 ¹⁵	+3
Day		-14		1	15	43	85	127	169	+1	225	281	323	365		+21
Time window (days)					±3	±7	±7	±7	±7	day	±7	±7	±7	±7		+7
Informed Consent ¹	X															
Pharmacogenomics ²				X												
Demographics		X														
Medical History		X														
COPD/patient characteristics		X														
In-/Exclusion criteria ³	X	X		X												
Physical examination		X							X					X	X ⁴	
Vital signs (seated) ⁵		X		X			X	X	X					X	X ⁴	
Laboratory tests		X		X			X	X	X					X	X ⁴	
Pregnancy test ¹⁶		X		X			X	X						X	X	
12-lead ECG ⁶		X		X			X	X						X	X ⁴	
Holter monitoring (subset) ⁷			X				X									
Training in use of RESPIMAT		X		X												
Issue electronic PEF meter /diary		X														
Download electronic PEF meter/diary				X	X	X	X	X	X		X	X		X	X	
Randomisation				X												
Medication washout check ⁸		X		X	X	X	X	X	X		X	X		X ¹⁸		
Dispense trial medication				X	X	X	X	X	X		X	X		X		
Collect trial medication				X	X	X	X	X	X		X	X		X		
Dispense rescue medication (as needed) ²⁰	X	X		X	X	X	X	X	X		X	X		X		
Administration of test medication in clinic				X	X	X	X	X	X		X	X		X ¹⁸		
Drug accountability check ¹⁴				X	X	X	X	X	X		X	X		X	X	
PFTs (FEV ₁ & FVC) ⁹		X ¹¹		X	X	X	X	X	X ¹⁰	X	X	X		X ¹³		
SGRQ				X			X	X						X ¹⁸		
BDI				X										X ¹⁸		
TDI					X	X	X	X						X ¹⁸		
EQ-5D				X	X	X	X	X		X	X			X ¹⁸		
Functional Performance Inventory (FPI) ¹²				X			X							X ¹⁸		
Healthcare Resource Utilisation (HCRU)				X	X	X	X	X	X		X	X		X	X	
Patient's Global Rating (PGR)							X	X			X			X ¹⁸		
Review smoking status		X						X						X		
Health status assessment								X ¹³							X ¹³	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Termination of trial med.														X		
Trial Completion															X	

- All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which includes medication washout and restrictions.
- Two blood samples will be taken from those eligible patients who signed the specific informed consent related to pharmacogenetic testing; participation in the pharmacogenetic testing is voluntary and is not a prerequisite for participation in the study.
- A telephone contact (TC) contact is scheduled between Visit 9 and Visit 10. The PI or designee will contact the patient and collect information regarding COPD exacerbation status, concomitant medication status and adverse events.
- To be performed only if relevant findings at Visit 10.
- Measured prior to pre-dose PFTs and prior to 60 mins post-dose PFTs.
- 12-lead ECG recording in all patients at Screening Visit (Visit 1) and repeated at the withdrawal visit if the patient does not complete all study visits. In addition, 12-lead ECG recording will be performed pre-dose and 40 minutes post-dose in all patients at Visits 2, 5, 7 and 10.
- At selected sites, Holter monitoring will be performed in a subset of 375 patients (i.e., 75 patients per treatment group) prior to randomization (Visit 2* in flow chart) and following Visit 5. **At these selected sites, all patients must be invited to participate in this sub-study.**
- Telephone contact required prior to each clinic visit to remind the patient of the timing of the trial medication administration and medication restriction requirements.
- Visits 2, 5, 7, 10:** 1 h pre-dose, 10 mins pre-dose, 5, 15, 30 mins post-dose, 1, 2, 3 h post-dose
 - Visit 7 (sub-set)** 1 h pre-dose, 10 mins pre-dose*, 5, 15, 30 mins post-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12 h post-dose
 - Visit 7* (all patients)** measurements at Visit 7* will be 23 hr and 23 hr 50 min after study medication administration at Visit 7
 - Visits 3, 4, 6, 8 and 9** 10 mins (± 5 min) pre-dose only
- At selected sites, PFTs up to 12 hours post dosing will be performed in a subset of 410 patients (i.e., 82 patients per treatment group). **At these selected sites, all patients must be invited to participate in this sub-study.**
- Reversibility testing using 400 µg salbutamol (albuterol) [note: reversibility is not an inclusion criterion].
- For patients in US only.
- To be completed only for patients who discontinue early. Patients will be contacted at the predicted 24 week (Visit 7) date (if they discontinue prior to 24 weeks of treatment), and at the predicted exit date from the trial (52 weeks plus 21 days = day 385 after randomization)
- Including drug accountability check of dispensed rescue medication.
- End of treatment examinations to be completed by all patients who complete the study and all patients who discontinue early. See also footnote 18.
- If applicable. Serum pregnancy test at Visit 1 and urine dipstick pregnancy test at Visits 2, 5, 7 and 10 and 11.
- Visit 2* can take place any time between Visit 1 and Visit 2, as long as 24 hour recording of Holter prior to any Visit 2 assessments is assured.
- Assessments are not required for early discontinuations.
- A preliminary check of in-/exclusion criteria is recommended at Visit 0 to avoid unnecessary washout procedures in non-eligible patients.
- At visit 0 the patient will receive directions on the as needed use of the salbutamol (albuterol) MDI (as rescue medication) that will be dispensed at this visit. In case the patient has to wash-out tiotropium, at the discretion of the investigator ipratropium will be dispensed at this visit.

Trial Population

The trial consisted of 2624 randomized COPD patients. They were randomized using an interactive voice randomization system (IVRS).

Key Inclusion Criteria

1. All patients signed an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which included medication washout and restrictions.
2. All patients had a diagnosis of chronic obstructive pulmonary disease and met the following spirometric criteria: Patients had relatively stable airway obstruction with a post-bronchodilator <80% of predicted normal and a post-bronchodilator FEV1/FVC <70% predicted at Visit 1.
3. Male or female patients, 40 years of age or older
4. Patients were current or ex-smokers with a smoking history of more than 10 pack-years. Patients who had never smoked cigarettes were excluded.
5. Patients were be able to perform technically acceptable pulmonary function tests (both supervised) and PEFr measurements, and were able to maintain records (Patient Daily e-Diary) during the study period as required in the protocol.
6. Patients were able to inhale medication in a competent manner from the Respimat inhaler and from a metered dose inhaler (MDI).

Key Exclusion Criteria

1. Patients with a significant disease other than COPD
2. Patients with clinically relevant abnormal baseline hematology, blood chemistry, or urinalysis; all patients with an AST (SGOT) >2x ULN, ALT (SGPT) >2x ULN, bilirubin >2x ULN or creatinine >2x ULN were excluded regardless of clinical condition (a repeat laboratory evaluation was not be conducted in these patients)
3. Patients with a history of asthma. For patients with allergic rhinitis or atopy, source documentation was required to verify that the patient did not have asthma. If a patient had a total blood eosinophil count 600/mm³, source documentation was required to verify that the increased eosinophil count was related to a non-asthmatic condition.
4. Patients with any of the following conditions:
 - a diagnosis of thyrotoxicosis (due to the known class side effect profile of beta-agonists)
 - a diagnosis of paroxysmal tachycardia (>100 beats per minute [due to the known class side effect profile of beta-agonists])
5. Patients with any of the following conditions:
 - a history of myocardial infarction within 1 year of Screening Visit (Visit 1)
 - unstable or life-threatening cardiac arrhythmia.
 - have been hospitalized for heart failure within the past year.
 - known active tuberculosis
 - a malignancy for which patient has undergone resection, radiation therapy or chemotherapy within last five years (patients with treated basal cell carcinoma are allowed)
 - a history of life-threatening pulmonary obstruction

- a history of cystic fibrosis
- 6. Clinically evident bronchiectasis
- 7. A history of significant alcohol or drug abuse
- 8. Patients who had undergone thoracotomy with pulmonary resection (patients with a history of thoracotomy for other reasons could have been evaluated as per exclusion criterion No. 1)
- 9. Patients being treated with any of the following concomitant medications:
 - oral beta-adrenergics
 - oral corticosteroid medication at unstable doses (i.e., less than six weeks on a stable dose) or at doses in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day
- 10. Patients who regularly used daytime oxygen therapy for more than one hour per day and in the investigator's opinion would have been unable to abstain from the use of oxygen therapy during clinic visits
- 11. Patients who had completed a pulmonary rehabilitation program in the six weeks prior to the Screening Visit (Visit 1) or patients who were currently in a pulmonary rehabilitation program
- 12. Patients who had taken an investigational drug within one month or six half lives (whichever is greater) prior to Screening Visit (Visit 1)
- 13. Patients with known hypersensitivity to beta-adrenergics drugs, EDTA or any other component of the Respimat inhalation spray delivery system
- 14. Pregnant or nursing women
- 15. Women of childbearing potential not using two effective methods of birth control (one barrier, one non-barrier method). Female patients would be considered to be of childbearing potential unless surgically sterilized by hysterectomy or bilateral tubal ligation, or postmenopausal for at least two years
- 16. Patients who had previously been randomized in this study or were currently participating in another study
- 17. Patients who were unable to comply with pulmonary medication restrictions prior to randomization

Enrollment Cautions:

1. Extreme caution was used when including patients:
 - with cardiovascular disorders, especially coronary insufficiency and hypertension
 - being treated with monoamine oxidase inhibitors or tricyclic antidepressants
2. Caution was used when including patients on treatment with non-potassium-sparing diuretics
3. Patients should not have been normally taking beta-blockers. However, under certain circumstances, e.g., prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.
4. Caution should be used when including patients with narrow angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction.

5. Patients with moderate to severe renal impairment.

Treatments

Treatment Groups

T+O (2.5mcg/5mcg) qD

T+O (5mcg/5mcg) qD

Olo 5mcg qD

Tio 2.5mcg qD

Tio 5mcg qD

Placebo qD

All were administered using the Respimat inhaler.

Concomitant/Restricted Medications:

All medications used during the trial were recorded in the eCRF. Use of short-acting bronchodilators (SABA) were allowed as necessary; however, if a patient required SABA treatment during PFTs, the testing was stopped. Temporary increases in the dose or addition of oral steroids and theophylline were allowed; however, PFTs could not be performed within 7 days of the last dose. PFTs could be postponed up to 14 days. The use of antibiotics was not restricted. However, PFTs would have been postponed for at least 2 days, but not more than 7 days. Medication limitations are summarized in Table 5.

Table 5. Trial 1237.5. Permitted Medications

Drug Class	Sub-class	Prior to study	Study Period		
			Screening Period	Treatment Period	Follow up Period
Corticosteroids	Inhaled corticosteroids (stabilized 6-wks prior to visit 1)	permitted	permitted	permitted	permitted
	Oral corticosteroids [≤10 mg prednisone per day or ≤20 mg prednisone every other day (or equivalent); stabilized 6-wks prior to visit 1]	permitted	permitted	permitted	permitted
Beta-adrenergics / beta-blockers	Inhaled short-acting beta-adrenergics	permitted	rescue	rescue	rescue
	Inhaled long-acting beta-adrenergics	permitted	not permitted	study medication	permitted
	Oral beta-adrenergics	not permitted	not permitted	not permitted	not permitted
	Beta blockers	permitted	permitted	permitted	permitted
Anticholinergics	Short-acting anticholinergics (inhalation aerosol and nasal spray)	permitted	permitted	not permitted	permitted
	Long-acting anticholinergics	permitted	not permitted	study medication	permitted
Combinations	ICS/LABA (switch to ICS monoprodu ct 48hr prior to visit 1)	permitted	not permitted	not permitted	permitted
	ICA/SABA (switch to ICS monoprodu ct 8hr prior to visit 1)	permitted	not permitted	not permitted	permitted
	Short-acting anticholinergic/SABA (8hr prior to visit 1)	permitted	not permitted	not permitted	permitted
Miscellaneous	Other investigational drugs	not permitted	not permitted	not permitted	not permitted
	Oral cromolyn sodium / nedocromil sodium	permitted	permitted	permitted	permitted
	Antihistamines, antileukotrienes	permitted	permitted	permitted	permitted
	Methylxanthines	permitted	permitted	permitted	permitted
	Mucolytics	permitted	permitted	permitted	permitted
	PDE-4 inhibitor	not permitted	not permitted	not permitted	not permitted

Source: Protocol 1237.5; table 4.2.2.1:1; pp 154-155

The trial design and patient population are typical for a COPD trial. It is also worth noting that this trial is similar in design and length to the pivotal trials used as support for the approvals of both olodaterol and tiotropium Respimat.

Efficacy Parameters

Primary Endpoint

The co-primary endpoints for this trial were trough FEV1 response and FEV1 AUC (0-3 hours) response at week 24 (day 169-170). Trough FEV1 was defined as the mean of the FEV1 obtained at 1 hour prior to daily medication and 10 minutes prior to daily trial medication. FEV1 AUC (0-3 hours) was defined as area under the curve from 0 to 3

hours post-dose using the trapezoid rule, divided by the time duration. Response for both parameters was defined as change from baseline. Baseline was defined as the mean of the 2 pre-dose PFTs at visit 2.

The protocol also pre-specified a pooled analysis of trials 1237.5 and 1237.6 with a primary endpoint of SGRQ at week 24 of treatment.

The co-primary endpoints are typical for a COPD trial meant to demonstrate a bronchodilator effect. These are the same co-primary endpoints used in the olodaterol Respimat pivotal trials.

Key Secondary Endpoint

For the pooled analysis of trials 1237.5 and 1237.6, the key secondary endpoint was Transitional Dyspnea Index (TDI focal score) after 24-weeks of treatment. Note that there were no key secondary endpoints for the individual analysis of the 52-week trials.

It is likely that the pooled analysis of TDI was included due to EU regulatory requirements. (b) (4)

Secondary Endpoints

The secondary endpoints included the following:

1. FEV1 AUC (0-3 hours) response at day 1, 85 and 365
2. Trough FEV1 response [L] on day 15, 43, 85, 169, and 365
3. FVC (forced vital capacity) AUC (0-3 hours) response at day 1, 85, 169, and 365
4. Trough FVC response [L] at day 15, 43, 85, 170, and 365

Secondary Endpoints for pooled trials

The secondary endpoints for the pooled trials included the following:

1. FEV1 AUC (0-12 hours) and (0-24 hours) response at day 169 (in the subset of patients with available data)
2. FVC AUC (0-12 hours) and (0-24 hours) response at day 169 (in the subset of patients with available data)
3. SGRQ total score on day 85 and 365
4. TDI focal score on day 43, 85, and 365.

Further endpoints

Spirometry

1. Trough FEV1 response [L] on Day 127, Day 225, and Day 281
2. Trough FVC response [L] on Day 127, Day 169, Day 225, and Day 281
3. FEV1 peak (0-3h) response [L] on Day 1, Day 85, Day 169, and Day 365
4. FVC peak (0-3h) response [L] on Day 1, Day 85, Day 169, and Day 365

5. FEV1 [L] and FVC [L] on Day 1, Day 85, Day 169, and Day 365 at 1 h and at 10 min pre-dose (not on Day 1), at 5, 15, and 30 min, and 1, 2, 3 h after inhalation of study medication and at 23 h as well as 23 h and 50 min after inhalation of study medication (Day 169 only)

Electronic peak flow meter with electronic diary (Asthma Monitor AM3®)

1. Weekly mean pre-dose morning and evening peak expiratory flow rates (PEFs) [L/min] for weeks 1 to 52
2. Weekly mean number of puffs of rescue therapy (salbutamol/albuterol) used per day (daytime/nighttime/total) for weeks 1 to 52

Quality of life

1. Patient's Global Rating (PGR) on Day 85, Day 169, Day 281, and Day 365

Further endpoints for pooled analysis

Spirometry

1. FEV1 [L] at 1 h and at 10 min pre-dose and at 5, 15, and 30 min, at 1, 2, 3, 4, 5, 6, 8, 10, 12, and 23 h, and at 23 h and 50 min after inhalation of study medication in the subset of patients with 12-h PFTs on Day 169
2. FVC [L] at 1 h and at 10 min pre-dose and at 5, 15, and 30 min, at 1, 2, 3, 4, 5, 6, 8, 10, and 12 and 23 h, and at 23 h and 50 min after inhalation of study medication in the subset of patients with 12-h PFTs on Day 169

Quality of life

1. SGRQ (impacts, activity and symptoms scores) on Day 85, Day 169, and Day 365
2. SGRQ responder analysis (based on total score) on Day 169. For the SGRQ total score, a responder is a patient who has an improvement from baseline of ≥ 4.0 units
3. FPI on Day 85 and Day 365 (US patients only) (total score and change from baseline)

Breathlessness

1. TDI focal score on Day 127
2. Mahler Dyspnea Indices (functional impairment, magnitude of task and magnitude of effort) on Day 43, Day 85, Day 127, Day 169, and Day 365
3. Mahler Dyspnoea Index responder analysis (based on focal score) on Day 169. For the Mahler TDI focal score, a responder is a patient who has an improvement from baseline of ≥ 1.0 unit.

COPD exacerbations

1. Time to first COPD exacerbation
2. Time to first moderate/severe COPD exacerbation
3. Time to first severe COPD exacerbation (i.e., exacerbation leading to hospitalisation)
4. Time to first COPD exacerbation in the subset of patients with a history of exacerbation
5. Time to first moderate/severe COPD exacerbation in the subset of patients with a

6. history of exacerbation
7. Time to first severe COPD exacerbation in the subset of patients with a history of exacerbation
8. Number of COPD exacerbations per patient year
9. Number of moderate/severe COPD exacerbations per patient year
10. Number of severe COPD exacerbations per patient year
11. Number of COPD exacerbations per patient year in the subset of patients with a history of exacerbation
12. Number of moderate/severe COPD exacerbations per patient year in the subset of patients with a history of exacerbation
13. Number of severe COPD exacerbations per patient year in the subset of patients with a history of exacerbation

For the secondary endpoints, AUC and response was defined as in the primary endpoint. Baseline was also defined as in the primary endpoint.

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
- Sputum production (volume)
- Occurrence of purulent sputum
- Cough
- Wheezing
- Chest tightness

And where “a required change in treatment” included the following:

- Prescription of antibiotics and/or systemic steroids
- And/or significant change for prescribed respiratory medication (bronchodilators including theophyllines)

For the Patient’s Global Rating, patients were asked to assess their health after 12, 24, 40, and 52 weeks of treatment before the first dose of study drug. There were 7 possible responses which were ‘very much better’, ‘much better’, ‘a little better’, ‘no change’, ‘a little worse’, ‘much worse’, or ‘very much worse’. Each response was given a point value 1-7, with 1 being ‘very much better’ and 7 being ‘very much worse.’

The definition used for exacerbation is the same as used in the olodaterol and tiotropium Respimat development programs and is similar to that used in the tiotropium Handihaler development programs. The definition is acceptable. It is also worth noting that despite the advice given during the EOP2 meeting, BI’s 24-hour spirometry actually 12-hour spirometry with the addition of trough FEV1 from the following day (post-dose hour 23 and 23:50), as such, its value in representing the 24-hour response is questionable.

Safety parameters:

Monitored safety parameters will include the following:

- AEs, vital signs and clinical labs were performed as per the schedule listed in Table 4.
- ECGs were performed at baseline and screening. ECGs were also performed at visits 2, 5, 7, 10, and 11. ECGs were performed pre-dose and 40 minutes post-dose.
- 24-hour Holter monitoring was performed in approximately 375 patients at selected sites.

Compliance

Compliance was determined based on eDiary entries and returned medications.

Ethics:

This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this protocol. No changes were made without the IRB's approval.

Statistical Analysis

Sample Size

Based on the Applicant's previous experience, the standard deviation for FEV1 AUC (0-3 hours) was estimated to be 226mL and for trough FEV1 was 225mL. BI estimated that a total of 500 patients/group would yield 90% power to detect a 46mL FEV1 AUC (0-3 hours) and trough FEV1 response with a one sided alpha of 0.025. As such BI planned to randomize 500 patients/group.

