CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation (Memo to File)

CLINICAL STUDIES

NDA/Serial Number:	NDA 206-756
Drug Name:	Tiotropium/Olodaterol
Indication(s):	Chronic Obstructive Pulmonary Disease (COPD)
Applicant:	Boehringer Ingelheim
Date(s):	Submission date: May 22, 2014 PDUFA due date: May 22, 2015
Review Priority:	Standard Review
Biometrics Division:	Division of Biometrics II
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Concurring Reviewers:	Ruthanna C Davi, Ph.D.
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Keywords: subgroup

This memo is in response to concerns regarding whether studies to support chronic obstructive pulmonary disease indications have adequately enrolled minority patients, especially African American patients and is in supplement to the Statistical Review and Evaluation of this submission dated May 22, 2014.

The proportion of Black/African American patients in the pivotal bronchodilator studies for this application, studies 5 and 6, were 0.9% (24/2624) and 2.0% (51/2538), respectively. These percentages are calculated as a fraction of the entire study population, including sites external to the United States (US) where Black/African American patients are uncommon. Expressed as a fraction of the US population recruited to the study, the proportion of Black/African American patients were 6.0% (23/382) and 9.1% (40/440) in studies 5 and 6, respectively. From a statistical perspective, the former calculation is the more appropriate metric for assessing the appropriateness of extrapolating conclusions of these studies to African American patients and the latter calculation is the more appropriate means to assess whether recruitment to the study was differential by race. Complete subject frequencies by race are provided in Tables 1 and 2.

Table 1: Subject Frequency by Race and Region (US and non-US) in Study 5

	Study 5					
	US		**Non US**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Not Reported	0	0.0	81	3.6	81	3.1
American Indian / Alaskan Native	2	0.5	21	0.9	23	0.9
Asian	0	0.0	672	30.0	672	25.6
Black / African American	23	6.0	1	0.0	24	0.9
Hawaiian Pacific Islander	0	0.0	1	0.0	1	0.0
White	357	93.5	1466	65.4	1823	69.5
Total	382	100.0	2242	100.0	2624	100.0

Table 2: Subject Frequency by Race and Region (US and non-US) in Study 6

	Study 6					
	US		**Non US**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Not Reported	1	0.2	5	0.2	6	0.2
American Indian / Alaskan Native	2	0.5	5	0.2	7	0.3
Asian	2	0.5	632	30.1	634	25.0
Black / African American	40	9.1	11	0.5	51	2.0
Hawaiian Pacific Islander	1	0.2	0	0.0	1	0.0
White	394	89.5	1445	68.9	1839	72.5
Total	440	100.0	2098	100.0	2538	100.0

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/s/

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04/30/2015

RUTHANNA C DAVI
04/30/2015

U.S. Department of Health and Human Services
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Keywords: fixed dose combination (FDC), hierarchical testing, MMRM

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1 EXECUTIVE SUMMARY

Boehringer Ingelheim Pharmaceuticals, Inc proposes STIOLTO RESPIMAT, a fixed dose combination (FDC) of tiotropium 5 µg and olodaterol 5 µg inhalation solution (Tio+Olo 5/5 µg) once daily for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Efficacy and safety of this FDC product and a lower dose combination (Tio+Olo 2.5/5 µg) were examined in three core phase III registration trials.