Missing Data

Data missing due to worsening symptoms were replaced with the least favorable non-missing data recorded during the same visit. Post-dose data missing at random was either linearly interpolated if the preceding and subsequent data points were available. If the adjacent data points were not available, then data were also imputed using last observation carried forward (LOCF).

Analysis populations

The sponsor pre-specified 3 analysis populations. The full analysis set (FAS) consisted of all patients who received study drug and had baseline data and at least one evaluable post-dosing data for either co-primary endpoint. The per protocol set (PPS) consisted of all FAS minus patients with important protocol deviations. If the PPS was <90% of the FAS, the primary analysis was to have been performed on the PPS as a sensitivity analysis. The safety population was made up of all treated patients.

Efficacy Analysis

The co-primary endpoints were analyzed in a hierarchical manner to protect against type 1 error. The primary endpoint comparisons for T+O (5 µg / 5 µg) were analyzed in the following order:

1. Superiority in mean FEV1 AUC0-3h response in patients treated with T+O (5 µg / 5 µg) compared with patients treated with olodaterol (5 µg), after 24 weeks
2. Superiority in mean FEV1 AUC0-3h response in patients treated with T+O (5 µg / 5 µg) compared with patients treated with tiotropium (5 µg), after 24 weeks
3. Superiority in mean FEV1 trough response in patients treated with T+O (5 µg / 5 µg) compared with patients treated with olodaterol (5 µg), after 24 weeks
4. Superiority in mean FEV1 trough response in patients treated with T+O (5 µg / 5 µg) compared with patients treated with tiotropium (5 µg), after 24 weeks

If the above tests were positive, the primary endpoint comparisons for T+O (2.5 µg / 5 µg) were then be analyzed in the following order:

1. Superiority in mean FEV1 AUC0-3h response in patients treated with T+O (2.5 µg / 5 µg) compared with patients treated with olodaterol (5 µg), after 24 weeks
2. Superiority in mean FEV1 AUC0-3h response in patients treated with T+O (2.5 µg / 5 µg) compared with patients treated with tiotropium (2.5 µg), after 24 weeks
3. Superiority in mean FEV1 trough response in patients treated with T+O (2.5 µg / 5 µg) compared with patients treated with olodaterol (5 µg), after 24 weeks
4. Superiority in mean FEV1 trough response in patients treated with T+O (2.5 µg / 5 µg) compared with patients treated with tiotropium (2.5 µg), after 24 weeks
5. Superiority in mean FEV1 AUC0-3h response in patients treated with T+O (2.5 µg / 5 µg) compared with patients treated with tiotropium (5 µg), after 24 weeks
6. Superiority in mean FEV1 trough response in patients treated T+O (2.5 µg / 5 µg) compared with patients treated with tiotropium (5 µg), after 24 weeks

Note that the U.S. hierarchal testing sequence did not include a pooled analysis of SGRQ. Analyses of the secondary endpoints were considered descriptive and the p-values did not account for multiple comparisons.

Protocol Amendments

There were three global protocol amendments. The first was submitted on 10/7/2011. This amendment changed the timing of visit 7 and added trough FEV1 measurements to this visit. This was to ensure that FEV1 AUC (0-3hours) and trough FEV1 measurements were from the same dosing intervals. The second amendment was submitted on 8/29/12. This amendment expanded adjudication to include all SAEs (instead of fatal cases only). The third amendment was submitted on 10/28/13. This amendment included moving a portion of the secondary endpoints to further endpoints and also adding the COPD exacerbation related further endpoints. These amendments were made prior to database lock and data unblinding and do not affect interpretation of the results.

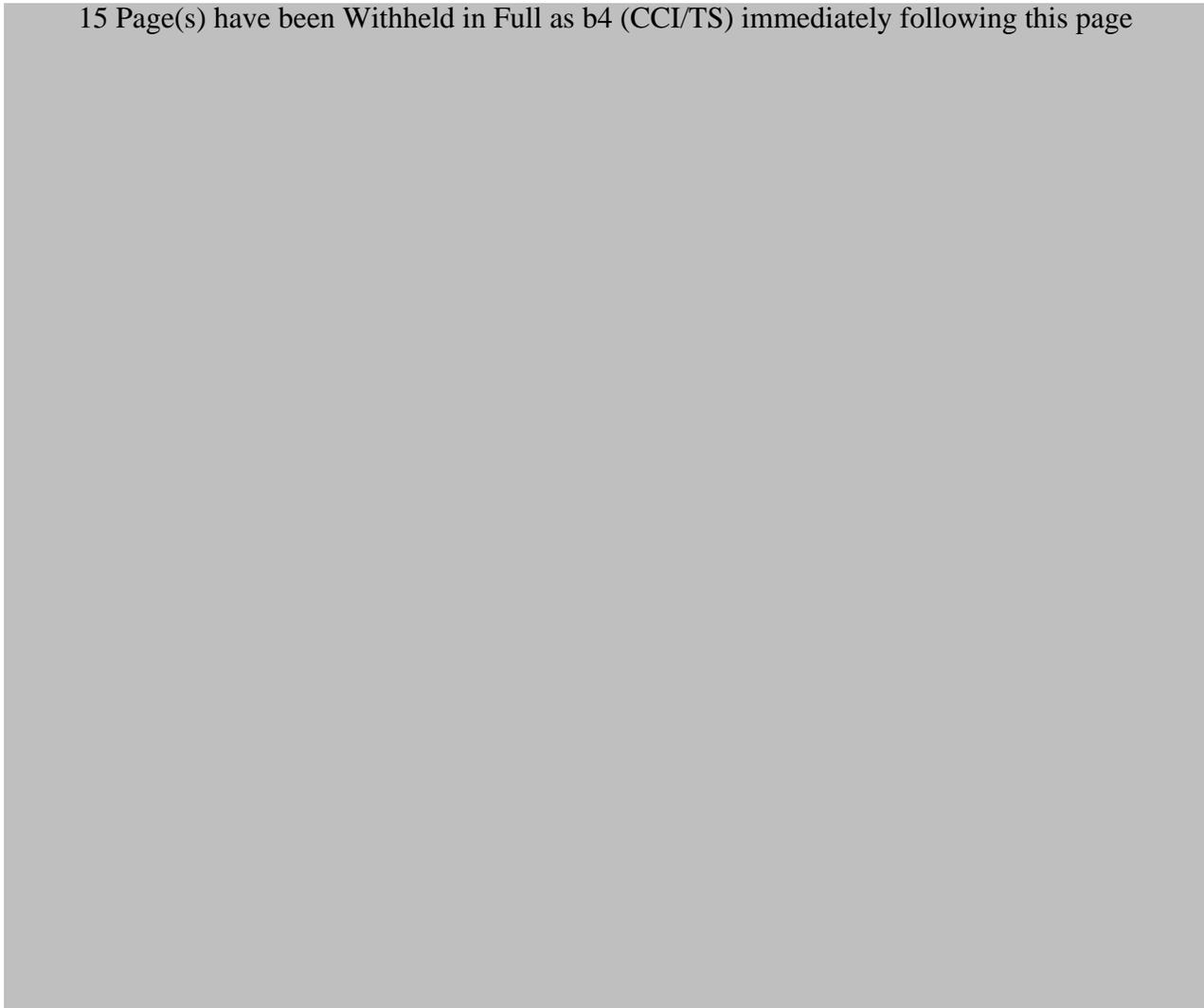
5.3.2 Trial 1237.6 (COPD)

Administrative Information

- **Study title:** A randomized, double-blind, parallel group study to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol (Tio+Olo) fixed dose combination (2.5 µg/5 µg; 5µg /5µg) (delivered by the Respimat Inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD)
- **Study dates:** 9/15/11-11/11/13
- **Study sites:** multinational (24 countries)
- **Study report date:** 4/10/14

This trial was identical in design to 1237.5.

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5.3.6 Trial 1237.20 (24-hour Spirometry Trial)

Administrative Information

- **Study title:** Randomized, double-blind, placebo-controlled, 6-treatment, 4-period, incomplete cross-over study to characterize the 24-hour lung function profiles of Tio+Olo (2.5/5mcg and 5/5 mcg), Tio (2.5 and 5mcg), and Olo (5mcg) after 6-weeks of treatment in patients with COPD
- **Study dates:** 3/27/12-8/12/13
- **Study sites:** Belgium, Canada, Denmark, Germany, Hungary, Netherlands and USA
- **Study report date:** 4/4/2014

Objectives

Primary Objectives

- To determine the 24-hour FEV1 time profile of Tio+Olo 2.5/5mcg and 5/5mcg after 6-weeks of treatment.

Secondary Objectives

- To compare the effects the 24-hour FEV1 time profile of Tio+Olo 2.5/5mcg and 5/5mcg with Tio 2.5mcg, 5mcg, and Olo 5mcg.
- To determine the 24-hour time profile of other spirometric parameters of Tio+Olo 2.5/5mcg and 5/5mcg compared to Tio 2.5mcg, 5mcg, and Olo 5mcg.
- To assess the PK profiles of tiotropium and olodaterol after administration of Tio+Olo 2.5/5 µg and Tio+Olo FDC 5/5 µg in COPD patients.

Trial design and conduct

Overview

This was a multi-center, multi-national, randomized, double-blind, four treatment period, incomplete cross-over trial in moderate to severe COPD patients. The four 6-week treatment arms included placebo, Tio+Olo 2.5/5mcg, Tio+Olo 5/5mcg, Tio 2.5mcg, 5mcg, and Olo 5mcg. Between each treatment period, there was a 21-day washout period. After signing consent and after the initial screening visit (visit 1), patients were randomized into their treatment sequence, baseline assessment performed, and the first 6-week treatment period began (visit 2). During the treatment period, patients had telephone contact at 3-weeks and a clinic visit at 6-weeks (visit 3). At visit 3, 24-hour serial spirometry testing was performed. After visit 3, and a 21 day washout period, patients returned to clinic for the next treatment period. For treatment periods 2, 3, and 4, there were also 2 clinic visits, one for initiation of therapy and baseline assessments (4, 6, and 8), and a second visit (5, 7, and 9) for 24-hour spirometry. A follow-up visit occurred approximately 21 days after the last clinic visit. The trial schedule is summarized in. The assessments performed at each visit are summarized in Table 11.

Table 11. Trial 1237.20. Assessment schedule

Trial Phases	Run-in		Treatment phase												FU		
	0	1	Period 1			Period 2			Period 3			Period 4					
Visit			2 ¹⁰	3 ¹⁰	4	5 ¹⁰	6	7 ¹⁰	8	9 ¹⁰	10						
Week (cumulative)	-	-6 to -2	-	3	6	9	12	15	18	21	24	27	30	33	36		
Day of Treatment (cumulative) (*) indicate overnight stay		-42 to -14	1	11	43	64	88	106	127	148	169	190	211	232	253		
Day of Treatment		-42 to -14	1	11	43	1	11	43	1	11	43	1	11	43	-		
Time window (days)		-	-	+3	-7*	+7*	+3	-7*	+7*	+3	-7*	+7*	+3	-7*	-2		
Informed consent ¹	X																
Pharmacogenetics ²			X														
Demographics		X															
Medical history/ Baseline conditions		X															
COPD/patient characteristics		X															
Review in-/ exclusion criteria		X	X														
Physical examination		X												X ³	X ⁴		
Vital signs (seated) ⁵		X	X		X	X		X	X		X	X		X	X		
Laboratory tests		X	X		X	X		X	X		X	X		X ⁶	X ⁷		
Pregnancy test ⁸		X	X		X	X		X	X		X	X		X	X		X
12-lead ECG ⁹		X	X	X	X	X		X	X		X	X		X ¹⁰	X ¹¹		X ¹²
Training in use of RESPIMAT		X	X ¹³		X ¹⁴	X ¹⁵		X ¹⁶	X ¹⁷		X ¹⁸	X ¹⁹		X ²⁰	X ²¹		X ²²
Randomisation		X															
Medication washout check ²³		X	X	X	X	X		X	X		X	X		X	X		X
Dispense study medication		X			X	X		X	X		X	X		X	X		X
Collect study medication		X		X	X	X		X	X		X	X		X ²⁴	X ²⁵		X ²⁶
Administration (dosing) of study medication at the site		X	X	X	X	X		X	X		X	X		X	X		X
Dispense and explain use of rescue medication (as needed)	X	X	X	X	X	X		X	X		X	X		X ²⁷	X ²⁸		X ²⁹
Collect rescue medication ³⁰		X	X	X	X	X		X	X		X	X		X	X		X
Drug accountability check ³¹		X	X	X	X	X		X	X		X	X		X	X		X
Issue patient paper diary		X	X	X	X	X		X	X		X	X		X	X		X
Collect patient paper diary		X	X	X	X	X		X	X		X	X		X	X		X
PFTs (FEV ₁ & FVC)		X ³²	X ³³	X ³⁴	X ³⁵	X ³⁶		X ³⁷	X ³⁸		X ³⁹	X ⁴⁰		X ⁴¹	X ⁴²		X ⁴³
PK ⁴⁴ (blood and urine sampling)		X	X														
Body plethysmography (substudy only)		X ⁴⁵	X ⁴⁶	X ⁴⁷	X ⁴⁸	X ⁴⁹		X ⁵⁰	X ⁵¹		X ⁵²	X ⁵³		X ⁵⁴	X ⁵⁵		X ⁵⁶
Review smoking status		X	X			X		X	X		X	X		X	X		X
Adverse events		X	X	X	X	X		X	X		X	X		X	X		X
Concomitant therapy	X	X	X	X	X	X		X	X		X	X		X	X		X
Termination of study medication			X			X					X			X			X
Trial completion																	X

* Sites were to make every effort to attain exactly 6 weeks of treatment when scheduling the visit days with the patient at the beginning of the trial. Visit window of up to +7 days were only to be used as an exception (i.e. if scheduled visit cannot be kept by the patient for an urgent reason) and after discussion with the sponsor (i.e. the Clinical Monitor Local). Visit scheduling was to always ensure that subsequent treatment periods were not shorter than 6 weeks and subsequent washout periods were not shorter than 3 weeks. Consequently, any time displacement of a visit means necessarily postponement of all subsequent visits. In the exceptional case of necessary rescheduling of the PFT visit after medically necessary additional pulmonary treatment, please refer to timing rules in Section 5.4.2.1. Consequently, any time displacement of a visit meant necessarily a postponement of all subsequent visits.

¹ All patients were to sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial, which included medication washout and restrictions. After informed consent, the patient received a trial identification card and a patient appointment card.

² One blood sample was to be taken from those eligible patients who agreed the specific informed consent related to unspecified pharmacogenetic testing at Visit 2 (or any subsequent visit); participation in the pharmacogenetic testing was voluntary and not a prerequisite for participation in the trial.

³ To be completed whenever trial participation ends, i.e. if the patient discontinued prematurely and did not complete all trial visits during treatment phase.

⁴ To be performed only if relevant findings at Visit 9 or premature withdrawal visit.

⁵ Vital signs were to be performed prior to PFTs with the patient seated and rested for a minimum of 5 min in conjunction with PFT pre-dose 30 min and post-dose 2 h and 3 h, additionally post-dose 50' in conjunction with ECG.

⁶ Women of child-bearing potential, serum pregnancy test at Visit 1 and urine pregnancy test (dipstick) at Visits 2, 4, 6, 8, and 10.

⁷ 12-lead ECG recording in all patients at screening visit (Visit 1). In addition, 12-lead ECG recording was to be performed 40 min pre-dose and 50 min post-dose in all patients at Visits 2 to 9.

⁸ The patient was instructed in the use of the RESPIMAT Inhaler but was not to inhale from the placebo inhaler at this visit.

⁹ Telephone contact required 2 days before the site visit to remind the patient of medication restriction requirements (Visit 1 to 9) and of the exact timing of the study medication administration the day before the site visit (applicable for Visit 3, 5, 7, and 9 only).

¹⁰ Collection of dispensed rescue medication during the course of the trial (whenever applicable) and during follow-up Visit 10 at the latest.

¹¹ Drug accountability for study medication including check of dispensed rescue medication and ipratropium bromide (if applicable).

¹² Visit 1:
 Reversibility testing using 400 µg salbutamol (albuterol). For details please refer to Section 10.5 of the trial protocol (note that reversibility was not an inclusion criterion).

¹³ Visits 2, 4, 6, 8:
 pre-dose PFT: 30 min prior to inhalation of dose of study medication
 post-dose PFT: 30 min, 1, 2 and 3 h post-dose

¹⁴ Visits 3, 5, 7, 9:
 pre-dose PFT: 30 min prior to inhalation of dose of study medication
 post-dose PFT: 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 22, 23 h and 23h 50 min post-dose

¹⁵ PK: blood and urine sampling at Visit 2 and Visit 3 (treatment period 1 only) for all patients. See chart below for timing.

¹⁶ Selected sites had their own body plethysmography equipment available, which was a prerequisite for the bodyplethysmography substudy. At these selected sites, all patients were to be invited to participate in this substudy in the informed consent process. For details please refer to Section 6.2.1 of the trial protocol.

¹⁷ Visit 1:
 determining if patient was able to perform technically acceptable body plethysmography tests; to be done prior to reversibility testing.

¹⁸ Visits 2, 4, 6, 8:
 pre-dose measurement: 1h prior to inhalation of dose of study medication.

¹⁹ Visits 3, 5, 7, 9:
 post-dose measurement: 2h30' and 22h30' post-dose

²⁰ Visit with overnight stay due to PK (Visit 3 only). PFT and body plethysmography (applicable for selected sites only) procedures. Visits 3, 5, 7, and 9 require the patient to remain at the site (or in a hotel in close proximity to the site) overnight; the days refer to the first and second day of each visit.

²¹ Visit with overnight activity, i.e. PK urine collection, to be returned to the site the next morning. No overnight stay was required.

Trial Population

The trial consisted of GOLD II-IV COPD patients. They were randomized using an IVRS system.

Key Inclusion Criteria

See trial 1237.5

Key Exclusion Criteria

Same as trial 1237.5

Treatments

Treatment Groups

T+O 2.5mcg/5mcg qD

T+O 5mcg/5mcg qD

Olodaterol 5mcg qD

Tiotropium 5mcg qD

Tiotropium 2.5mcg qD

Placebo

All were administered using the Respimat inhaler.

Concomitant/Restricted Medications:

See trial 1237.15.

Efficacy Parameters

Primary Endpoint

The primary endpoint was FEV1 AUC (0-24 hours) response after 6 weeks of treatment.

Key Secondary Endpoints

The key secondary endpoints were FEV1 AUC (0-12 hours) and FEV1 AUC (12-24 hours) response after 6 weeks of treatment.

Other Secondary Endpoints

Secondary endpoints assessed after 6-weeks of treatment and were as follows:

- Trough FEV1 and FVC
- Peak (0-3hr) FEV1 and FVC
- FVC AUC (0-24hrs), (0-12hrs), and (12-24hrs)

While the primary and secondary endpoints include spirometric AUC data from 0-24 hours, it is worth noting that in the second 12 hour period (12-24 hours), there are only three measured time-points (22, 23, and 23:50 hours post-dose). As such, whether or not this can truly characterize the 24-hour spirometric profile is uncertain. Additionally, the treatment period is only 6-weeks and whether or not 24-hour serial spirometry from this trial would be representative of chronic use is an open question. It should also be noted that in the 52-week trials after 24-weeks of treatment, in a subset of patients, 12-

hour post-dose spirometry was measured as well as trough FEV1. By combining this data, BI was able to generate 24-hour serial spirometry data. The post-dose time points were virtually identical when comparing this trial to the 52-week trials, except for the addition of one time point (22hours) in this trial.

Safety parameters

Monitored safety parameters included the following:

- Vital signs
- Physical exam
- Clinical labs
- 12-lead ECG
- All adverse events

Compliance

Compliance was determined based on daily diary entries and returned medications.

Ethics:

This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this protocol.