The submission demonstrated benefits of both FDCs over the constituent monotherapy products in terms of pulmonary function evaluations. Two replicated randomized parallel arm trials (Trial 5 and Trial 6) showed that the individual components of the FDC contributed to the treatment effect. Both Tio+Olo FDCs provided statistically significant benefits over the appropriate mono-component in the primary endpoints: Forced expiratory volume in 1 second (FEV_1) $AUC_{0\text{-}3h}$ response [L] and trough FEV_1 response [L] after 24 weeks of treatment. In Trial 5, treatment of Tio+Olo 5/5 µg showed an average benefit of 0.123 L vs. Olo 5 µg and 0.117 L vs. Tio 5 µg in FEV_1 $AUC_{0\text{-}3h}$ response, while the average benefit in trough FEV1 was 0.082 L vs. Olo 5 µg and 0.071 L vs. Tio 5 µg ($p<0.0001$ for each comparison). For Tio+Olo 2.5/5 µg, the increase in adjusted mean FEV_1 $AUC_{0\text{-}3h}$ response was 0.109 L vs. Olo 5 µg and 0.093 L vs. Tio 2.5 µg ($p<0.0001$ for both comparisons), while the increase in adjusted mean trough FEV1 response was 0.058 L vs. Olo 5 µg and 0.029 L vs. Tio 2.5 µg ($p<0.0001$ and $p=0.0174$, respectively). Similarly in Trial 6, treatment of Tio+Olo 5/5 µg provided an average benefit of 0.132 L vs. Olo 5 µg and 0.103 L vs. Tio 5 µg in FEV_1 $AUC_{0\text{-}3h}$ response (Day 169) ($p<0.0001$ for both comparisons), while the average benefit in trough FEV1 response (Day 170) was 0.088 L vs. Olo 5 µg ($p<0.0001$) and 0.050 L vs. Tio 5 µg ($p=0.0001$). For Tio+Olo 2.5/5 µg, the increase in adjusted mean FEV_1 $AUC_{0\text{-}3h}$ response was 0.121 L vs. Olo 5 µg and 0.131 L vs. Tio 2.5 µg, while the increase in adjusted mean trough FEV1 response was 0.067 L vs. Olo 5 µg and 0.062 L vs. Tio 2.5 µg ($p<0.0001$ for all comparisons).

Statistically significant benefits of Tio+Olo FDCs were also seen in a crossover study (Trial 20) that characterized a 24 hour bronchodilator profile. The Tio+Olo FDCs were superior to the comparator treatments for the primary efficacy endpoint, FEV_1 $AUC_{0\text{-}24h}$ response. Treatment with Tio+Olo 5/5 µg resulted in a statistically significant increase in FEV_1 $AUC_{0\text{-}24h}$ response compared to placebo (0.280 L), Olo 5 µg (0.115 L), and Tio 5 µg (0.110 L). Similarly, treatment with Tio+Olo 2.5/5 µg resulted in a statistically significant increase in FEV_1 $AUC_{0\text{-}24h}$ response compared to placebo (0.277 L), Olo 5 µg (0.111 L), and Tio 2.5 µg (0.124 L).

Analyses of other spirometry endpoints generated consistent results and provided additional support for the lung function benefit of both doses of Tio+Olo compared to the monotherapies. Alternative analyses verified the results of the primary analyses. The efficacy conclusions were robust against choice of covariance structure and/or concerns regarding handling of missing data.

2 INTRODUCTION

2.1 OVERVIEW

2.1.1 Drug Class and Indication

Boehringer Ingelheim Pharmaceuticals, Inc proposes STIOLTO RESPIMAT, a fixed dose combination (FDC) of tiotropium 5µg and olodaterol 5µg inhalation solution (Tio+Olo 5/5 µg) once daily for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

2.1.2 History of Drug Development

The clinical development program for tiotropium + olodaterol (Tio+Olo) FDC was introduced to the Division of Pulmonary, Allergy, and Rheumatology Products in 2008 under IND 76,397. The applicant had several interactions with the Agency. The End-of-Phase II meeting was held on 20 Jul 2011 and pertinent parts of the statistical portion of the meeting are summarized herein.

The Division agreed that for the pivotal Phase III studies,

- No placebo comparator arm would be required if monotherapies were shown to be approvable.
- While the overall treatment duration were 52 weeks, the primary efficacy analysis would be conducted after 24 weeks of treatment
- The primary efficacy endpoints were lung function endpoints ($FEV_1AUC_{0\text{-}3h}$ and trough FEV_1); both must be statistically significant vs. each individual component to satisfy the US registration requirement
- Separate hypothesis testing strategies would be pre-specified for US and EU submission. The US hierarchical testing strategy is adequate for the control of Type I error.