Statistical Analysis

Sample Size

Based on BI's previous experience, the standard deviations for FEV1 AUC (0-24 hours) was estimated to be 190mL. BI estimated that a total of 180 completed patients would yield 90% power to detect a 60mL FEV1 AUC (0-24 hours) with a two-sided alpha of 0.05.

Missing Data

Missing data was imputed by the available data from the patient at that visit.

Analysis populations

The sponsor pre-specified 5 analysis populations. The randomized set (RS) consisted of all randomized patients. The treated set (TS) consisted of all RS patients who were took at least one dose of medication. The full analysis set (FAS) consisted of all patients who received study drug and had baseline data and any evaluable post-dosing data for the primary endpoint. The per protocol set (PPS) consisted of all FAS minus patients with important protocol deviations. The body box set (BBS) consisted of all TS patients who consented for the body plethysmography sub-study and had a baseline and at least one post-baseline measurement.

Efficacy Analysis

The primary endpoint comparisons were analyzed in a hierarchal manner, with subsequent statistical comparisons only being performed when the previous comparison demonstrated statistical significance. The order was as follows:

- Superiority of Tio+Olo 5/5 µg compared with placebo
- Superiority of Tio+Olo 5/5 µg compared with olodaterol (5 µg)
- Superiority of Tio+Olo 5/5 µg compared with tiotropium (5 µg)
- Superiority of Tio+Olo 2.5/5 µg compared with placebo
- Superiority of Tio+Olo 2.5/5 µg compared with olodaterol (5 µg)
- Superiority of Tio+Olo 2.5/5 compared with tiotropium (2.5 µg)

For the key secondary endpoints, a similar hierarchal approach was used first for FEV1 AUC (0-12hours) and then for FEV1 AUC (12-24 hours).

Other secondary endpoints were not analyzed in a hierarchal manner, nor were p-values corrected for multiplicity.

Protocol Amendments

There were two global protocol amendments. The first was submitted on 3/21/12. This amendment expanded adjudication to include all SAEs (instead of fatal cases only). The second amendment was submitted on 10/11/12. This amendment added clinical evaluations for potential drug induce liver injury to comply with FDA guidance to industry "Drug-induced Liver Injury: Premarketing Clinical Evaluation." These amendments do not affect interpretation of study data.

6 Review of Efficacy

Efficacy Summary

The proposed indication for T+O is for the long-term, once daily maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The proposed dose is 5mcg for both the tiotropium (Tio) and olodaterol (Olo) components once daily.

The core phase 3 COPD development program consisted of two replicate 52-week safety and efficacy trials (1237.5 and 1237.6), (b) (4)
[REDACTED] and one 6-week treatment period crossover 24-hour spirometry trial (1237.20).

The two replicate 52-week COPD trials were used as primary support of efficacy. These trials included 5-treatment arms which were as follows: olodaterol (Olo) 5mcg, tiotropium (Tio) 2.5mcg, Tio 5mcg, T+O 2.5/5mcg, and T+O 5/5mcg. There were no placebo arms in these trials as there was sufficient evidence to support the efficacy of both Olo 5mcg and Tio 5mcg compared to placebo (see clinical reviews of NDAs 203108 and 021936). As such, demonstration of efficacy of the T+O FDC over the constituent monoproducts was sufficient to support efficacy. The primary endpoints of

these trials were trough forced expiratory volume in 1 second (FEV1) and FEV1 AUC (0-3hours) response at week 24. For both primary endpoints, both FDC doses demonstrated statistically significant improvements compared to both the constituent monotherapy products, demonstrating that both the Tio and Olo components of the FDC contributed to the treatment effect. The treatment effect was also numerically larger when comparing T+O 5/5 to the 2.5/5mcg dose. Efficacy was further supported by the secondary spirometric endpoints in these trials, which included trough FEV1 response and FEV1 AUC (0-3 hours) throughout the treatment period. Throughout the treatment period, for both parameters, the FDC doses demonstrated a larger treatment effect compared to both constituent monotherapy products. Moreover, there was also consistent numerical separation between the two 5/5mcg and 2.5/5mcg FDC doses. These trials also measure serial spirometry for 24-hours post dosing at week 24. The results demonstrated that at all time points, both FDC doses had a larger treatment effect compared to their constituent monotherapy products. Additionally, there was clear dose separation over the 24-hour interval when comparing T+O 2.5/5 to 5/5mcg. The results from the 24-hour spirometry trial (1237.20) were also generally consistent with the serial spirometry data from the 52-week trials in that both doses of the FDC demonstrated a larger treatment effect compared to their constituent monotherapy products. However, in contrast, there was no clear dose separation between the two FDC doses.

(b) (4)

Based on the available data, both doses of the T+O FDC appear to have a significant effect on bronchodilation compared to their constituent monotherapy products. The 5/5mcg dose also appears to have a numerical benefit above the 2.5/5mcg dose, which supports selection of the T+O 5/5mcg dose. Overall, these data support efficacy of T+O 5/5mcg. (b) (4)

6.1 Indication

The proposed indication for T+O is for the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The proposed dose is 5mcg for both the Tio and Olo components once daily.

6.1.1 Methods

Support for efficacy as a bronchodilator is derived primarily from the two replicate parallel group 52-week COPD trials (1237.5 and 1237.6). The design of these trials is outlined in section 5 Sources of Clinical Data. Briefly, both were 52-week randomized, double-blind, active-controlled trials in moderate to severe COPD patients. The co-primary endpoints were FEV1 AUC (0-3 hours) response and trough FEV1 at week 52. Trial 1237.5 and 1237.6 were adequately designed to assess for efficacy. It is important to note that these trials were active control trials where the active controls (Tio 5mcg and Olo 5mcg) have previously demonstrated a statistically significant treatment effect compared to placebo in their respective development programs.



(b) (4) the sponsor also submitted one 6 week treatment period cross-over trials in patients with COPD (trial 1237.20). This primary endpoint of this trial was FEV1 AUC (0-24hrs) after 6 weeks of treatment. Analysis of this trial is also summarized in section 6.1.10 Additional Efficacy Issues/Analyses.

6.1.2 Demographics

52-week trials

Pooled patient demographics for trials 1237.5 and 1237.6 are summarized in Table 12. Between trials the demographic data were similar.

Table 12. Pooled 52-week trials. Patient Demographics

	Olo 5mcg	Tio 2.5 mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg	Total
Number of patients	1038	1032	1033	1030	1029	5162
Sex [N(%)]						
Male	764 (73.6)	753 (73.0)	755 (73.1)	757 (73.5)	733 (71.2)	3762 (72.9)
Female	274 (26.4)	279 (27.0)	278 (26.9)	273 (26.5)	296 (28.8)	1400 (27.1)
Race [N (%)]						
Asian	279 (26.9)	248 (24.0)	278 (26.9)	251 (24.4)	250 (24.3)	1306 (25.3)
Black/African American	12 (1.2)	19 (1.8)	12 (1.2)	16 (1.6)	16 (1.6)	75 (1.5)
White	729 (70.2)	744 (72.1)	714 (69.1)	743 (72.1)	732 (71.1)	3662 (70.9)
Missing	17 (1.6)	15 (1.5)	17 (1.6)	14 (1.4)	24 (2.3)	87 (1.7)
Age [years]						
N	1038	1032	1033	1030	1029	5162
Mean	64.2	64.0	63.9	64.1	63.8	64.0
SD	8.2	8.7	8.6	7.8	8.3	8.3
Smoking history [N (%)]						
Ex-smoker	660 (63.6)	644 (62.4)	663 (64.2)	658 (63.9)	629 (61.1)	3254 (63.0)
Currently smokers	378 (36.4)	388 (37.6)	370 (35.8)	372 (36.1)	400 (38.9)	1908 (37.0)
Pack years history						
Mean	47.1	44.7	46.3	46.1	46.7	46.2
SD	25.2	23.8	27.6	25.1	25.6	25.5
Pre-bronchodilator FEV1 [L]						
Mean	1.209	1.218	1.200	1.208	1.180	1.203
SD	0.505	0.489	0.504	0.473	0.493	0.493
% predicted FEV1 [%]						
Mean	44.056	43.944	43.501	43.836	43.216	43.711
SD	15.291	14.816	15.590	14.758	15.123	15.117
FEV1/FVC [%]						
Mean	43.819	43.896	43.799	43.287	43.851	43.731
SD	11.6	11.7	12.0	11.4	11.6	11.7
Post-bronchodilator FEV1 [L]						
Mean	1.377	1.393	1.370	1.385	1.344	1.374
SD	0.520	0.511	0.521	0.496	0.505	0.511
FEV1 % change from pre-bronchodilator						
Mean	16.3	16.7	16.7	16.8	16.5	16.6
SD	14.5	14.7	14.7	13.6	14.4	14.4

Source: SCS; tables 9, 18, 21; pp 36-37, 48, 51

In trials 1237.5 and 1237.6, approximately 6% and 9% of the U.S. patients were black, respectively. From 1999-2011, the percentage of U.S. COPD patients who were black has ranged from approximately 8-12%¹¹. As such, the percentage of black U.S. COPD patients in these trials was generally reflective of the U.S. COPD population.

11 Ford ES, Croft JB, Mannino DM, et al. COPD Surveillance—United States, 1999-2011. CHEST 2013; 144 (1):284-305.

Baseline demographics for the 6-week cross-over trial 1237.20 (b) (4) summarized in Table 13.

Table 13. Patient demographics for 6-week cross-over trial 1237.20 (b) (4)

	1237.20
Number of patients	219
Sex [N(%)]	
Male	129 (58.9)
Female	61.1 (7.7)
Race [N (%)]	
Asian	2 (0.9)
Black/African American	0
White	217 (99.1)
Age [years]	
Mean	61.1
SD	7.7
Smoking history [N (%)]	
Ex-smoker	82 (37.4)
Currently smokers	137 (62.6)
Pack years history	
Mean	44.4
SD	19.5
Pre-bronchodilator FEV1 [L]	
Mean	1.36
SD	0.47
% predicted FEV1 [%]	
Mean	47.4
SD	13.3
FEV1/FVC [%]	
Mean	45.8
SD	10.8
Post-bronchodilator FEV1 [L]	
Mean	1.55
SD	0.49
FEV1 % change from pre-bronchodilator	
Mean	15.9
SD	12.8

Source: (b) (4)

1237.20 CSR; tables 11.2.1:1, 11.2.4:1, 11.2.4:2; pp.100, 104, 104

(b) (4)

6.1.3 Subject Disposition

In the 52-week trials, a total of 5,163 COPD patients were randomized and 5,162 were treated (Table 14). Approximately 15% of patients across groups discontinued. The most common reason for discontinuation was adverse events.

Table 14. Pooled 52-week trials. Patient disposition

Pooled 52-week trials	Olo 5mcg N(%)	Tio 2.5mcg N(%)	Tio 5mcg N(%)	T+O 2.5/5 N(%)	T+O 5/5 N(%)
Entered/randomized	1038	1032	1034	1030	1029
Not treated	0	0	1	0	0
Treated	1038 (100.0)	1032 (100.0)	1033 (100.0)	1030 (100.0)	1029 (100.0)
Not prematurely discontinued from trial medication	843 (81.2)	857 (83.0)	865 (83.7)	907 (88.1)	896 (87.1)
Prematurely discontinued from trial medication	195 (18.8)	175 (17.0)	168 (16.3)	123 (11.9)	133 (12.9)
Adverse event	110 (10.6)	94 (9.1)	96 (9.3)	63 (6.1)	78 (7.6)
Worsening of disease under study	46 (4.4)	45 (4.4)	42 (4.1)	12 (1.2)	26 (2.5)
Worsening of other pre-existing disease	8 (0.8)	9 (0.9)	3 (0.3)	4 (0.4)	8 (0.8)
Other adverse event	56 (5.4)	40 (3.9)	51 (4.9)	47 (4.6)	44 (4.3)
Non-compliant with protocol	11 (1.1)	14 (1.4)	9 (0.9)	10 (1.0)	9 (0.9)
Lost to follow-up	6 (0.6)	10 (1.0)	3 (0.3)	7 (0.7)	1 (0.1)
Consent withdrawn	58 (5.6)	50 (4.8)	51 (4.9)	39 (3.8)	40 (3.9)
Other	10 (1.0)	7 (0.7)	9 (0.9)	4 (0.4)	5 (0.5)

Source: SCS; table 6; pg 32

Between groups, discontinuations were more common in the monoproduct groups compared to the FDC groups. This was driven by “worsening of disease under study,” which may indicate that the FDC groups had a clinically significant effect on COPD compared to the monoproduct groups.

(b) (4)

In (b) (4) 1237.20) approximately 14% of patients discontinued from the trials early, and discontinuations across the treatment periods were similar.

6.1.4 Analysis of Primary Endpoint(s)

Both 52-week trials share the same two spirometric co-primary endpoints, which were trough FEV1 response and FEV1 AUC (0-3hrs) response assessed at week 24 of

treatment. Trough FEV1 was defined as the mean of the FEV1 obtained at 1 hour and 10 minutes prior to daily trial medication. FEV1 AUC (0-3 hours) was defined as area under the curve from 0 to 3 hours post-dose using the trapezoid rule, divided by the time duration. Response for both parameters was defined as change from baseline. Both spirometric co-primary endpoints are appropriate and are commonly used in COPD trials. The trough FEV1 is meant to demonstrate persistence of effect throughout the dosing interval and the FEV1 AUC (0-3 hours) is meant to characterize initial effect. Trough FEV1 response and FEV1 AUC (0-3hours) response at week 24 is summarized in Table 15.

Table 15. Trials 1237.5 and 1237.6. Mean trough FEV1 and FEV1 AUC (0-3hrs) 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

Source: SCE tables 41, 43; pp.92-93

In both trials, based on the pre-specified hierarchal testing sequence, trough FEV1 response and FEV1 AUC (0-3) response for the FDCs were all statistically significantly greater than each of their constituent monoproducts, for which efficacy in terms of bronchodilation has already been demonstrated [see reviews for tiotropium Respimat (NDA 021,936) and olodaterol Respimat (NDA 203,108)]. When comparing the two FDC doses, the difference was not consistently statistically significant, although there was a numerical difference. This is summarized in Table 16.

Table 16. Trials 1237.5 and 1237.6. Difference between T+O and its monoproducts. For trough FEV1 and FEV1 AUC (0-3hrs) at week 24.

Treatment	Trial 1237.5		Trial 1237.6	
	Trough FEV1	FEV1 AUC (0-3)	Trough FEV1	FEV1 AUC (0-3)
Tio+Olo 2.5/5				
Δ from Olo 5	0.058	0.109	0.067	0.121
Δ from Tio 2.5	0.029	0.093	0.062	0.131
Tio+Olo 5/5				
Δ from Olo 5	0.082	0.123	0.088	0.132
Δ from Tio 5	0.071	0.117	0.050	0.103
Δ from Tio+Olo 2.5/5	0.041	0.014 (NS)	0.021 (NS)	0.012 (NS)

Source: SCE tables 42, 44; pp.92 and 94

These results demonstrate that for both trough FEV1 and FEV1 AUC (0-3hours), both Tio and Olo contributed to the treatment effect for T+O.

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. This analysis was only pre-specified as primary endpoint for the European regulatory submission and not for the U.S. submission. When comparing the FDC to its monoproducts, neither FDC dose demonstrated a difference greater than the MCID (-4). Although for the T+O 5/5, the difference when compared to Tio 5mcg and Olo 5mcg was statistically significant [-1.2 points (p=0.0252) and -1.7 points, p=0.0022), respectively]. It is also worth noting that in the development programs for the Olo and Tio, neither individual product demonstrated an improvement compared to placebo of greater than the MCID.

Overall the data for the spirometric primary endpoint demonstrate that both doses of T+O have a significantly greater bronchodilatory effect compared to either monoproduct. As both Olo 5mcg and Tio 5mcg have previously demonstrated efficacy in terms of bronchodilation compared to placebo, data from these spirometric co-primary endpoints are supportive of efficacy.

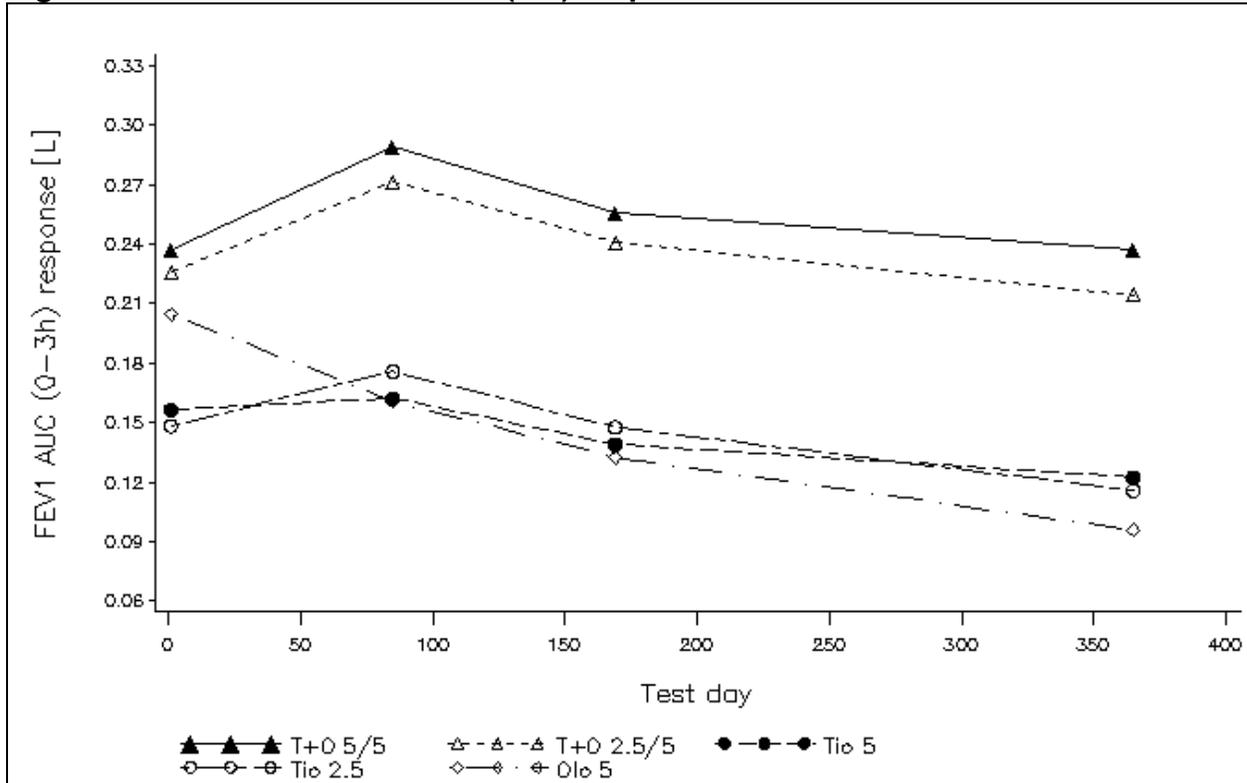
6.1.5 Analysis of Secondary Endpoints(s)

The 52-week trials included the following secondary endpoints for the individual trials:

- FEV1 AUC (0-3 hours) response at day 1, 85 and 365
- Trough FEV1 response [L] on day 15, 43, 85, 169, and 365
- FVC (forced vital capacity) AUC (0-3 hours) response at day 1, 85, 169, and 365
- Trough FVC response [L] at day 15, 43, 85, 170, and 365

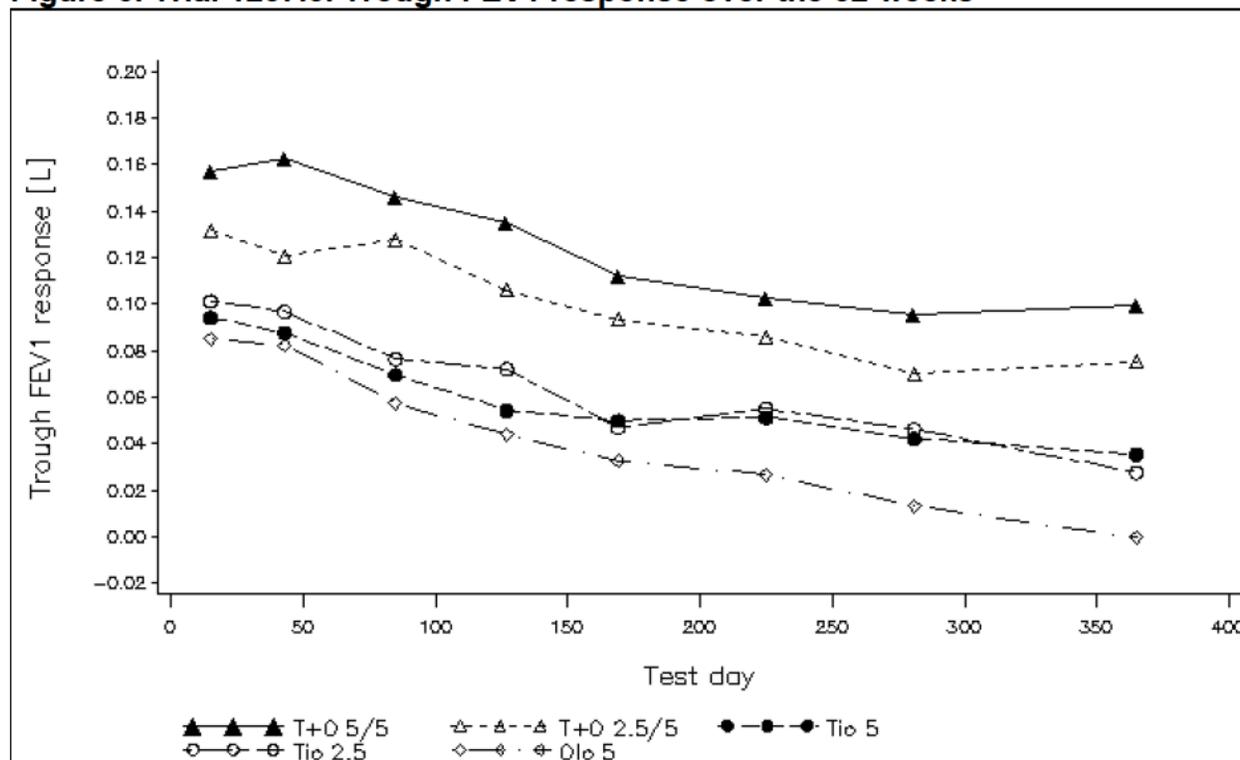
None of these analyses were corrected for multiplicity. General results for the FEV1 related secondary endpoints from trial 1237.5 can be estimated from Figure 5 and Figure 6. Results were similar in trial 1237.6.

Figure 5. Trial 1237.5. FEV1 AUC (0-3) response over 52-weeks



Source: trial 1237.5; figure 11.4.1.2.1:1; pg 106

Figure 6. Trial 1237.5. Trough FEV1 response over the 52-weeks



Source: trial 1237.5; figure 11.4.1.2.1.2; pg 108

These results demonstrated that for both parameters, both of the FDC doses had a larger effect than either of their constituent monoproducts and that this difference was numerically sustained over the treatment period. Additionally, there was also consistent separation between the T+O 2.5/5mcg and 5/5mcg doses at all time-points, which supports the Applicant's proposed dosage (5/5mcg). Results for the analogous FVC endpoints were also similar.

The Applicant also included pre-specified secondary endpoints for the pooled analysis of trials 1237.5 and 1237.6. For the pooled analyses, the secondary endpoints were as follows:

- Transitional Dyspnea Index after 24-weeks of treatment (key secondary)
- FEV1 AUC (0-12 hours) and (0-24 hours) response at day 169 (in the subset of patients with available data)
- FVC AUC (0-12 hours) and (0-24 hours) response at day 169 (in the subset of patients with available data)
- SGRQ total score on day 85 and 365
- TDI focal score on day 43, 85, and 365.

(b) (4)

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(b) (4)

For FEV1 AUC (0-12) at day 169, the results demonstrated that both doses of the FDC had larger treatment effects compared to their constituent monoproducts with nominal statistical significance. This is consistent with the results from the co-primary endpoints. The higher FDC dose demonstrated a larger treatment effect compared to the lower dose (nominally statistically significant).

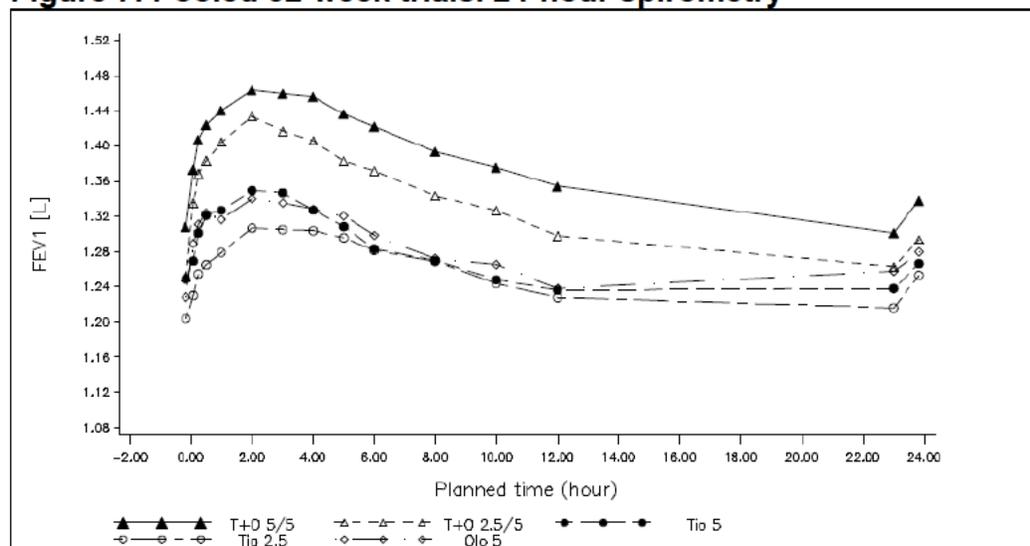
Table 17. Trials 1237.5 and 1237.6 Pooled analysis. FEV1 AUC (0-12) at day 169

Comparison	Treatment Difference		
	Adjusted Mean (SE)	p-value*	(95% CI)
T+O 5/5 – Olo 5	0.118 (0.022)	<.0001	(0.074, 0.162)
T+O 5/5 – Tio 5	0.123 (0.023)	<.0001	(0.077, 0.169)
T+O 2.5/5 – Olo 5	0.071 (0.022)	0.0012	(0.028, 0.114)
T+O 2.5/5 – Tio 2.5	0.094 (0.022)	<.0001	(0.050, 0.137)
T+O 2.5/5 – Tio 5	0.076 (0.023)	0.0010	(0.031, 0.121)
T+O 5/5 – T+O 2.5/5	0.047 (0.023)	0.0384	(0.003, 0.092)

*not adjusted for multiplicity
 Source: SCE table 46; pg 96

FEV1 AUC (0-24) as defined by the Applicant only differed from FEV1 AUC (0-12) by the addition of two post-dose time points (23:00 and 23:50) which corresponded to trough FEV1. These results were consistent with the FEV1 AUC (0-12) results and are summarized in Figure 7. It is also worth noting that there was clear dose separation between the T+O 2.5/5 and 5/5 doses, which supports the proposed dosing.

Figure 7. Pooled 52-week trials. 24-hour spirometry



Source: SCE; figure 5; pg95

For SGRQ at day 85 and 365, the data were consistent the primary endpoint for the pooled analysis. Neither dose of the FDC demonstrated an improvement of greater than the MCID compared to its monoproducts.

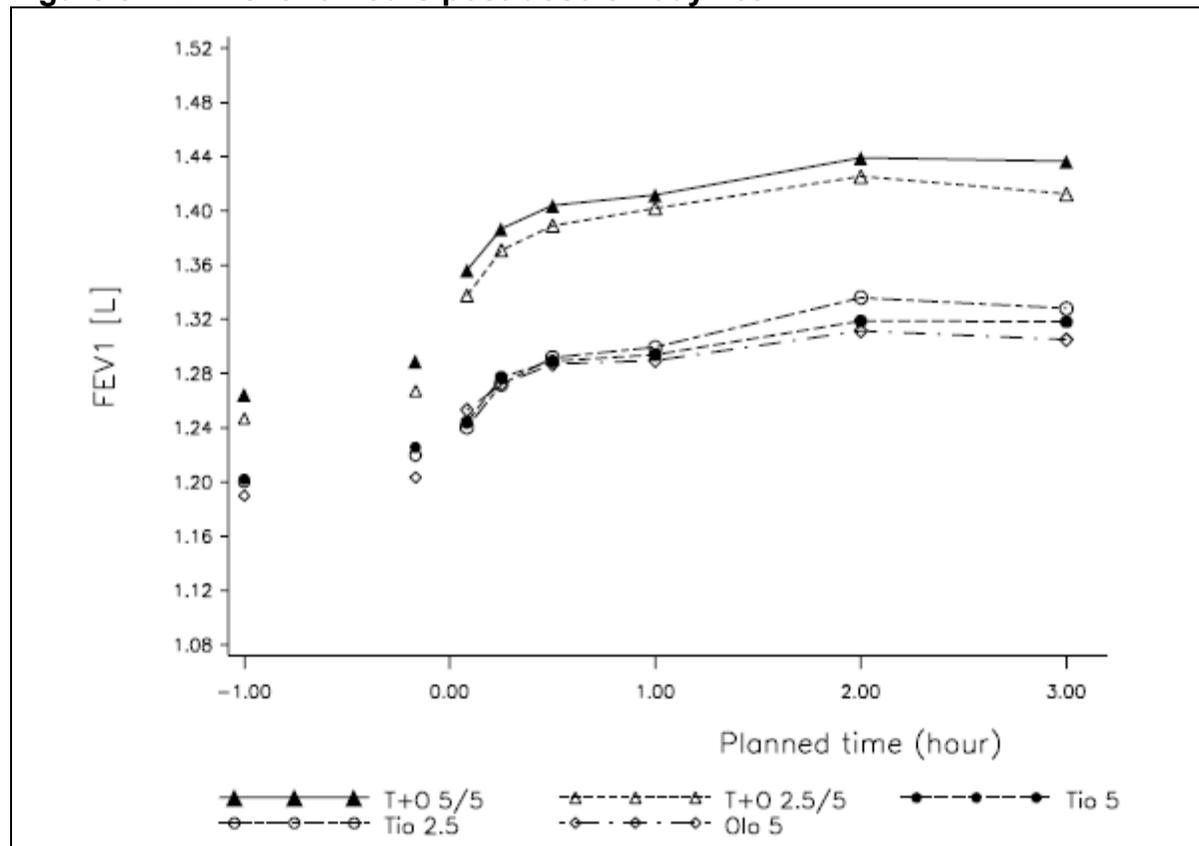
Although none of the comparisons for the secondary endpoints corrected for multiplicity, the results for the spirometric endpoints were consistent with the primary endpoints demonstrating that patients treated with either dose of the FDC had greater improvement in FEV1 related parameters compared to patients treated with the corresponding monoproducts. Additionally, the higher FDC dose (5/5mcg) also appeared to offer a numerically larger treatment effect compared to the lower dose. No clinically significant effects in terms of SGRQ were observed.

6.1.6 Other Endpoints

The 52-week trials included multiple other endpoints for the analysis of the individual trials, as well as the pooled data. Note that none of these analyses corrected for multiplicity, as such, the analyses can only be considered descriptive. Included endpoints were related to spirometric assessments, peak flows, rescue medication use, COPD exacerbations, SGRQ, and TDI.

The spirometric endpoints included trough FEV1 response and FEV1 AUC (0-3hrs) response at various time points through-out the treatment period. For trial 1237.5, these time-points were included in Figure 6 and Figure 5. Similar results were seen for trial 1237.6. Results for the analogous FVC related endpoints were generally consistent with the FEV1 results. Other spirometric endpoints included FEV1 on Day 1, Day 85, Day 169, and Day 365 at 5, 15, and 30 min, and 1, 2, 3 h after inhalation of study medication. The results at day 169 for trial 1237.5 are summarized in Figure 8.

Figure 8. FEV1 over 3-hours post-dose on day 169



Source: trial 1237.5 CSR; 15.2.1.4:2; pg298

At day 365, similar trends were seen, with separation between the FDC doses and the monoproducts. Generally, similar results were also seen for the analogous FVC related endpoints. Overall these spirometric data suggest that the FDC has a greater spirometric effect compared to its constituent monoproducts. This is consistent with the primary endpoint.

Morning and even peak flows were also included as additional endpoints. In general, morning and evening peak flows averaged weekly were higher in the FDC groups compared to the monoproducts (data not shown). This is consistent with the spirometric endpoints.

Rescue medication use was also lower in the FDC groups compared to their monoproducts. With regard to SGRQ related endpoints, the differences between groups was less than the MCID of 4 when comparing the FDC to their constituent monoproducts.

Exacerbation related endpoints were analyzed only in the pooled data. 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/patient year. These results are summarized in Table 18 and Table 19. It should be noted that the approved Olo 5mcg monoproduct does not carry an exacerbation indication, however, the approved Tio 5mcg monoproduct does.

Table 18. Trials 1237.5 and 1237.6 Pooled analysis for time to first COPD exacerbations

Parameter	Comparison	Hazard Ratio	(95% CI)
Time to first COPD exacerbation	T+O 5/5 – Olo 5	0.8553	(0.6937, 1.0545)
	T+O 5/5 – Tio 5	0.8347	(0.6789, 1.0264)
	T+O 2.5/5 – Olo 5	0.8581	(0.6959, 1.0579)
	T+O 2.5/5 – Tio 2.5	0.8011	(0.6518, 0.9846)
Time to first moderate/severe COPD exacerbation	T+O 5/5 – Olo 5	0.8664	(0.6984, 1.0748)
	T+O 5/5 – Tio 5	0.8112	(0.6567, 1.0021)
	T+O 2.5/5 – Olo 5	0.8845	(0.7137, 1.0962)
	T+O 2.5/5 – Tio 2.5	0.8224	(0.6659, 1.0157)

Source: trial 1237.9991 CSR; table 15.2.8:6; pg 694

Table 19. Trials 1237.5 and 1237.6 Pooled analysis rate of COPD exacerbations

Parameter	Comparison	Rate Ratio	(95% CI)
Rate of any COPD exacerbation	T+O 5/5 – Olo 5	0.8752	(0.7082, 1.0817)
	T+O 5/5 – Tio 5	0.8637	(0.7018, 1.0630)
	T+O 2.5/5 – Olo 5	0.8219	(0.6631, 1.0186)
	T+O 2.5/5 – Tio 2.5	0.8035	(0.6496, 0.9939)
	T+O 5/5 – T+O 2.5/5	1.0650	(0.8601, 1.3185)
Rate of Moderate/severe COPD exacerbation	T+O 5/5 – Olo 5	0.8887	(0.7147, 1.1051)
	T+O 5/5 – Tio 5	0.8581	(0.6935, 1.0618)
	T+O 2.5/5 – Olo 5	0.8173	(0.6549, 1.0200)
	T+O 2.5/5 – Tio 2.5	0.8060	(0.6469, 1.0042)
	T+O 5/5 – T+O 2.5/5	1.0874	(0.8725, 1.3552)

Source: trial 1237.9991 CSR; table 15.2.8:8; pg 697

For these exacerbation endpoints, there were no statistical differences when comparing the FDC to their monoproducts, except when comparing T+O 2.5/5 to Tio 2.5. These data do not support an additional benefit of the FDC over the monoproducts in terms of exacerbations.

6.1.7 Subpopulations

The sponsor performed multiple subgroup analyses using the co-primary endpoints of FEV1 AUC (0-3 hours) and trough FEV1, as well as SGRQ for trials 1237.5 and 1237.6 (pooled). The subgroups were based on demographic and baseline parameters. With regard to baseline demographic parameters, there were no significant differences between subgroups when comparing the FDC to its constituent monoproducts. There were also no differences based on background pulmonary medication use, nor differences based on age ≥65 years. There were also no statistically significant

differences in treatment effect based on baseline respiratory parameters in terms of the spirometric measures. However, for SGRQ, patients with worse disease and/or lower baseline FEV1 had a larger SGRQ response.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This NDA proposes to market a single dose of the T+O FDC at 5/5mcg once daily. Both monoproduct programs included comprehensive dose ranging trials and both tiotropium and olodaterol Respimat are approved at 5mcg once daily. In the 52-week trials, BI explored two doses of T+O (2.5/5mcg and 5/5mcg). In these trials, the 5/5mcg dose had a numerically larger benefit in terms of the primary endpoints compared to the 2.5/5mcg dose. Additionally, the 24-hour spirometry data at week 24 as well the spirometry data throughout the treatment period demonstrated clear dose separation between the two doses. As such, the proposed dose of 5/5mcg once daily is appropriate.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

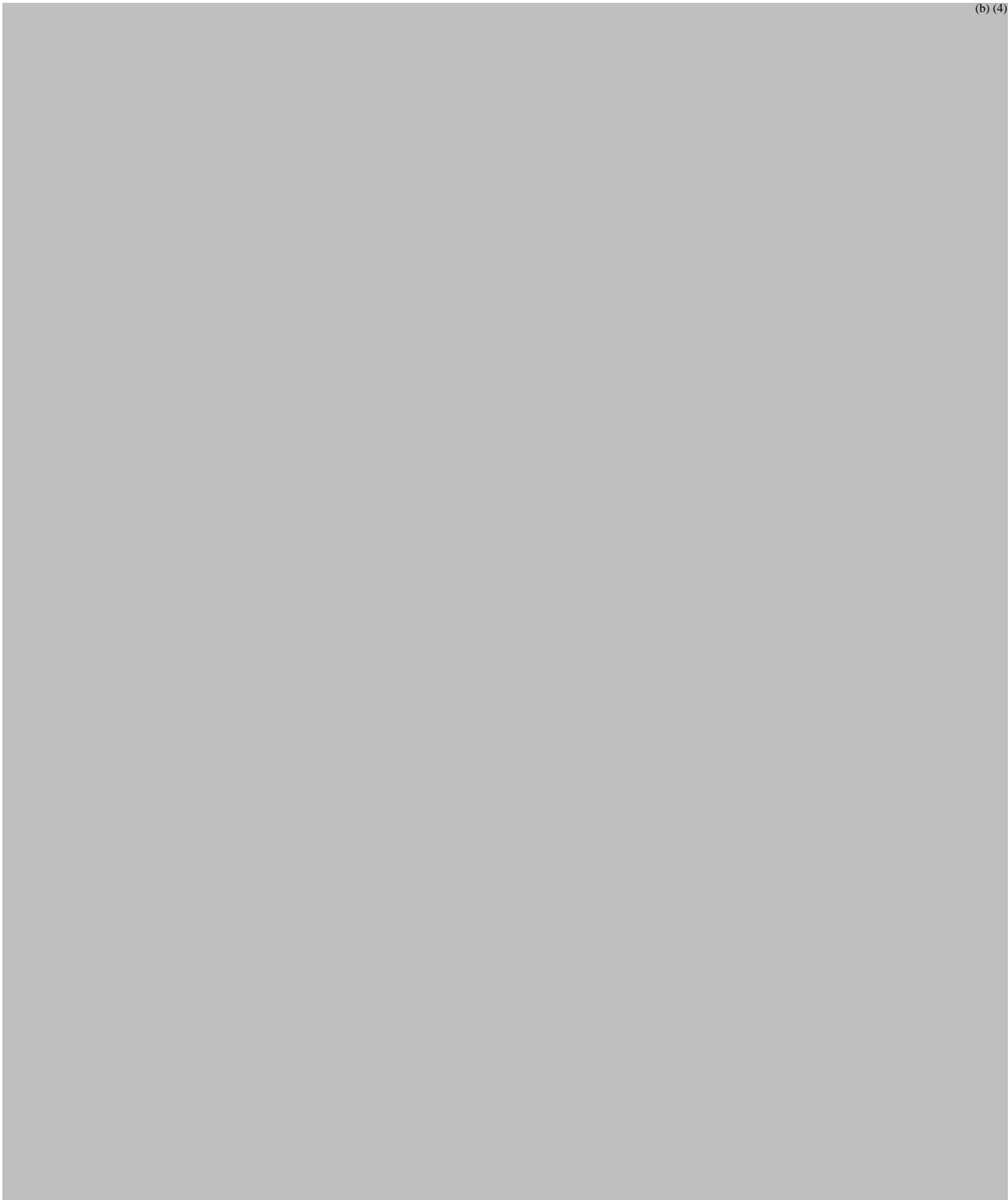
For the 52 week treatment period, T+O 5/5mcg demonstrated a larger treatment compared to its monoproducts and the lower FDC dose (2.5/5mcg) (Figure 5 and Figure 6) and remained effective.