With regards to the proposed statistical analysis model, the Division recommended that justification for the choice of covariance structure be provided and sensitivity analysis be conducted to examine the robustness of the conclusions. With regards to the proposed methods for handling missing data, the Division suggested that additional imputation methods be considered to gauge the sensitivity of primary analysis.

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

2.1.3 Current Submission

The clinical program for Tio+Olo FDC comprised of 4 Phase I trials (2 in healthy subjects, 2 in COPD patients), 3 Phase II trials, and 6 Phase III trials in COPD patients. The proposed indication for long-term maintenance treatment of airflow obstruction in patients with COPD is based on a set of replicate, randomized, double-blind, parallel group Phase III trials with 52-week treatment duration (1237.5 and 1237.6; hereafter referred to as Trial 5, Trial 6). Supportive evidence that characterizes patient's 24-hour bronchodilating profile is provided from a randomized, double-blind, crossover trial with 6-week treatment duration (1237.20; hereafter referred to as Trial 20). (b) (4) Three Phase II trials (1237.4, 1237.9, and 1237.18) which supported dosing recommendations are also included in the current submission.

This statistical review focuses on the 3 Phase III core registration trials, Trials 5, 6, and 20. These trials included 5 active treatment arms which were as follows: olodaterol 5 µg (Olo 5), tiotropium 2.5 µg (Tio 2.5), tiotropium 5 µg (Tio 5), tiotropium+ olodaterol 2.5/5 µg (T+O 2.5/5), and tiotropium+ olodaterol 5/5 µg (T+O 5/5). The combination of tiotropium and olodaterol will sometimes be referred to as Tio+Olo FDC or T+O FDC in the remainder of the review.

2.2 DATA SOURCES

NDA 296-765 was submitted on May 24, 2014. The study reports including protocols, statistical analysis plan, and all referenced literature were submitted by the applicant to the Agency. The data and final study report for the electronic submission were archived under the network path location \\Cdsesub1\evsprod\NDA206756\0000.

3 STATISICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

In general, the electronic data submitted by the applicant were of sufficient quality to allow a thorough review of the data. This reviewer was able to reproduce the analyses of the primary and secondary efficacy endpoints for each clinical study submitted.

3.2 EVALUATION OF EFFICACY

The core registration Phase III program consists of two replicate, 52-week parallel group trials and one 6-week cross-over trial, which are reviewed in this document. Summary of the study designs is given in Table 1.

Protocol 1237.005 (referred to as Trial 5): 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 fixed dose combination (2.5µg/5µg; 5µg/5µg) (delivered by the Respimat® Inhaler) compared with the individual components (2.5µg and 5µg tiotropium, 5µg olodaterol) (delivered by the Respimat® Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD)

Protocol 1237.006 (referred to as Trial 6): 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 fixed dose combination (2.5µg/5µg; 5µg/5µg) (delivered by the Respimat® Inhaler) compared with the individual components (2.5µg and 5µg tiotropium, 5µg olodaterol) (delivered by the Respimat® Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD)

Protocol 1237.0020 (referred to as Trial 20): Randomized, double-blind, placebo-controlled, 6 treatment, 4 period, incomplete cross-over trial to characterise the 24-hour lung function profiles of tiotropium + olodaterol fixed dose combination (2.5/5 µg, 5/5 µg), tiotropium (2.5µg, 5µg) and olodaterol (5µg) (oral inhalation, delivered by the Respimat® Inhaler) after 6 weeks once daily treatment in patients with Chronic Obstructive Pulmonary Disease (COPD)