6.1.10 Additional Efficacy Issues/Analyses

Included in this submission (b) (4) one 24-hour spirometry trial. These will be discussed here.

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(b) (4)



24 hour spirometry

Trial 1237.20 was meant to characterize the treatment effect of T+O over the 24 hour dosing interval. The primary endpoint of this trial was FEV1 AUC (0-24hrs) after 6-

weeks of treatment. The key secondary endpoints were FEV1 AUC (0-12 hours) response and FEV1 AUC (12-24 hours) response following a 6-week treatment period. For the primary and key secondary endpoints, both FDC dose groups demonstrated statistically significant improvement compared to placebo and their constituent monoproducts. The monoproduct groups also demonstrated improvement compared to placebo for the primary and key-secondary endpoints (although this analysis was considered descriptive as this comparison was not pre-specified). These results are summarized in Table 23, Table 24, and Figure 9.

Table 23. Trial 1237.20. Primary endpoint. FEV1 AUC (0-24) after 6-weeks of treatment

	Treatment difference FEV1 AUC (0-24)		
Comparison	Adjusted mean	95% CI	p-value
T+O 5/5 - Placebo	0.280 (0.014)	0.252, 0.309	<0.0001
T+O 5/5 - Olo 5	0.115 (0.014)	0.087, 0.143	<0.0001
T+O 5/5 - Tio 5	0.110 (0.014)	0.082, 0.139	<0.0001
T+O 2.5/5 - Placebo	0.277 (0.015)	0.249, 0.306	<0.0001
T+O 2.5/5 - Olo 5	0.111 (0.014)	0.083, 0.140	<0.0001
T+O 2.5/5 - Tio 2.5	0.124 (0.014)	0.096, 0.152	<0.0001
Olo 5- placebo	0.166 (0.015)	0.137, 0.194	<0.0001 ^a
Tio 2.5- placebo	0.153 (0.15)	0.125, 0.182	<0.0001 ^a
Tio 5 - placebo	0.170 (0.014)	0.141, 0.198	<0.0001 ^a

^a nominal p-value because not pre-specified comparison

Source: trial 1237.20 CSR; table 11.4.1.1.1:2; pg 108

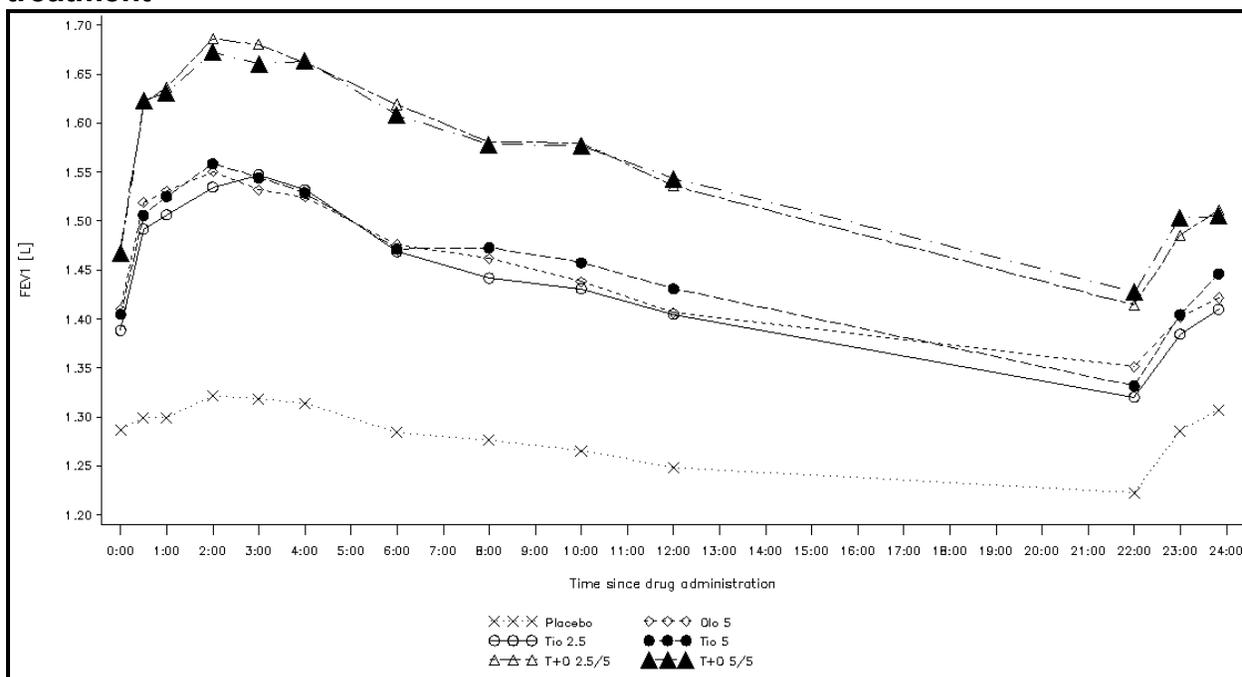
Table 24. Trial 1237.20. Key Secondary endpoints. FEV1 AUC (0-12) and (12-24) after 6-weeks of treatment

	Treatment difference		
	Adjusted mean	95% CI	p-value
FEV1 AUC (0-12)			
Comparison			
T+O 5/5 - Placebo	0.319 (0.015)	0.289, 0.349	<0.0001
T+O 5/5 - Olo 5	0.126 (0.015)	0.096, 0.156	<0.0001
T+O 5/5 - Tio 5	0.119 (0.015)	0.089, 0.149	<0.0001
T+O 2.5/5 - Placebo	0.323 (0.015)	0.293, 0.354	<0.0001
T+O 2.5/5 - Olo 5	0.131 (0.015)	0.101, 0.161	<0.0001
T+O 2.5/5 - Tio 2.5	0.139 (0.015)	0.109, 0.169	<0.0001
Olo 5- placebo	0.193 (0.015)	0.162, 0.223	<0.0001 ^a
Tio 2.5- placebo	0.185 (0.185)	0.154, 0.215	<0.0001 ^a
Tio 5 – placebo	0.200 (0.015)	0.169, 0.230	<0.0001 ^a
FEV1 AUC (12-24)			
Comparison			
T+O 5/5 - Placebo	0.243 (0.015)	0.212, 0.273	<0.0001
T+O 5/5 - Olo 5	0.103 (0.015)	0.074, 0.133	<0.0001
T+O 5/5 - Tio 5	0.102 (0.015)	0.072, 0.132	<0.0001
T+O 2.5/5 - Placebo	0.232 (0.015)	0.201, 0.262	<0.0001
T+O 2.5/5 - Olo 5	0.093 (0.015)	0.063, 0.123	<0.0001
T+O 2.5/5 - Tio 2.5	0.110 (0.015)	0.080, 0.140	<0.0001
Olo 5- placebo	0.139 (0.15)	0.109, 0.169	<0.0001 ^a
Tio 2.5- placebo	0.141 (0.015)	0.111, 0.171	<0.0001 ^a
Tio 5 – placebo	0.122 (0.015)	0.092, 0.152	<0.0001 ^a

^a nominal p-value because not pre-specified comparison

Source: trial 1237.20 CSR; table 11.4.1.2.1:2; pg 111

Figure 9. Trial 1237.20. FEV1 over the 24-hour post-dosing period after 6-weeks of treatment



Source: trial 1237.20 CSR; figure 11.4.1:1; pg 106

These data are generally consistent with the FEV1 AUC (0-12 hour) and (0-24 hour) data from the 52-week pivotal trials, as well as data from the monoproduct development programs. Overall, data from this trial demonstrate that the FDC demonstrates an added benefit above each of the constituent monoproducts. However, it is worth noting that compared to the serial spirometry taken at week 24 from the 52-week trials, in trial 1237.20, there is no clear dose separation. This may be related to the shorter duration of this trial. As such, 24-hour data from the 52-week trials may be more representative of chronic use.

7 Review of Safety

Safety Summary

The safety information for T+O comes primarily from the 52-week COPD trials. The 52-week trials included a total of 5162 patients. Of these, 1029 received T+O 5/5mcg and 1030 received T+O 2.5/5mcg. While there was no placebo comparison, as the safety of both Tio 5mcg and Olo 5mcg have previously been established (see NDA 203108 and 021936), comparisons of the FDC to their constituent monoproduct was sufficient to evaluate safety. The percentages of patients who died were fairly similar across treatment groups and when comparing both FDC doses to their respective monoproducts. The observed causes of death were consistent with the trial population. The most common cause of death was COPD. This was true for the adjudicated and

non-adjudicated analysis of death. Non-fatal serious adverse events (SAE) were also generally similar between treatment groups. The types of SAEs were fairly typical for the study population. An adjudicated analysis of SAEs was also performed to determine if hospitalizations, intubations, and deaths were respiratory-, cardiovascular-, cerebrovascular-, or other- related. Overall, this analysis did not demonstrate any large differences between treatment groups or when comparing either FDC dose to its monoproduct. An analysis of major cardiac events (MACE) was also conducted. This analysis demonstrated no imbalances. The sponsor's MACE analysis was also complemented by a cardiovascular assessment based on grouped terms [Standard MedDRA Queries (SMQs) and Applicant defined groupings]. The percentage of patients with events were generally similar across treatment groups and when comparing the FDC doses to their constituent monotherapy products.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety information for T+O comes primarily from the 52-week COPD trials (1237.5 and 1237.6). As the 52-week trials did not include a placebo arm, this safety analysis relies on previous findings of safety for olodaterol and tiotropium Respimat monoproducts (see NDA 203108 and 021936). Pooled safety data from these trials were reviewed in depth and are presented in this section. (b) (4)



7.1.2 Categorization of Adverse Events

Adverse events (AE) were defined as any untoward medical occurrence, including the worsening of a pre-existing condition that occurred in conjunction with the use of trial drug. Serious AEs were defined as AEs that resulted in death, were immediately life-threatening, required hospitalization/prolongation of hospitalization, resulted in persistent or significant disability/incapacity, or were congenital birth defects. All verbatim terms reported by the investigator were coded using MedDRA version 16.1 for the Integrated Summary of Safety (ISS). The sponsor also grouped AEs based on Standardized MedDRA Queries (SMQ) (MedDRA 16.1) and BI defined pharmacovigilance (PV) endpoints.

The Applicant defined PV endpoints were created by grouping multiple MedDRA PTs by similar concepts, that did not necessarily correspond to SOCs or high level grouping terms (HLGTs). The PTs included in the PV endpoints were reviewed and were reasonable. Definitions are available in the SCS supplement (listing 2.11.1)

Major adverse cardiovascular event (MACE) analysis was also performed. MACE events were defined as fatal events in the cardiac disorder and vascular disorder SOCs; any events in the SMQ Ischemic heart disease sub-SMQ myocardial infarction (broad) and stroke PV; the PTs sudden death, cardiac death, and sudden cardiac death.

An adjudicated analysis of SAEs were also performed by an external adjudication committee. The adjudication committee (AC) assessed all SAEs and determined if any of the deaths, hospitalizations, and intubations (composite endpoint) were respiratory-related, cardiovascular related, cerebrovascular related, or other event related. If the event was adjudicated to be respiratory related, the event was further sub-classified as COPD or pneumonia related.

Studies included in the adjudicated SAE analysis had treatment durations of ≥ 7 day and met the following criteria:

- All blinded, parallel-arm, randomized, controlled trials that were conducted with T+O FDC or free combination for the treatment of COPD
- All randomized, double-blind cross-over trials. Only the first crossover period and the washout period immediately following the first part of the crossover period of the trials were assessed.

Three populations were used in the adjudicated analysis. They were as follows:

- All-treated COPD safety population I- primary analysis: patients who took at least one dose of trial medication in the two 52-week trials
- All-treated COPD safety population I- supportive analysis: patients who took at least one dose of trial medication any of the COPD trials
- All-treated COPD safety population II- supportive analysis: patients who took at least one dose of trial medication in one of the four placebo controlled trials.

As deaths, SAEs and hospitalization are not common events and are more likely to occur in longer duration trials, only the all-treated COPD safety population I – primary analysis will be discussed in this review. Results for the supportive analysis populations were similar to the primary analysis population demonstrating no large differences between treatment groups or when comparing the FDC doses to their constituent monoproducts.

Cause of death was also adjudicated by a separate independent mortality adjudication committee (MAC).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

For this application, evidence for safety is primarily derived from pooled data from the 52-week COPD trials (1237.5 and 1237.6). Safety data from these trials will be reviewed in depth in this section.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall the size of the database was adequate for this application. In the phase 3 trials, a total of 3497 patients were exposed T+O. Of these, 1757 received T+O 5/5mcg once daily and 1740 at 2.5/5mcg once daily.

A total of 5162 patients were included in the 52-week trials. Of these patients, 2059 patients were exposed to T+O at 2.5/5mcg or 5/5mcg. The extent of exposure for the 52-weeks trials was similar between treatment groups, with the lowest mean exposure time occurring in the Olo 5mcg group and the highest in the T+O 2.5/5mcg group. Mean exposure across all treatment groups was similar and ranged from 326-344 days. Exposure data for the 52- week trials is summarized in Table 25.

Table 25. 52-week trials (1237.5 and 1237.6). Extent of Exposure

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg	Total
N	1038	1032	1033	1030	1029	5162
Extent of Exposure (days)						
Mean	326.3	330.3	331.8	343.5	340.0	334.4
SD	96.6	92.5	91.3	73.2	79.6	87.3
Minimum	1	1	1	1	1	1
Median	365	365	365	365	365	365
Maximum	411	426	421	418	438	438
Extent of exposure [N(%)]						
≤ 14 days	13 (1.3)	14 (1.4)	10 (1.0)	6 (0.6)	6 (0.6)	49 (0.9)
15 - 42 days	18 (1.7)	20 (1.9)	20 (1.9)	10 (1.0)	15 (1.5)	83 (1.6)
43 - 84 days	38 (3.7)	19 (1.8)	30 (2.9)	15 (1.5)	20 (1.9)	122 (2.4)
85 - 126 days	29 (2.8)	32 (3.1)	23 (2.2)	16 (1.6)	15 (1.5)	115 (2.2)
127 - 168 days	28 (2.7)	15 (1.5)	20 (1.9)	14 (1.4)	13 (1.3)	90 (1.7)
169 - 224 days	13 (1.3)	29 (2.8)	18 (1.7)	22 (2.1)	33 (3.2)	115 (2.2)
225 - 280 days	21 (2.0)	22 (2.1)	18 (1.7)	20 (1.9)	14 (1.4)	95 (1.8)
281 - 364 days	90 (8.7)	82 (7.9)	75 (7.3)	68 (6.6)	78 (7.6)	393 (7.6)
≥ 365	788 (75.9)	799 (77.4)	819 (79.3)	859 (83.4)	835 (81.1)	4100 (79.4)

Source: SCS table 3; pg28

7.2.2 Explorations for Dose Response

The phase 3 trials evaluated two doses of T+O (2.5/5 and 5/5) to allow for an analysis of dose related safety. These analyses are embedded throughout this review of safety.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Clinical laboratory testing was performed as per tables in the individual trials reviewed in section 5.3.

7.2.5 Metabolic, Clearance, and Interaction Workup

In the olodaterol and tiotropium Respimat monoproduct development programs studies examining drug metabolism, clearance, and potential for interaction were performed by the Applicant.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The pivotal trials incorporated monitoring for toxicities associated with LABAs and anticholinergics, by evaluating for specific AEs/pharmacovigilance(PV) endpoints/standard MedDRA queries (SMQs), and monitoring laboratory, vital sign, and ECG parameters for adrenergic/anticholinergic cardiac and metabolic effects

7.3 Major Safety Results

As there was no placebo comparison, the assessment of safety is based on the comparison of events in the T+O group to its constituent monotherapy products. This comparison relies on the already established safety of tiotropium Respimat and olodaterol Respimat which were approved under the tradenames Spiriva Respimat and Striverdi Respimat, respectively.

7.3.1 Deaths

In the 52-week trials, deaths were grouped into 3 categories; on treatment, post-treatment, and post-study. On-treatment was defined as events with onset any time after the first dose of trial medication until 21 days after the last dose. Post-treatment was defined as events with onset greater than 21 days after last dose until trial completion date (52-weeks, 365 days). Post-study was subdivided into two categories: within vital status follow-up and outside of vital status follow-up. Post-study within vital status follow-up was defined as events with onset after trial completion (day 365), but within the vital status period (day 386). Post-study outside of vital status follow-up included was defined as events that occurred after day 386.

In the 52-week COPD trials there were a total of 75 deaths during the on-treatment period. The system organ class (SOC) 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 by preferred term (PT) were COPD (0.2%), cardiac arrest (0.1%), and death (0.1%). When comparing causes of death by SOC or PT, events were generally similar between

treatment groups. No clear dose responses were observed. These data are summarized in Table 26.

Table 26. Pooled 52-week trials. On-treatment deaths (up to 21-days after last treatment)

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg	Total
Number of patients	1038	1032	1033	1030	1029	5162
Deaths	14 (1.3)	12 (1.2)	17 (1.6)	14 (1.4)	18 (1.7)	75 (1.5)
Cardiac disorders	4 (0.4)	4 (0.4)	3 (0.3)	5 (0.5)	3 (0.3)	19 (0.4)
Cardiac arrest	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.2)	1 (0.1)	5 (0.1)
Cardiac failure	1 (0.1)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.1)
Cardio-respiratory arrest	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	3 (0.1)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Arteriosclerosis coronary artery	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Cardiac failure acute	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.0)
Cardiopulmonary failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Myocardial ischaemia	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Ventricular fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.0)
Gastrointestinal disorders	1 (0.1)	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	4 (0.1)
Hematemesis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Ileus	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Pancreatitis acute	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.0)
General disorders and administration site conditions	2 (0.2)	1 (0.1)	5 (0.5)	1 (0.1)	3 (0.3)	12 (0.2)
Death	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	5 (0.1)
Multi-organ failure	1 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	3 (0.1)
Drowning	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Generalized oedema	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Sudden death	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.0)
Infections and infestations	0 (0.0)	1 (0.1)	2 (0.2)	2 (0.2)	1 (0.1)	6 (0.1)
Pneumonia	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	3 (0.1)
Biliary sepsis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Lung infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Sepsis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Septic Shock	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	2 (0.0)
Neoplasms benign, malignant and unspecified	1 (0.1)	2 (0.2)	7 (0.7)	3 (0.3)	4 (0.4)	17 (0.3)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	4 (0.1)
Brain neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Bronchial carcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Glioblastoma multiforme	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Lung cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Metastases to bone	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Metastases to central nervous	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.0)
Oesophageal carcinoma	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.0)
Pancreatic carcinoma	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Prostate cancer	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Prostate cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Renal cancer	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)

Small cell lung cancer	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.0)
Nervous system disorders	2 (0.2)	1 (0.1)	2 (0.2)	0 (0.0)	1 (0.1)	6 (0.1)
Amyotrophic lateral sclerosis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Cerebral hemorrhage	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Cerebral infarction	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Cerebrovascular accident	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Hemorrhage intracranial	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Hemorrhagic stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Psychiatric Disorders	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Delirium	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Renal failure	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Respiratory, thoracic and mediastinal disorders	2 (0.2)	4 (0.4)	6 (0.6)	4 (0.4)	4 (0.4)	20 (0.4)
COPD	2 (0.2)	2 (0.2)	4 (0.4)	1 (0.1)	1 (0.1)	10 (0.2)
Respiratory failure	0 (0.0)	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	4 (0.1)
Acute respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Dyspnea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
Pulmonary mass	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.0)
Pulmonary edema	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.0)
Vascular disorders	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	4 (0.1)
Aortic aneurysm rupture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Hypertensive crisis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Hypotension	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Peripheral vascular disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Shock	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

Source: SCS supplement; table 2.4.3; pp1085-1087

Following the on-treatment period, there were an additional 23 deaths. Of these, 9 occurred during the post-treatment period and 14 during the post-study period. Of the events in the post-study period, 11 occurred during the planned observation period (up to day 386). These additional deaths did not result in any new mortality imbalances between treatment groups based on SOC and preferred term. However, during the post-treatment period, there were more deaths reported in the Tio 5mcg group compared to all other groups. For the Olo 5mcg, Tio 2.5mcg, Tio 5mcg, T+O 2.5/5mcg, and T+O 5/5mcg, when combining all periods, there were a total of 18 (1.7%), 16 (1.6%), 23 (2.2%), 18 (1.7%), and 21 (2.0%) deaths, respectively. In terms of deaths, for both FDC doses, deaths occurred in a similar/lower percentage of patients compared their monoproducts.