Table 1 Study Designs for Trial 5, Trial 6, and Trial 20

	Trial 5 and Trial 6	Trial 20
Objective	Efficacy and Safety	24-hour spirometry
Design	Randomized, double-blind, active-controlled parallel group	Randomized, double-blind, placebo- and active-controlled, crossover
Treatment arms	Tio + Olo 2.5/5µg Tio + Olo 5/5 µg Tio 2.5µg Tio 5µg Olo 5µg;	Tio + Olo 2.5/5µg Tio+ Olo 5/5 µg Tio 2.5µg Tio 5µg Olo 5µg; Placebo
Patient Diagnosis	COPD ≥40 years Smoker>10 pack years GOLD Stage II/III/IV	COPD ≥40 years Smoker>10 pack years GOLD Stage II/III/IV
Duration	52 weeks	6 weeks
Lung function test	• Up to 3 hours and at 23 to 24 hours post-dose • Up to 12-hour post-dose in a subset of patients after 24 weeks	Up to 12 hours and at 22 to 24 hours post-dose after 6 weeks
Primary Efficacy Endpoint(s)	• FEV_1 AUC_{0-3h} response on Day 169 • Trough FEV1 response on Day 170	FEV_1 AUC_{0-24h} response after 6-weeks

3.2.1 Trial 5 and Trial 6

The replicate, pivotal Phase 3 studies 5 and 6 were designed to satisfy both the US and EU regulatory requirements with regards to confirmatory evidence of the long term efficacy and safety of tiotropium + olodaterol FDC. This review will only discuss information relevant to US approval.

3.2.1.1 Study Design and Endpoints

Both Trial 5 and Trial 6 are confirmatory Phase III designs with identical protocol. The overall objective of each trial was to assess the efficacy and safety of 52 weeks of once daily treatment with orally inhaled tiotropium + olodaterol fixed dose combination (T+O 5/5 µg; T+O 2.5/5 µg) compared with the individual components [tiotropium 2.5 µg (Tio 2.5); tiotropium 5 µg (Tio 5); olodaterol 5 µg (Olo 5)] in patients with COPD. Each trial was a 12-month, multicenter, randomized, double-blind study with 5 parallel groups. Patients were randomized (1:1:1:1:1) to one of the following treatments: T+O 5/5, T+O 2.5/5, Olo 5, Tio 2.5, and Tio 5. During the 52-week treatment period, patients inhaled 2 puffs from the RESPIMAT inhaler once daily in the morning. The scheduled visits consisted of qualification/baseline, randomization (Day 1), Weeks 2, 6, 12, 18, 24, 32, 40, and 52. A follow-up visit was performed 3 weeks after the last dose of study medication.

In a subset of patients at selected sites, pulmonary function tests (PFTs) were performed up to 12-hour post dosing at the week 24 visit. Trial 5 was conducted in 239 centers in 25 countries from 9/15/2011 to 9/19/2013. Trial 6 was conducted in 241 centers in 24 countries from 9/15/2011 to 11/11/2013.

In both studies, the primary endpoints were:

- Forced expiratory volume in 1 second (FEV_1) AUC_{0-3h} response [L] on Day 169. FEV_1 AUC_{0-3h} was calculated as the area under the FEV_1- time curve from 0 to 3 h post-dose using the trapezoidal rule, divided by the duration (3 hour) to report in liters. FEV_1 AUC_{0-3h} response was defined as FEV_1 AUC_{0-3h} minus baseline FEV_1.
- Trough FEV_1 response [L] on Day 170. Trough FEV_1 was defined as the FEV_1 value at the end of the dosing interval (24 hours). For the primary endpoint, it was calculated as the mean of the two FEV_1 measurements performed at 23 hour and at 23 hour 50 minutes after inhalation of study medication at the clinic visit on the previous day. Trough FEV_1 response was defined as trough FEV_1 minus baseline FEV_1.

Baseline was defined as the mean of the 2 pre-dose measurements performed 1 hour and 10 minutes prior to administration of the first dose of randomized treatment at Visit 2. Note that both endpoints are appropriate and are commonly used in COPD trials. While the FEV_1 AUC_{0-3h} is meant to characterize initial effect, the trough FEV_1 is intended to demonstrate persistence of effect throughout the dosing interval.