All deaths were also reviewed by a mortality adjudication committee (MAC). Not surprisingly there was some disagreement between cause of death assigned by MAC versus investigator. In general, where there were disagreements, the investigator tended to assign cause of death to the terminal cause, whereas the MAC assigned based on root cause (e.g. multi-organ failure versus COPD). Despite some disagreements, overall, the MAC analysis was consistent with primary analysis of death in that large imbalances in deaths were not identified when comparing treatment

groups. As with the non-adjudicated analysis, the most common cause of death was COPD. The second most common was sudden cardiac death. For both, numbers were similar between treatment groups. In general, based on preferred term, for both doses of the FDC, causes of death were similar to their constituent monoproducts. Adjudicated causes of death during the combined on-treatment, post-treatment, and post-study period are summarized in Table 27.

Table 27. Poole 52-week trials. Adjudicated deaths (on-treatment, post-treatment, post-study)

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg	Total
Number of patients	1038	1032	1033	1030	1029	5162
Total Deaths	18 (1.7)	16 (1.6)	23 (2.2)	18 (1.7)	21 (2)	96 (1.9)
COPD	3 (0.3)	3 (0.3)	4 (0.4)	3 (0.3)	6 (0.6)	19 (0.4)
Sudden cardiac death	2 (0.2)	2 (0.2)	3 (0.3)	5 (0.5)	3 (0.3)	15 (0.3)
Lung neoplasm malignant	1 (0.1)	1 (0.1)	5 (0.5)	3 (0.3)	4 (0.4)	14 (0.3)
Death	1 (0.1)	2 (0.2)	4 (0.4)	0	1 (0.1)	8 (0.2)
Sudden death	2 (0.2)	1 (0.1)	0	0	2 (0.2)	5 (0.1)
Esophageal cancer	1 (0.1)	0	0	2 (0.2)	0	3 (0.1)
Cerebrovascular accident	2 (0.2)	1 (0.1)	0	0	0	3 (0.1)
Pneumonia	0	1 (0.1)	1 (0.1)	1 (0.1)	0	3 (0.1)
Injury	0	1 (0.1)	2 (0.2)	0	0	3 (0.1)
Myocardial Infarction	1 (0.1)	0	0	1 (0.1)	0	2 (0)
Peripheral vascular disorder	0	1 (0.1)	1 (0.1)	(0)	0	2 (0)
Pancreatitis acute	0	1 (0.1)	0	1 (0.1)	0	2 (0)
Cerebral Hemorrhage	1 (0.1)	0	0	0	0	1 (0)
Cardiac failure	1 (0.1)	0	0	0	0	1 (0)
Crohns Disease	1 (0.1)	0	0	0	0	1 (0)
Lung adenocarcinoma metastatic	0	0	1 (0.1)	0	0	1 (0)
Glioblastoma	0	0	0	1 (0.1)	0	1 (0)
Renal cancer	0	0	1 (0.1)	0	0	1 (0)
Brain neoplasm	0	0	0	0	1 (0.1)	1 (0)
Prostate cancer	0	0	0	0	1 (0.1)	1 (0)
Neoplasm malignant	1 (0.1)	0	0	0	0	1 (0)
GI hemorrhage	0	1 (0.1)	0	0	0	1 (0)
Duodenal ulcer perforation	1 (0.1)	0	0	0	0	1 (0)
Pancreatic carcinoma	0	1 (0.1)	0	0	0	1 (0)
Amyotrophic lateral sclerosis	0	0	1 (0.1)	0	0	1 (0)
Peripheral vascular thrombosis	0	0	0	0	1 (0.1)	1 (0)
Drowning	0	0	0	0	1 (0.1)	1 (0)
Aortic aneurysm	0	0	0	0	1 (0.1)	1 (0)
Renal failure	0	0	0	1 (0.1)	0	1 (0)

Source: SCS; tables 35 and 36; pp81-85 and 86-87

7.3.2 Nonfatal Serious Adverse Events

In the 52-week trials, there were 798 (15.5%) patients with on-treatment SAEs. These were balanced across groups. SAEs were most commonly reported in the respiratory, thoracic, and mediastinal SOC (6.7%); followed by the infections and infestations SOC (2.8%). The most common SAEs by preferred term were by far COPD (5.7%) and pneumonia (1.3%). For the cardiac SOC; respiratory, thoracic, and mediastinal SOC; and general disorders and site administration SOC; SAEs were slightly more frequent in the T+O 5/5mcg group compared to both its monoproducts, however, the differences were relatively small based on both percent and total number. This observation is likely related to chance. Cardiac and respiratory related adverse events are discussed in more depth in section 7.3.5 Submission Specific Primary Safety Concerns. Otherwise, non-fatal SAEs were similar when comparing the FDC doses to their monotherapy components. Non-fatal adverse events are summarized in Table 28.

Table 28. Pooled 52-week trials. Non-fatal serious adverse events that occurred in ≥2 patients (on-treatment)

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg	Total
Number of patients	1038	1032	1033	1030	1029	5162
Total with non-fatal serious adverse events	172 (16.6)	148 (14.3)	161 (15.6)	158 (15.3)	159 (15.5)	798 (15.5)
Blood and lymphatic system disorders	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)	1 (0.1)	9 (0.2)
Cardiac disorders	15 (1.4)	13 (1.3)	17 (1.6)	12 (1.2)	20 (1.9)	77 (1.5)
Acute myocardial infarction	3 (0.3)	2 (0.2)	0 (0.0)	1 (0.1)	4 (0.4)	10 (0.2)
Angina pectoris	4 (0.4)	1 (0.1)	1 (0.1)	0 (0.0)	4 (0.4)	10 (0.2)
Atrial fibrillation	3 (0.3)	2 (0.2)	3 (0.3)	2 (0.2)	1 (0.1)	11 (0.2)
Coronary artery disease	2 (0.2)	1 (0.1)	5 (0.5)	1 (0.1)	3 (0.3)	12 (0.2)
Myocardial infarction	1 (0.1)	0 (0.0)	2 (0.2)	3 (0.3)	3 (0.3)	9 (0.2)
Angina unstable	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	3 (0.1)
Cardiac failure	1 (0.1)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	4 (0.1)
Cardiac failure congestive	1 (0.1)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.1)
Myocardial ischemia	0 (0.0)	0 (0.0)	3 (0.3)	1 (0.1)	0 (0.0)	4 (0.1)
Ear and labyrinth disorders	1 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.1)
Vertigo	1 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.1)
Gastrointestinal disorders	23 (2.2)	13 (1.3)	8 (0.8)	14 (1.4)	14 (1.4)	72 (1.4)
Inguinal hernia	3 (0.3)	2 (0.2)	0 (0.0)	3 (0.3)	3 (0.3)	11 (0.2)
Abdominal pain	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	4 (0.1)
Abdominal pain upper	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	3 (0.1)
Gastritis	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Gastrointestinal hemorrhage	2 (0.2)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.1)
Pancreatitis acute	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	3 (0.1)
Small intestinal obstruction	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	4 (0.1)
General disorders and administration site conditions	3 (0.3)	2 (0.2)	6 (0.6)	9 (0.9)	8 (0.8)	28 (0.5)
Chest pain	1 (0.1)	1 (0.1)	2 (0.2)	2 (0.2)	1 (0.1)	7 (0.1)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.2)	4 (0.1)
Edema peripheral	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	3 (0.1)

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Hepatobiliary disorders	2 (0.2)	6 (0.6)	3 (0.3)	3 (0.3)	1 (0.1)	15 (0.3)
Bile duct stone	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	3 (0.1)
Cholecystitis acute	0 (0.0)	2 (0.2)	2 (0.2)	2 (0.2)	0 (0.0)	6 (0.1)
Cholelithiasis	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	3 (0.1)
Infections and infestations	39 (3.8)	23 (2.2)	21 (2.0)	29 (2.8)	34 (3.3)	146 (2.8)
Pneumonia	14 (1.3)	11 (1.1)	5 (0.5)	18 (1.7)	18 (1.7)	66 (1.3)
Bronchitis	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	3 (0.3)	6 (0.1)
Bronchopneumonia	3 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.1)
Cellulitis	3 (0.3)	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)	6 (0.1)
Gastroenteritis	3 (0.3)	1 (0.1)	2 (0.2)	0 (0.0)	1 (0.1)	7 (0.1)
Infective exacerbation of COPD	2 (0.2)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	4 (0.1)
Influenza	2 (0.2)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	6 (0.1)
Lobar pneumonia	0 (0.0)	2 (0.2)	0 (0.0)	3 (0.3)	1 (0.1)	6 (0.1)
Lung infection	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.1)
Pyelonephritis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	3 (0.1)
Sepsis	1 (0.1)	3 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	5 (0.1)
Urinary tract infection	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)	5 (0.1)
Injury, poisoning and procedural compliactions	11 (1.1)	9 (0.9)	9 (0.9)	9 (0.9)	11 (1.1)	49 (0.9)
Fall	4 (0.4)	1 (0.1)	1 (0.1)	4 (0.4)	3 (0.3)	13 (0.3)
Femur fracture	2 (0.2)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	5 (0.1)
Humerus fracture	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.1)
Rib fracture	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	3 (0.1)
Tendon rupture	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.1)
Metabolism and nutrition disorders	2 (0.2)	0 (0.0)	5 (0.5)	3 (0.3)	6 (0.6)	16 (0.3)
Musculoskeletal and connective tissue disorders	5 (0.5)	10 (1.0)	7 (0.7)	9 (0.9)	5 (0.5)	36 (0.7)
Back pain	0 (0.0)	1 (0.1)	0 (0.0)	3 (0.3)	0 (0.0)	4 (0.1)
Intervertebral disc protrusion	0 (0.0)	1 (0.1)	2 (0.2)	1 (0.1)	0 (0.0)	4 (0.1)
Lumbar spinal stenosis	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	3 (0.1)
Osteoarthritis	2 (0.2)	2 (0.2)	2 (0.2)	0 (0.0)	1 (0.1)	7 (0.1)
Spinal column stenosis	0 (0.0)	3 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	4 (0.1)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	24 (2.3)	20 (1.9)	23 (2.2)	20 (1.9)	13 (1.3)	100 (1.9)
Lung neoplasm malignant	2 (0.2)	2 (0.2)	4 (0.4)	4 (0.4)	1 (0.1)	13 (0.3)
Lung adenocarcinoma	2 (0.2)	3 (0.3)	3 (0.3)	0 (0.0)	0 (0.0)	8 (0.2)
Prostate cancer	2 (0.2)	2 (0.2)	2 (0.2)	4 (0.4)	1 (0.1)	11 (0.2)
Basal cell carcinoma	2 (0.2)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	5 (0.1)
Bladder cancer	2 (0.2)	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)	5 (0.1)
Bronchial carcinoma	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.1)	3 (0.1)
Colon cancer	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.1)
Gastric cancer	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.2)	0 (0.0)	4 (0.1)
Hepatic cancer	1 (0.1)	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	4 (0.1)
Lung cancer metastatic	2 (0.2)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.1)
Nervous system disorders	11 (1.1)	13 (1.3)	12 (1.2)	12 (1.2)	8 (0.8)	56 (1.1)
Cerebrovascular accident	2 (0.2)	2 (0.2)	2 (0.2)	0 (0.0)	2 (0.2)	8 (0.2)
Cerebral infarction	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.2)	0 (0.0)	4 (0.1)
Syncope	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.2)	0 (0.0)	6 (0.1)

Transient ischemic attack	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	6 (0.1)
Psychiatric disorders	3 (0.3)	3 (0.3)	2 (0.2)	4 (0.4)	4 (0.4)	16 (0.3)
Renal and urinary disorders	5 (0.5)	2 (0.2)	7 (0.7)	4 (0.4)	5 (0.5)	23 (0.4)
Hematuria	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.1)
Renal colic	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.1)
Renal failure acute	2 (0.2)	1 (0.1)	2 (0.2)	1 (0.1)	1 (0.1)	7 (0.1)
Urinary retention	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.1)
Reproductive system and breast disorders	5 (0.5)	1 (0.1)	7 (0.7)	2 (0.2)	3 (0.3)	18 (0.3)
Benign prostatic hyperplasia	2 (0.2)	1 (0.1)	5 (0.5)	2 (0.2)	2 (0.2)	12 (0.2)
Respiratory, thoracic and mediastinal disorders	73 (7.0)	71 (6.9)	63 (6.1)	60 (5.8)	77 (7.5)	344 (6.7)
COPD	66 (6.4)	60 (5.8)	53 (5.1)	49 (4.8)	68 (6.6)	296 (5.7)
Acute respiratory failure	4 (0.4)	2 (0.2)	1 (0.1)	1 (0.1)	1 (0.1)	9 (0.2)
Dyspnea	0 (0.0)	2 (0.2)	3 (0.3)	2 (0.2)	2 (0.2)	9 (0.2)
Pulmonary embolism	2 (0.2)	3 (0.3)	0 (0.0)	2 (0.2)	3 (0.3)	10 (0.2)
Hemoptysis	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.1)
Hypoxia	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.1)	1 (0.1)	4 (0.1)
Pleural effusion	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	3 (0.1)
Pneumothorax	0 (0.0)	0 (0.0)	4 (0.4)	0 (0.0)	1 (0.1)	5 (0.1)
Respiratory failure	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	3 (0.3)	5 (0.1)
Vascular disorders	10 (1.0)	5 (0.5)	7 (0.7)	5 (0.5)	4 (0.4)	31 (0.6)
Deep vein thrombosis	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	3 (0.1)
Hypertension	2 (0.2)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)	5 (0.1)
Hypotension	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.1)

7.3.3 Dropouts and/or Discontinuations

In the 52-week trials, of the 5162 patients who were treated with study drug, 794 prematurely discontinued (Table 14). A total of 419 discontinued due to on-treatment adverse events (events occurring within 21-days of last study drug). Approximately 15% of patients discontinued from the trial. More patients in monotherapy arms discontinued compared to the T+O arms. The most common reason for discontinuation was worsening of COPD, and this was more common in the monotherapy arms. This implies that both doses of T+O may have a beneficial effect compared to monotherapy arms, and is consistent with efficacy data reviewed in 6 Review of Efficacy. It should also be noted the differential in discontinuations may exaggerate imbalances between monotherapy and FDC groups for safety findings as the sickest patients may have dropped out in the monotherapy groups. On-treatment adverse events leading to discontinuation are summarized in Table 29.

Table 29. Adverse events leading to discontinuation (on-treatment) that occurred in ≥2 patients/treatment group

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg	Total
Number of patients	1038	1032	1033	1030	1029	5162
Total with AE leading to discontinuation	103 (9.9)	90 (8.7)	93 (9.0)	57 (5.5)	76 (7.4)	419 (8.1)

Ear and labyrinth disorders	3 (0.3)	1 (0.1)	0	0	0	4 (0.1)
Vertigo	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Infections and infestations	6 (0.6)	8 (0.8)	6 (0.6)	6 (0.6)	6 (0.6)	32 (0.6)
Pneumonia	2 (0.2)	2 (0.2)	3 (0.3)	4 (0.4)	1 (0.1)	12 (0.2)
Neoplasms benign,malignant and unspecified	15 (1.4)	12 (1.2)	14 (1.4)	14 (1.4)	9 (0.9)	64 (1.2)
Lung neoplasm malignant	2 (0.2)	1 (0.1)	5 (0.5)	4 (0.4)	0	12 (0.2)
Lung adenocarcinoma	2 (0.2)	3 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)	7 (0.1)
Nervous system disorders	6 (0.6)	6 (0.6)	6 (0.6)	4 (0.4)	4 (0.4)	26 (0.5)
Cerebrovascular accident	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Respiratory, thoracic and mediastinal disorders	50 (4.8)	52 (5.0)	49 (4.7)	13 (1.3)	34 (3.3)	198 (3.8)
COPD	36 (3.5)	41 (4.0)	35 (3.4)	9 (0.9)	25 (2.4)	146 (2.8)
Dyspnea	9 (0.9)	6 (0.6)	10 (1.0)	1 (0.1)	3 (0.3)	29 (0.6)
Cough	0	3 (0.3)	1 (0.1)	3 (0.3)	2 (0.2)	9 (0.2)

Source: SCS; table 40; pg 94

7.3.4 Significant Adverse Events

Adverse events of interest for this product are discussed in Section 7.3.5. AEs leading to discontinuation are discussed in Section 7.3.3. Lab and ECG abnormalities are discussed in section 7.4.2 and 7.4.4, respectively.

7.3.5 Submission Specific Primary Safety Concerns

Due to specific safety concerns with LABA and anticholinergic agents, the sponsor conducted analyses using respiratory, cardiovascular, beta-agonist class effect, and anticholinergic class effect related pharmacovigilance (PV)/SMQ safety endpoints. A Major Adverse Cardiovascular Events (MACE) analysis and an adjudicated analysis of SAEs and deaths were also performed. The sponsor defined PV endpoints primarily consisted of PTs grouped by similar concepts, but that did not necessarily correspond to SOCs. The PTs included in the PV endpoints were reasonable. SMQs used were from MedDRA 16.1. See section 7.1.2 Categorization of Adverse Events for the definition of MACE and the method of adjudication.

Respiratory Safety

Because of the patient population and disease, respiratory adverse events were further analyzed based on a variety of respiratory related PV endpoints. This analysis did not reveal any large differences when comparing either dose of the FDC to its constituent monoproducts. Notably, for the PV endpoints of COPD exacerbation, COPD exacerbation with pneumonia, and respiratory failure; events were generally similar between treatment groups (Table 30). While there were some numerical differences, they were small in magnitude. When comparing the FDCs to their constituent monoproducts in terms respiratory related SMQs, results were similar. Additionally, no

clear dose response was observed when comparing T+O 2.5/5 and 5/5 dose. A similar analysis with both SMQs and PV endpoints was performed on SAE data with similar results.

Table 30. Pooled 52-week trials. On-treatment adverse events by select respiratory pharmacovigilance endpoints

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg	Total
Number of patients	1038	1032	1033	1030	1029	5162
Total with adverse events	795 (76.6)	758 (73.4)	757 (73.3)	769 (74.7)	761 (74.0)	3840 (74.4)
PV COPD exacerbation	372 (35.8)	353 (34.2)	341 (33.0)	301 (29.2)	332 (32.3)	1699 (32.9)
PV COPD exacerbation (broad)	403 (38.8)	377 (36.5)	363 (35.1)	325 (31.6)	356 (34.6)	1824 (35.3)
PV COPD exacerbation (broad) with pneumonia	421 (40.6)	390 (37.8)	373 (36.1)	344 (33.4)	371 (36.1)	1899 (36.8)
PV Respiratory failure	8 (0.8)	10 (1.0)	7 (0.7)	5 (0.5)	6 (0.6)	36 (0.7)
PV Respiratory failure (broad)	8 (0.8)	10 (1.0)	8 (0.8)	5 (0.5)	7 (0.7)	38 (0.7)
PV Pneumonia	41 (3.9)	29 (2.8)	27 (2.6)	36 (3.5)	36 (3.5)	169 (3.3)

Source: SCS supplement; table 2.10.1.1; pp 1604-1610

Cardiovascular Safety

Cardiovascular related SMQ and PV endpoints were also analyzed. As with the analysis of the respiratory PV endpoints, this analysis did not reveal and large differences when comparing T+O to its constituent monoproducts. Given the previous concerns with anticholinergics of stroke and MI, it is notably, for the SMQs ischemic heart disease and cerebrovascular disorders, events were generally similar between treatment groups. Additionally, no dose response was observed. Results from SMQs related to arrhythmia, ischemic heart disease, cardiac failure, and cerebrovascular disorders are summarized in Table 31. The sub-SMQs Myocardial infarction, hemorrhagic cerebrovascular conditions, and ischemic cerebrovascular conditions are included in the table given historical concerns regarding anticholinergic agents. Note that other sub-SMQs were also analyzed, however, because the results were consistent with the overall SMQ analysis, these are not shown. BI performed a similar analysis using PV endpoints which was consistent with the SMQ analysis. Similar SAE analyses were also performed with similar results.

Table 31. Pooled 52-week trials. On-treatment adverse events by cardiovascular SMQs.

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg	Total
Number of patients	1038	1032	1033	1030	1029	5162
Total with adverse events	795 (76.6)	758 (73.4)	757 (73.3)	769 (74.7)	761 (74.0)	3840 (74.4)
SMQ Cardiac arrhythmias (broad)	41 (3.9)	49 (4.7)	47 (4.5)	52 (5.0)	41 (4.0)	230 (4.5)
SMQ Ischemic heart disease (broad)	26 (2.5)	23 (2.2)	22 (2.1)	19 (1.8)	22 (2.1)	112 (2.2)
Sub-SMQ Myocardial Infarction	10 (1.0)	10 (1.0)	8 (0.8)	12 (1.2)	11 (1.1)	51 (1.0)
SMQ Cardiac failure	12 (1.2)	8 (0.8)	8 (0.8)	9 (0.9)	5 (0.5)	42 (0.8)
SMQ Cerebrovascular disorders (broad)	11 (1.1)	12 (1.2)	9 (0.9)	10 (1.0)	8 (0.8)	50 (1.0)
Sub-SMQ hemorrhagic cerebrovascular conditions	6 (0.6)	5 (0.5)	4 (0.4)	2 (0.2)	3 (0.3)	9 (0.2)
Sub-SMQ ischemic cerebrovascular conditions	7 (0.7)	10 (1.0)	7 (0.7)	8 (0.8)	7 (0.7)	39 (0.8)

Source: SCS supplement; table 2.10.2.1; pp1618-1631

There were no imbalances noted in the sponsor's MACE analysis (fatal and non-fatal events). Results of the MACE analysis are summarized in Table 32.

Table 32. Pooled 52-week trials. MACE analysis

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg	Total
MACE	25 (2.4)	21 (2.0)	19 (1.8)	20 (1.9)	24 (2.3)	109 (2.1)
Cardiac disorders SOC (fatal)	4 (0.4)	4 (0.4)	3 (0.3)	5 (0.5)	3 (0.3)	19 (0.4)
Vascular disorders SOC (fatal)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	4 (0.1)
Sub-SMQ Myocardial infarction (broad) (any)	10 (1.0)	10 (1.0)	8 (0.8)	12 (1.2)	11 (1.1)	51 (1.0)
PV Stroke (any)	10 (1.0)	7 (0.7)	7 (0.7)	4 (0.4)	7 (0.7)	35 (0.7)
Sudden death PT	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.0)
Cardiac death PT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sudden cardiac death PT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal MACE	7 (0.7)	5 (0.5)	5 (0.5)	5 (0.5)	7 (0.7)	29 (0.6)
Cardiac disorders SOC (fatal)	4 (0.4)	4 (0.4)	3 (0.3)	5 (0.5)	3 (0.3)	19 (0.4)
Vascular disorders SOC (fatal)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	4 (0.1)
Sub-SMQ Myocardial infarction (broad) (fatal)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.0)
PV Stroke (fatal)	2 (0.2)	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	5 (0.1)
Sudden death PT	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.0)
Cardiac death PT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sudden cardiac death PT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: SCS supplement; table 2.13.1.1; pg3200

Systemic effects

The sponsor also analyzed AEs using multiple PV/SMQ endpoints which were potentially representative of beta2-adrenergic or anticholinergic class effects. For the

PVs, the grouped PTs were reasonable. The PV/SMQs with the highest frequency were the arthralgia/myalgia/muscle weakness PV and the accident and injuries SMQ. There were no clinically significant imbalances in the PV/SMQ analysis when comparing the two T+O doses to their constituent monoproducts.

Bronchoconstriction

The sponsor also analyzed the data for respiratory events indicative of bronchoconstriction. These events included drops in FEV1 \geq 15%; rescue medication use within 30 minutes of test medication inhalation during a clinic visit; and aggravated bronchospasm AE reported within 30 minutes of test medication inhalation during a clinic visit. Based on this analysis, the percentage of patients with events were similar across treatment groups.

Adjudicated SAEs

An adjudicated analysis of all SAEs was performed by an independent adjudication committee (AC). The AC assessed all SAEs to determine if the deaths, hospitalizations, and intubation were due to respiratory-, cardiovascular-, cerebrovascular-, or other-related causes. Overall, there were no large differences between treatment groups or when comparing the FDC doses to their constituent monoproducts. Results are summarized Table 33.

Table 33. Adjudicated SAEs. Death, hospitalizations, and intubations

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg	Total
Total patients	1038 (100)	1032 (100)	1033 (100)	1030 (100)	1029 (100)	5162 (100)
Adjudicated SAEs	171 (16.5)	148 (14.3)	162 (15.7)	157 (15.2)	161 (15.6)	799 (15.5)
Respiratory-related SAEs	85 (8.2)	82 (7.9)	84 (8.1)	78 (7.6)	91 (8.8)	420 (8.1)
COPD-related SAEs	67 (6.5)	63 (6.1)	65 (6.3)	53 (5.1)	71 (6.9)	319 (6.2)
Pneumonia-related SAEs	15 (1.4)	15 (1.5)	9 (0.9)	22 (2.1)	18 (1.7)	79 (1.5)
Other respiratory-related SAEs	7 (0.7)	10 (1.0)	17 (1.6)	11 (1.1)	11 (1.1)	56 (1.1)
Cardiovascular-related SAEs	15 (1.4)	13 (1.3)	19 (1.8)	17 (1.7)	19 (1.8)	83 (1.6)
Cerebrovascular-related SAEs	6 (0.6)	6 (0.6)	5 (0.5)	5 (0.5)	5 (0.5)	27 (0.5)
Stroke-related SAEs	3 (0.3)	3 (0.3)	5 (0.5)	4 (0.4)	2 (0.2)	17 (0.3)
Other cerebrovascular-related SAEs	4 (0.4)	3 (0.3)	0 (0.0)	1 (0.1)	3 (0.3)	11 (0.2)
Non-respiratory non-cardiovascular or non-cerebrovascular-related SAEs	78 (7.5)	67 (6.5)	74 (7.2)	73 (7.1)	71 (6.9)	363 (7.0)

Source: SCS; table 54; pg120

When examining SAEs sub-divided as deaths, hospitalizations, and intubations, the results were similar.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common AEs reported in the 52-week COPD trials were within the respiratory thoracic and mediastinal and infections and infestations SOC. The most common PTs were COPD exacerbation (32.8%), nasopharyngitis (12.3%), upper respiratory infection (5.8%), cough (4.0%), and dyspnea (4.0%). No AEs based on SOC or PT demonstrated a clear dose response. In general, common adverse events were similar between treatment groups. These results are summarized in Table 34.

Table 34. 52-week pooled trials. Adverse events that occurred in $\geq 2\%$ of patients per treatment group

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg	Total
Number of patients	1038	1032	1033	1030	1029	5162
Total with adverse events	795 (76.6)	758 (73.4)	757 (73.3)	769 (74.7)	761 (74.0)	3840 (74.4)
Gastrointestinal disorders	165 (15.9)	152 (14.7)	154 (14.9)	146 (14.2)	143 (13.9)	760 (14.7)
Diarrhea	33 (3.2)	23 (2.2)	27 (2.6)	29 (2.8)	24 (2.3)	136 (2.6)
Constipation	16 (1.5)	17 (1.6)	16 (1.5)	22 (2.1)	13 (1.3)	84 (1.6)
General disorders and administration site conditions	87 (8.4)	64 (6.2)	98 (9.5)	82 (8.0)	73 (7.1)	404 (7.8)
Chest pain	17 (1.6)	17 (1.6)	22 (2.1)	15 (1.5)	14 (1.4)	85 (1.6)
Infections and infestations	393 (37.9)	363 (35.2)	348 (33.7)	394 (38.3)	374 (36.3)	1872 (36.3)
Nasopharyngitis	131 (12.6)	123 (11.9)	121 (11.7)	134 (13.0)	128 (12.4)	637 (12.3)
Upper respiratory tract infection	56 (5.4)	61 (5.9)	57 (5.5)	69 (6.7)	54 (5.2)	297 (5.8)
Pneumonia	36 (3.5)	24 (2.3)	26 (2.5)	31 (3.0)	34 (3.3)	151 (2.9)
Bronchitis	33 (3.2)	23 (2.2)	23 (2.2)	28 (2.7)	31 (3.0)	138 (2.7)
Influenza	25 (2.4)	25 (2.4)	22 (2.1)	28 (2.7)	31 (3.0)	131 (2.5)
Urinary tract infection	13 (1.3)	18 (1.7)	30 (2.9)	23 (2.2)	22 (2.1)	106 (2.1)
Sinusitis	18 (1.7)	22 (2.1)	13 (1.3)	19 (1.8)	21 (2.0)	93 (1.8)
Musculoskeletal and connective tissue disorders	124 (11.9)	119 (11.5)	117 (11.3)	155 (15.0)	156 (15.2)	671 (13.0)
Back Pain	35 (3.4)	23 (2.2)	19 (1.8)	40 (3.9)	37 (3.6)	154 (3.0)
Nervous system disorders	87 (8.4)	93 (9.0)	101 (9.8)	100 (9.7)	84 (8.2)	465 (9.0)
Headache	31 (3.0)	23 (2.2)	41 (4.0)	30 (2.9)	27 (2.6)	152 (2.9)
Respiratory, thoracic and mediastinal disorders	470 (45.3)	453 (43.9)	441 (42.7)	393 (38.2)	405 (39.4)	2162 (41.9)
Chronic obstructive pulmonary disease	370 (35.6)	352 (34.1)	340 (32.9)	301 (29.2)	332 (32.3)	1695 (32.8)
Cough	31 (3.0)	46 (4.5)	45 (4.4)	43 (4.2)	40 (3.9)	205 (4.0)
Dyspnea	38 (3.7)	44 (4.3)	51 (4.9)	37 (3.6)	39 (3.8)	209 (4.0)

Vascular Disorders	72 (6.9)	54 (5.2)	50 (4.8)	58 (5.6)	62 (6.0)	296 (5.7)
Hypertension	48 (4.6)	28 (2.7)	30 (2.9)	35 (3.4)	30 (2.9)	171 (3.3)

Source: SCS; table 27; pp63-64

Overall, the common AEs were typical for the patient population and for LABA and anticholinergic medications.

7.4.2 Laboratory Findings

Clinical laboratories were measured at day 1, 85, 169, and 365. In general, review of clinical laboratory findings did not identify any specific safety concerns. Mean changes from baseline to the last value on treatment were generally small and similar between groups. Possible clinically significant (PCS) lab changes were relatively infrequent and evenly distributed. Additionally, shift table analysis was performed. These results are summarized in Table 35 and Table 36. These tables denote the percentages of patients whose baseline values were \geq the lower limit of normal (LLN), but had a minimum on-treatment value $<$ LLN (“To Low”); and whose baselines were \leq the upper limit of normal, but had a maximum on treatment value $>$ ULN (“To high”). Note that in these tables, the total N includes patients with available data. With regard to hematological and chemistry parameters in general, shifts occurred in a similar or lower percentage of patients when comparing the FDCs groups to their monoproductions. However, for creatinine kinase, for both FDC doses, shifts from $<$ ULN to $>$ ULN were more common as compared to their monotherapy components. However, there is no apparent dose response when comparing FDC doses or Tio doses, which would imply that this is a chance finding.

Table 35. Pooled 52-week trials. Shift table analysis of hematological parameters

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg
WBC Count					
N	1008	1000	996	1012	998
To Low, n (%)	18 (1.8)	24 (2.4)	10 (1.0)	20 (2.0)	19 (1.9)
To High, n (%)	106 (11.2)	95 (10.1)	90 (9.6)	71 (7.5)	88 (9.3)
Lymphocytes					
N	1007	998	996	1012	997
To Low, n (%)	111 (11.9)	120 (12.9)	129 (13.9)	114 (12.3)	99 (10.5)
To High, n (%)	42 (4.3)	42 (4.3)	29 (3.0)	38 (3.8)	40 (4.1)
Neutrophils					
N	1007	998	996	1012	997
To Low, n (%)	33 (3.3)	25 (2.5)	27 (2.7)	33 (3.3)	32 (3.2)
To High, n (%)	135 (14.6)	147 (16.1)	145 (15.9)	120 (13.1)	129 (14.0)
Eosinophils					
N	1007	998	996	1012	997
To High, n (%)	76 (8.1)	72 (7.7)	91 (9.8)	94 (9.8)	71 (7.5)
Monocytes					
N	1007	998	996	1012	997
To High, n (%)	45 (4.6)	47 (4.8)	39 (4.0)	44 (4.5)	53 (5.4)
Hemoglobin					
N	1009	1000	998	1012	1001
To Low, n (%)	68 (7.2)	57 (6.0)	46 (4.9)	52 (5.5)	44 (4.7)

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To High, n (%)	37 (3.9)	51 (5.4)	42 (4.4)	42 (4.3)	44 (4.7)
Platelet Count					
N	1004	993	993	1009	998
To Low, n (%)	27 (2.8)	28 (2.9)	27 (2.8)	18 (1.8)	22 (2.3)
To High, n (%)	25 (2.5)	25 (2.5)	22 (2.2)	21 (2.1)	18 (1.8)

N=total patients with data

(%)= percentage of patients at risk for shift, where at risk was defined as patients with baseline values \geq lower limit of normal for low shifts and baseline values \leq upper limit of normal for high shifts.

Source: SCS supplement; table 3;pp 3394-4003

Table 36. Pooled 52-week trials. Shift table analysis of chemistry parameters

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg
Alanine aminotransferase N	1007	1000	1000	1014	1000
To High, n (%)	36 (3.6)	38 (3.9)	33 (3.4)	42 (4.2)	27 (2.7)
Alkaline phosphatase N	1007	1000	1000	1014	1000
To Low, n (%)	0	0	0	1 (0.1)	0
To High, n (%)	46 (4.8)	46 (4.9)	58 (6.1)	49 (5.0)	42 (4.4)
Aspartate aminotransferase N	1007	1000	999	1014	1000
To High, n (%)	32 (3.2)	33 (3.4)	35 (3.6)	36 (3.6)	27 (2.7)
Bilirubin, Total N	1007	1000	999	1014	1000
To High, n (%)	22 (2.2)	17 (1.7)	17 (1.7)	23 (2.3)	16 (1.6)
Calcium N	1007	1000	1000	1014	1000
To Low, n (%)	17 (1.7)	15 (1.5)	17 (1.7)	24 (2.4)	15 (1.5)
To High, n (%)	25 (2.6)	46 (4.7)	36 (3.7)	35 (3.5)	34 (3.5)
Chloride N	1007	1000	1000	1014	1000
To Low, n (%)	14 (1.4)	9 (0.9)	13 (1.3)	14 (1.4)	14 (1.4)
To High, n (%)	59 (6.0)	62 (6.4)	60 (6.2)	68 (6.9)	61 (6.3)
Creatine kinase N	1007	1000	1000	1014	1000
To High, n (%)	92 (9.6)	67 (7.0)	67 (7.0)	118 (12.2)	96 (10.1)
Creatinine N	1007	1000	999	1014	1000
To Low, n (%)	90 (10.7)	75 (8.8)	82 (9.9)	77 (9.1)	77 (9.4)
To High, n (%)	19 (1.9)	19 (1.9)	19 (1.9)	27 (2.7)	19 (1.9)
GGT N	1007	1000	1000	1014	1000
To High, n (%)	69 (7.7)	58 (6.4)	61 (6.9)	77 (8.6)	65 (7.2)
Glucose N	1007	1000	999	1014	1000
To Low, n (%)	33 (3.3)	43 (4.4)	31 (3.2)	35 (3.5)	44 (4.5)
To High, n (%)	99 (11.1)	104 (11.6)	87 (9.8)	104 (11.3)	87 (9.8)
Potassium N	1007	999	1000	1014	1000
To Low, n (%)	14 (1.4)	11 (1.1)	11 (1.1)	7 (0.7)	9 (0.9)
To High, n (%)	51 (5.3)	58 (6.0)	51 (5.1)	61 (6.2)	40 (4.1)
Sodium N	1007	1000	1000	1014	1000
To Low, n (%)	29 (2.9)	22 (2.2)	38 (3.9)	24 (2.4)	31 (3.1)
To High, n (%)	12 (1.2)	11 (1.1)	7 (0.7)	7 (0.7)	4 (0.4)
Urea (BUN) N	1007	1000	1000	1014	1000
To Low, n (%)	2 (0.2)	18 (1.8)	19 (1.9)	14 (1.4)	13 (1.3)
To High, n (%)	38 (3.9)	47 (4.8)	48 (4.9)	37 (3.7)	34 (3.4)
Uric acid N	1007	1000	1000	1014	1000
To Low, n (%)	31 (3.2)	36 (3.7)	36 (3.7)	37 (3.8)	30 (3.1)

To High, n (%)	53 (5.7)	67 (7.1)	84 (9.0)	82 (8.6)	73 (7.8)
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N=total patients with data

(%)= percentage of patients at risk for shift, where at risk was defined as patients with baseline values \geq lower limit of normal for low shifts and baseline values \leq upper limit of normal for high shifts.

Source: SCS supplement; table 3;pp3394-4003

7.4.3 Vital Signs

Vital signs were monitored at all clinic visits in conjunction with pulmonary function testing. Based on mean values, there were small decreases in both systolic and diastolic blood pressures at the majority of post-baseline assessments. In general, the decreases were similar between groups. Similar results were seen with pulse rate. Marked changes (defined in the table below) in blood pressure and pulse rates generally occurred with similar frequency between treatment groups. The results for marked changes are summarized in Table 37.

Table 37. Pooled data 52-week trials. Marked changes in vital signs

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg
Number of patients	1033 (100.0)	1026 (100.0)	1025 (100.0)	1025 (100.0)	1019 (100.0)
Systolic blood pressure					
Increase	68 (6.6)	57 (5.6)	61 (6.0)	52 (5.1)	54 (5.3)
Decrease	44 (4.3)	54 (5.3)	50 (4.9)	44 (4.3)	48 (4.7)
Diastolic blood pressure					
Increase	89 (8.6)	75 (7.3)	95 (9.3)	73 (7.1)	76 (7.5)
Decrease	48 (4.6)	54 (5.3)	40 (3.9)	63 (6.1)	37 (3.6)
Pulse rate					
Increase	21 (2.0)	31 (3.0)	48 (4.7)	29 (2.8)	33 (3.2)
Decrease	94 (9.1)	95 (9.3)	75 (7.3)	85 (8.3)	80 (7.9)

Marked increase: SBP >150mmHg and an increase \geq 25 mmHg above baseline, DBP >90 mmHg and an increase >10 mmHg above baseline, Pulse > 100 bpm if not at that level at baseline and >10 % above baseline.