Secondary endpoints include FEV_1 AUC_{0-3h} response [L] on Days 1, 85, 365; Trough FEV_1 response [L] on Days 15, 43, 85, 169, 365; FVC (forced vital capacity) AUC_{0-3h} response [L] on Days 1, 85, 169, 365; and trough FVC response [L] on Days 15, 43, 85, 170, and 365.

3.2.1.2 Statistical Methodologies

The following analysis datasets of interest were defined in the protocol:

- Randomized set (RS): included all patients who signed informed consent form and were randomized, regardless whether the patient was treated with study medication or not.
- Treated set (TS): included all patients in the randomized set who were dispensed study medication and were documented to have taken any dose of study drug.
- Full analysis set (FAS): included all patients in the TS who had a non-missing baseline and at least one non-missing post-baseline measurement before or at Week 24 for any of the primary and key secondary efficacy endpoints.
- Per protocol set (PPS): included all patients in the FAS who had no important protocol violations of relevance for the efficacy analyses.
- 12-hour PFT set (12-h PFT): included all patients in the FAS who had given informed consent for the 12-h PFT testing and who had a spirometry measurement after 3-h and before or at 12 h post-dose at Visit 7 (Day 169) and Visit 7* (Day 170).

The primary efficacy analysis was testing superiority of Tio+Olo FDC compared with the individual components (Tio, Olo) with respect to lung function. Comparisons between treatment groups for the change from baseline in FEV_1 AUC_{0-3h} and change from baseline in trough FEV_1 after 24 weeks of treatment were analyzed using a restricted maximum likelihood (REML)-based mixed effects model repeated measures (MMRM) approach. The MMRM included treatment, test day and treatment-by-test day interaction as fixed, categorical effects, baseline and baseline-by-test day interaction as continuous fixed covariates, and patient as random effect. The planned

test days for Day 1 through Day 169 were used in the MMRM. A spatial power covariance structure was used to model within patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The primary comparisons were contrasts between groups after 24 weeks of treatment.

Two additional analyses were employed to gauge the robustness of the primary analysis method: 1) an asymptotically consistent empirical 'sandwich' estimator approach to calculate a variance-covariance matrix of the fixed effects; 2) a pattern mixture model based on the patterns of missing data and took into account any differences in the percentage of patients discontinuing at Week 24.

The primary analysis and analysis of secondary endpoints were performed on the FAS except for the analysis of 12-hour serial spirometry which was based on the 12-h PFT dataset. If the number of patients in the PPS was less than 90% of the number of patients in the FAS, the primary analysis was also to be performed on the PPS for the primary endpoint. There was no interim analysis during the trial.

A hierarchical testing scheme, each at the 5% level of significance (2-sided), was employed to protect the overall probability of type I error. For each individual trial, the comparisons for the 2 lung function primary endpoints were first performed in the following order:

1) FEV_1 $AUC_{0\text{-}3h}$: T+O 5/5 vs Olo 5
2) FEV_1 $AUC_{0\text{-}3h}$: T+O 5/5 vs Tio 5
3) Trough FEV_1: T+O 5/5 vs Olo 5
4) Trough FEV_1: T+O 5/5 vs Tio 5
5) FEV_1 $AUC_{0\text{-}3h}$: T+O 2.5/5 vs Olo 5
6) FEV_1 $AUC_{0\text{-}3h}$: T+O 2.5/5 vs Tio 2.5
7) Trough FEV_1: T+O 2.5/5 vs Olo 5
8) Trough FEV_1: T+O 2.5/5 vs Tio 2.5
9) FEV_1 $AUC_{0\text{-}3h}$: T+O 2.5/5 vs Tio 5
10) Trough FEV_1: T+O 2.5/5 vs Tio 5

A hypothesis test in this chain was only considered confirmatory if all previous tests were statistically significant at the 2-sided 5% level and the treatment effect favored Tio+Olo FDC; if a test failed, all results from subsequent tests were considered descriptive (nominal p-values). Note the comparison of Tio+Olo 2.5/5 µg vs. Tio 5 µg was also included since Tio 5 µg is an approved and marketed product in the EU and several other countries worldwide.

According to the trial Statistical Analysis Plan and for the purpose of primary efficacy analysis, missing data were handled as follows:

- Data missing due to worsening of symptoms or need for rescue medication was replaced with the least favorable data for that visit (including pre-dose values).
- If patients discontinued the trial due to worsening of COPD, subsequent missing data were imputed by the patient's least favorable value observed up to that time point.

- Randomly missing data (not due to worsening of symptoms or use of rescue medication) after inhalation were linearly interpolated if data were available before and after inhalation for the same visit.
- Randomly missing data with no subsequent non-missing values for that visit were imputed using the last observation carried forward. An exception was pre-dose measurements and measurements at 23:00 and 23:50 post-dose at Visit 7 for cases where the patient did not discontinue the visit due to worsening COPD. In cases where there was at least 1 pre-dose measurement but both 23:00 and 23:50 measurements were missing, the pre-dose data was used to impute the missing 23:00/23:50 data. Similarly, non-missing 23:00/23:50 data were used to impute completely missing pre-dose data.
- All other cases of completely missing visits were not imputed and therefore as part of the protocol specified primary analysis method (MMRM) were assumed to be "missing at random" (reader is referred to section 3.2.1.4.3 for further comment and an assessment of the impact of missing data).

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Table 2 shows disposition of patients in Study 5. A total of 2624 subjects were randomized into the trial; all received at least one dose of study medication and were included in the treated set. Of those 2262 patients (86.2%) completed the trial and 362 (13.8%) discontinued study drug prematurely. The most frequent reasons for premature discontinuation in all 5 treatment groups were occurrence of AEs (7.5% overall) and withdrawal of consent (3.7% overall). Premature study drug discontinuation was more frequent in the monotherapy groups (13.7% to 18.4%) than in the FDC groups (10.7% to 11.5%). The FAS dataset excluded 2 patients who were also enrolled in another trial. A further 119 patients with important protocol violation related to efficacy were excluded from the PPS, leading to 2503 patients in the PPS set which is >90% of the number of patients in the FAS.

Table 2 Number of subjects and disposition Trial 5

	Olo 5 N (%)	**Tio 2.5 N (%)**	**Tio 5 N (%)**	**T+O 2.5/5 N (%)**	**T+O 5/5 N (%)**	**Total N (%)**
Entered/Randomized	528	525	527	522	522	2624
Never Dosed	0	0	0	0	0	0
Completed trial medication	431 (81.6)	448 (85.3)	455 (86.3)	462 (88.5)	466 (89.3)	2262 (86.2)
Prematurely discontinued trial medication	97 (18.4)	77 (14.7)	72 (13.7)	60 (11.5)	56 (10.7)	362 (13.8)
Adverse event (AE)	51(9.7)	37 (7.0)	43 (8.2)	30 (5.7)	37 (7.1)	198 (7.5)
Consent withdrawn not due to AE	29 (5.5)	20 (3.8)	17 (3.2)	20 (3.8)	11 (2.1)	97 (3.7)
Non-compliance to protocol	5 (0.9)	8 (1.5)	4 (0.8)	4 (0.8)	4 (0.5)	25 (1.0)
Lost to follow-up	6 (1.1)	7 (1.3)	1 (0.2)	4 (0.8)	0 (0.0)	18 (0.7)
Other reason	6 (1.1)	5 (1.0)	7 (1.3)	2 (0.4)	4 (0.8)	24 (0.9)
Analysis Datasets						
Treated Set (TS)	528	525	527	522	522	2624
Full analysis set (FAS)	528 (100.0)	524 (99.8)	526 (99.8)	522 (100.0)	522 (100.0)	2622 (99.9)
Patients excluded from FAS	0	1	1	0	0	2
Per protocol set (PPS)	513 (97.2)	501 (95.4)	507 (96.2)	498 (95.4)	484 (92.7)	2503 (95.4)
Patients with important protocol violation related to efficacy analysis and excluded from PPS	15	23	19	24	38	119
12-h PFT set (12 PFT)	104 (19.7)	100 (19.0)	85 (16.1)	97 (18.6)	83 (15.9)	469 (17.9)