Marked decrease: SBP <100 mmHg and a decrease >10 mmHg below baseline, DBP <60 mmHg and a decrease >10 mmHg below baseline, pulse = <60 bpm if not at that level at baseline and >10 bpm <baseline.

Source: SCS supplement; table 55; pg125

7.4.4 Electrocardiograms (ECGs)

During the 52-week COPD trials, 12-lead ECG data was obtained on all participants. ECGs were performed at days 1, 85, 169, and 365. Based on mean values, there were no significant changes from baseline in heart rate, PR interval, and QRS interval. Mean changes from baseline in QTcF were also similar between groups (changes from baseline across groups ranged from -2.1 to 3.8msec). ECGs were also assessed for U-waves, ST segment, T-wave, rhythm, myocardial infarction, ECG conduction and morphological abnormalities. The percentage of patients with abnormalities was generally similar between treatment groups. Based on the ECGs, 31 AEs were reported. These AEs included QT prolongation, T-wave inversion, T-wave amplitude decreased, ST segment depression, abnormal ECG, PR prolongation, and T-wave biphasic. These AEs did not demonstrate a dose response.

Twenty-four hour Holter monitoring was also performed in a subset of patients (N=837) in the 52-week COPD trials at baseline and day 85 (N=743). Based on mean values, there were no dose nor time related trends with regard to heart rate, supraventricular premature beats (SVPB), or ventricular premature beats (VPB). These are summarized in Table 38. While there were some numerical differences between groups, there was no clear pattern indicating that events or changes from baseline were greater in the FDC groups compared to their respective monotherapy components.

Table 38. Pooled 52-week trials, Holter subset. Change from baseline in heart rate, supraventricular premature beats, and ventricular premature beats

	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5mcg	T+O 5/5mcg
Heart rate (beat/min)					
N	156	157	154	142	134
Δ from baseline	0.5	0.0	1.8	0.1	-0.6
Supraventricular premature beats (# of runs)					
N	156	157	154	142	134
Δ from baseline	-19.1	-8.8	-8.6	-10.0	4.8
Ventricular premature beats (# of runs)					
N	156	157	154	142	134
Δ from baseline	15.5	-4.2	2.7	-1.2	-0.2

Source: SCS supplement; tables 4.1, 4.2, and 4.3; pp4070-4072

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As noted in Section 7.2.2, the dose dependency for adverse events is discussed throughout this safety review.

7.5.2 Time Dependency for Adverse Events

No specific analysis of time dependency was conducted for adverse events.

7.5.3 Drug-Demographic Interactions

The sponsor performed a variety of subgroup safety analyses based on baseline demographic information. There were no meaningful differences regarding the pattern/frequency of AEs based on sex and race. Based on age, SAEs were less frequent in <65 years olds (14.1%) compared to the ≥ 65 year olds (17.5%) but were balanced between across treatment groups with the age brackets. Based on region, patterns and frequencies of AEs were generally similar between U.S., European, and Asian populations. However, the PT nasopharyngitis was much more frequent in Europe (21.8%) and East Asia (13.5%) compared to other regions. However, the pattern between treatment groups for each region was similar to the total population.

7.5.4 Drug-Disease Interactions

Subgroup analyses based on baseline COPD disease severity demonstrated that patients with more severe COPD (GOLD criteria), reported similar numbers/frequencies of total AEs. However, COPD exacerbations were reported more frequently in GOLD IV (44.9%) patients versus GOLD III (41.0%) and GOLD II (28.8%). Overall SAEs were also more common in GOLD IV compared to GOLD II or III. This is not surprising as one would expect that those with more severe disease would be more likely to experience SAEs.

The sponsor also analyzed the safety data for the subset of patients with a history of cardiac disease (N=1300). While total AEs and AEs in the cardiac disorder SOC were more common compared to the total population, the distribution between treatment groups was similar and consistent with the total population. This finding is not surprising as one may expect that patients with cardiac disease would be more likely to experience SAEs and that this difference may be accentuated in the cardiac SOC.

7.5.5 Drug-Drug Interactions

The sponsor performed multiple subgroup analyses based on background COPD medications. In general, for patients on baseline LAMAs, SAMA/LAMAs, ICS, LABAs, or xanthines, overall AEs were higher; however, the distribution of AEs were similar and no new safety signals were revealed. This increase in overall AEs is not surprising given that patients who were on baseline COPD maintenance medications are likely more symptomatic or have more severe disease.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No specific trials were conducted to assess for carcinogenicity in humans. See non-clinical review for animal studies.

7.6.2 Human Reproduction and Pregnancy Data

No specific trials were conducted in pregnant women. There is no human data on exposure during pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

It is expected that overdose with T+O would produce typical class effects for LABA and anticholinergic agents.

7.7 Additional Submissions / Safety Issues

The sponsor submitted a 120 day update. Data from that submission did not reveal any new issues not already commented on.

8 Postmarket Experience

This is no post-marketing experience with this combination product.

9 Appendices

9.1 Literature Review/References

1. November 2009 FDA Pulmonary-Allergy Drugs Advisory Committee Meeting.
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9.2 Labeling Recommendations

Labeling negotiations are ongoing at the time of this review.

(b) (4)

9.3 Advisory Committee Meeting

Not applicable.

9.4 Financial Disclosure Review Template

Clinical Investigator Financial Disclosure Review Template

Application Number: 206756

Submission Date(s): 5/22/14

Applicant: Boehringer-Ingelheim

Product: Tiotropium+Olodaterol Respimat

Reviewer: Robert Lim

Date of Review: 1/25/15

Covered Clinical Study (Name and/or Number): 1237.5 and 1237.6

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 480 (Primary investigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>5</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined		

in 21 CFR 54.2(a), (b), (c) and (f): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

From trials 1237.5 and 1237.6, BI certified the absence of financial arrangement for 480 primary investigators. From trial 1237.5 and 1237.6, there were 5 investigators with significant payments of other sorts: (b) (6)

These significant payments of other sorts were determined to not have significant impact upon the conduct of these clinical trials, given that the study was randomized, double-blinded, and placebo controlled with objective spirometric and exacerbation related endpoints. Additionally, each investigator was only responsible for enrolling a small number of patients to these multi-center trials.

From trials 1237.5 and 1237.6, BI performed due diligence on 45 primary investigators and financial interest was not certified. In all cases, the reasons that this information was not certified was the site did not initiate, did not participate, or did not enroll any patients in these trials.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT H LIM
01/23/2015

ANTHONY G DURMOWICZ
01/23/2015

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION: NDA 206756	TRADE NAME: None
APPLICANT/SPONSOR: Boehringer Ingelheim	USAN NAME: Tiotropium/Olodaterol
MEDICAL OFFICER: Robert Lim, M.D.	
TEAM LEADER: Anthony Durmowicz, M.D.	CATEGORY: LAMA/LABA
DATE: 07/15/14	ROUTE: Inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
5/22/14	5/22/14	NDA 206756, SD#1	Initial NDA

RELATED APPLICATIONS

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>

REVIEW SUMMARY:

Boehringer Ingelheim (BI) has submitted a new NDA for tiotropium/olodaterol solution fixed dose combination for oral inhalation (Tio/Olo) for the proposed indication of the long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema (NDA 206,756). It will be administered via the Respimat inhaler. The proposed dose for Tio/Olo for both monocomponents is 5mcg once daily. Currently both Tiotropium Respimat (TR) and Olodaterol Respimat (OR) NDAs are under review. In the monoproduct applications, the proposed dose for TR is 5mcg once daily and for OR, 5mcg once daily. Both TR and OR had adequate dose-ranging trials (phase 2) and confirmatory trials to support this dosing.

This clinical development program for Tio/Olo included multiple clinical trials. Three (3) phase 2 dose-ranging trials in COPD patients were performed with the fixed dose combination (1237.4, 1237.9, and 1237.18). The phase 3 trials consisted of replicated 52-week factorial design safety and efficacy trials in patients with COPD (1237.5 and 1237.6), one 6 week serial spirometry trial in COPD patients (1237.20), (b) (4)

Doses used in the phase 3 trials were T/Olo at a doses of 2.5/5 and 5/5.

Based on preliminary review of trials 1237.5 and 1237.6, both doses of the combination demonstrated added benefit above each monoproduct with regard to trough FEV1 at week 24. With regard to treatment effect over the 52-week treatment period, both doses of Tio/Olo appeared to have a sustained effect over the monoproducts, although the treatment effect across all treatment arms appeared to wane over the treatment period. Additionally, the preliminary review of safety has not raised any new safety concerns for this product.

This submission is adequately indexed, organized, and complete to allow for review. At this time, no OSI site inspection is being requested given the large number of study sites which make it unlikely that any single site could impact overall efficacy analysis. In addition, both monoproducts that constitute this fixed dose combination are under review and will likely be approved. At this time, no major issues have been identified which would limit the review of this application.

The filing checklist and slides from the filing meeting held on 7/10/14 are attached.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	FILEABLE <input checked="" type="checkbox"/>	NOT FILEABLE _____
	APPROVAL _____	APPROVABLE _____ NOT APPROVABLE _____
OTHER ACTION:	COMMENTS FOR SPONSOR _____	

1. Filing checklist

NDA/BLA Number: 206756

Applicant: Boehringer-Ingelheim

Stamp Date: 5/22/14

Drug Name:
Tiotropium/olodaterol

NDA/BLA Type: new

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: 1237.4 Sample Size: 360 Arms: see attached slides Location in submission: 5.3.5.1 Study Number: Study Title: 1237.9 Sample Size: 141 Arms: see attached slides Location in submission: 5.3.5.1	X			Dose ranging for the monocomponents was also performed in monoprodut NDAs.

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes__

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No comments

Reviewing Medical Officer

Date

Clinical Team Leader

Date

2. Filing meeting presentation



NDA 206,756
Tiotropium+Olodaterol Respimat
Boehringer Ingelheim

Bob Lim
Filing Meeting

General Information

- Name: Tiotropium/Olodaterol
- Class: LAMA/LABA
- Indication:
 - For the long-term once daily maintenance of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
 - FEV1 AUC(0-3) and trough FEV1
 - No exacerbation indication
- Dose: 5/5mcg once daily
- Route: oral inhalation via Respimat inhaler

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Additional Label Claims

(b) (4)



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Regulatory History

- EOP2 (7/11)
 - No placebo arm needed provided that monotherapies are approvable
 - Agreement with primary endpoints in pivotal phase 3 trials
 - Recommended 24-hour spirometry in subset of patients in pivotal phase 3 trials
 - QT study for combo not needed
- Related products
 - Olodaterol – resubmission under review (PDUFA 8/2/14)
 - CMC issues resolved
 - Tiotropium – resubmission under review (PDUFA 9/24/14)
 - AC 8/14/14

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Phase 2 - Dose-ranging trials

Study	Objective	Design	Population	Treatment arms	Treatment duration	Primary endpoints
1237.4	Dose-range	R, DB, PG	COPD ≥40 years N=360	Tio+Olo 5/2mcg Tio+Olo 5/5 mcg Tio+Olo 5/10 mcg Tio 5mcg	4-weeks	Trough FEV1
1237.9	Dose-range	R, DB, XO	COPD ≥ 40 years N=141	Tio+Olo 5/2mcg Tio+Olo 5/5 mcg	4-weeks	Trough FEV1
1237.18	Dose-range	R, DB, XO	COPD ≥ 40 years N=232	Tio+Olo 1.25/5 mcg Tio+Olo 2.5/5 mcg Tio+Olo 5/5 mcg Tio+Olo 1.25/10 mcg Tio+Olo 2.5/10 mcg Tio+Olo 5/10 mcg Olo 5mcg Olo 10mcg	4-weeks	Trough FEV1

Performed dose ranging for each monoproduct in olodaterol and tiotropium program

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Phase 3- Trials

Study	Objective	Design	Population	Treatment arms	Treatment duration	Primary endpoints
1237.5 1237.6	Safety, Efficacy	R, DB, AC, MC, PG	COPD ≥40 years N=5162 (total)	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@24wk SGRQ pooled 12-hour PFTs @24 wk in a subset
1237.20	24-hour spirometry curve	R, DB, XO	COPD ≥ 40 years N=219	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) @6weeks

(b) (4)

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52- Week pivotal trials

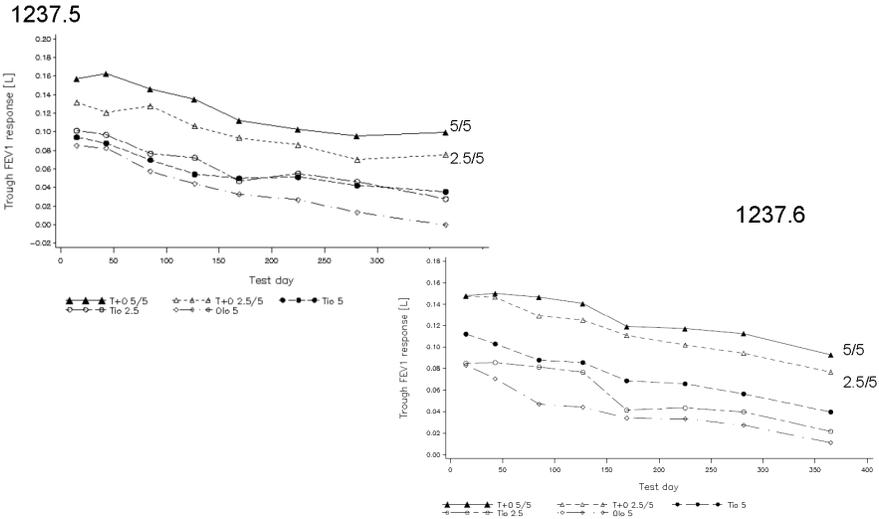
Treatment	Trial 1237.5		Trial 1237.6	
	Trough FEV1	FEV1 AUC (0-3)	Trough FEV1	FEV1 AUC (0-3)
Olo 5	0.054	0.133	0.057	0.136
Tio 2.5	0.083	0.148	0.062	0.125
Tio 5	0.065	0.139	0.096	0.165
Tio+Olo 2.5/5	0.111	0.241	0.125	0.256
Tio+Olo 5/5	0.136	0.256	0.145	0.268
Δ from Olo 5	0.082	0.123	0.088	0.132
Δ from Tio 5	0.071	0.117	0.050	0.103
Δ from Tio+Olo 2.5/5	0.041	0.014 (NS)	0.021 (NS)	0.012 (NS)

- Tio+Olo 5/5 statistically significant treatment effect above each mono
- Not a large difference between 2.5/5 and 5/5 dose

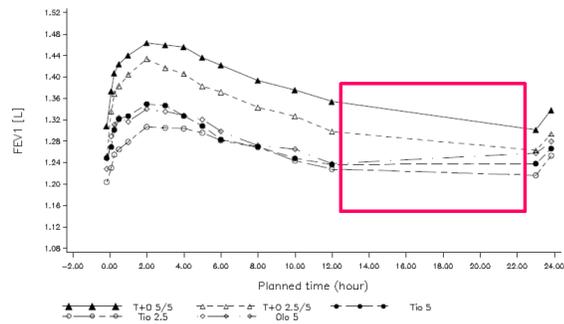
week 24

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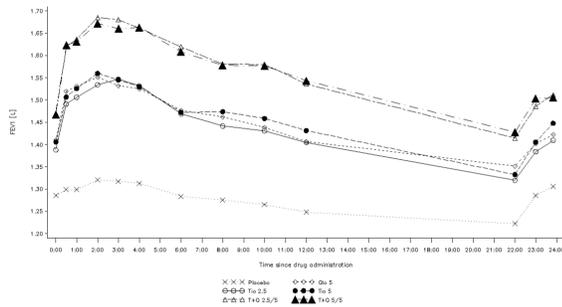
52- Week pivotal trials



52-week trials: “24-hour” spirometry @wk 24



24-hour Spirometry at 6-weeks



- 2.5/5 with similar curve to 5/5
- Persistence of effect over the 24-hour period

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Safety – Exposure

Pooled 52-week trials	Olo 5mcg	Tio 2.5mcg	Tio 5mcg	T+O 2.5/5	T+O 5/5
Number of patients	1038	1032	1033	1030	1029
Extent of Exposure (Days)					
Mean	326.3	330.3	331.8	343.5	340.0
Median	365	365	365	365	365
Extent of Exposure [n(%)]					
281-364 days	90 (8.7)	82 (7.9)	75 (7.3)	68 (6.6)	78 (7.6)
≥365 days	788 (75.9)	799 (77.4)	819 (79.3)	859 (83.4)	835 (81.1)

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Safety -- Disposition

Pooled 52-week trials	Olo 5mcg N(%)	Tio 2.5mcg N(%)	Tio 5mcg N(%)	T+O 2.5/5 N(%)	T+O 5/5 N(%)
Entered/randomized	1038	1032	1034	1030	1029
Not treated	0	0	1	0	0
Treated	1038 (100.0)	1032 (100.0)	1033 (100.0)	1030 (100.0)	1029 (100.0)
Not prematurely discontinued from trial medication	843 (81.2)	857 (83.0)	865 (83.7)	907 (88.1)	896 (87.1)
Prematurely discontinued from trial medication	195 (18.8)	175 (17.0)	168 (16.3)	123 (11.9)	133 (12.9)
Adverse event	110 (10.6)	94 (9.1)	96 (9.3)	63 (6.1)	78 (7.6)
Worsening of disease under study	46 (4.4)	45 (4.4)	42 (4.1)	12 (1.2)	26 (2.5)
Worsening of other pre-existing disease	8 (0.8)	9 (0.9)	3 (0.3)	4 (0.4)	8 (0.8)
Other adverse event	56 (5.4)	40 (3.9)	51 (4.9)	47 (4.6)	44 (4.3)
Non-compliant with protocol	11 (1.1)	14 (1.4)	9 (0.9)	10 (1.0)	9 (0.9)
Lost to follow-up	6 (0.6)	10 (1.0)	3 (0.3)	7 (0.7)	1 (0.1)
Consent withdrawn	58 (5.6)	50 (4.8)	51 (4.9)	39 (3.8)	40 (3.9)
Other	10 (1.0)	7 (0.7)	9 (0.9)	4 (0.4)	5 (0.5)

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Safety – Adverse events

Pooled 52-week trials	Olo 5mcg N(%)	Tio 2.5mcg N(%)	Tio 5mcg N(%)	T+O 2.5/5 N(%)	T+O 5/5 N(%)
Number of patients	1038	1032	1033	1030	1029
Death	14 (1.3)	12 (1.2)	17 (1.6)	14 (1.4)	18 (1.7)
Patients with serious AEs	181 (17.4)	156 (15.1)	172 (16.7)	168 (16.3)	169 (16.4)
Patients with AEs leading to discontinuation of trial drug	103 (9.9)	90 (8.7)	93 (9.0)	57 (5.5)	76 (7.4)
Patients with any AE	795 (76.6)	758 (73.4)	757 (73.3)	769 (74.7)	761 (74.0)

- Deaths, SAEs, AEs similar between treatment groups (SOC/PT)

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DSI/Audit

- DSI audit may not be needed
 - No “high” enrolling sites in 1237.5/6
 - Both monoproducts are likely approvable
 - Assumes no outlier sites with regard to safety/efficacy

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Issues

- Label

(b) (4)

- Which trials to review in depth
 - 52-week trials (1237.5 and 1237.6)
 - 6-week 24-hour spirometry trial (1237.20)
 - (b) (4)
 - [Redacted]

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/s/

ROBERT H LIM
07/15/2014

ANTHONY G DURMOWICZ
07/15/2014