Source: Clinical Study Report, Trial 1237.5, Table 10.1:1 and Table 11.1:1 (with modifications in format)

Table 3 shows disposition of patients in Study 6. A total of 2539 subjects were randomized into the trial; all but one received at least one dose of study medication and were included in the treated set. Of those 2106 patients (83.0%) completed the trial and 432 (17.0%) discontinued study drug prematurely. The most frequent reasons for premature discontinuation in all 5 treatment groups were occurrence of AEs (9.6% overall) and withdrawal of consent (5.6% overall). Premature study drug discontinuation was more frequent in the monotherapy groups (19.0% to 19.3%) than in the FDC groups (12.4% to 15.2%). The FAS dataset excluded 10 patients due to having been previously randomized in this study or currently participating in another study or having no baseline or post-baseline data. A further 84 patients with important protocol violation related to efficacy were excluded from the PPS, leading to 2444 patients in the PPS set which is >90% of the number of patients in the FAS.

Table 3 Number of subjects and disposition Trial 6

	Olo 5 N (%)	**Tio 2.5 N (%)**	**Tio 5 N (%)**	**T+O 2.5/5 N (%)**	**T+O 5/5 N (%)**	**Total N (%)**
Entered/Randomized	510	507	507	508	507	2539
Never Dosed	0	0	1	0	0	1
Completed trial medication	412 (80.8)	409 (80.7)	410 (81.0)	445 (87.6)	430 (84.8)	2106 (83.0)
Prematurely discontinued trial medication	98 (19.2)	98 (19.3)	96 (19.0)	63 (12.4)	77 (15.2)	432 (17.0)
Adverse event (AE)	59 (11.6)	57 (11.2)	53 (10.5)	33 (6.5)	41 (8.1)	243 (9.6)
Consent withdrawn not due to AE	29 (5.7)	30 (5.9)	34 (6.7)	19 (3.7)	29 (5.7)	141 (5.6)
Non-compliance to protocol	6 (1.2)	6 (1.2)	5 (1.0)	6 (1.2)	5 (1.0)	28 (1.1)
Lost to follow-up	0 (0.0)	3 (0.6)	2 (0.4)	3 (0.6)	1 (0.2)	9 (0.4)
Other reason	4 (0.8)	2 (0.4)	2 (0.4)	2 (0.4)	1 (0.2)	11 (0.4)
Analysis Datasets						
Treated Set	510	507	506	508	507	2538
Full analysis set (FAS)	507 (99.4)	505 (99.6)	503 (99.4)	508 (100.0)	505 (99.6)	2528 (99.6)
Patients excluded from FAS	3	2	3	0	2	10*
Per protocol set (PPS)	490 (96.1)	488 (96.3)	489 (96.6)	485 (95.5)	492 (97.0)	2444 (96.3)
Patients with important protocol violation related to efficacy analysis and excluded from PPS	17	17	??	23	13	84
12-h PFT set (12 PFT)	92 (18.0)	86 (17.0)	75 (14.8)	82 (16.1)	87 (17.2)	422 (16.6)

Source: Clinical Study Report, Trial 1237.6, Table 10.1:1 and Table 11.1:1 (with modifications in format)

In both studies since the number patients excluded from the PPS is less than 10% of those in the FAS, no sensitivity analysis of the primary efficacy endpoint using PPS was performed. Trial 5 and Trial 6 each had 469 and 422 patients in the 12-h PFT set, which achieved the goal of at least 410 patients planned for this analysis set.

Selected demographic features and baseline covariates were compared among treatment groups for both studies in Tables 4 and 5. The physical characteristics, pulmonary function, smoking and COPD history were evenly balanced between the various treatment groups in each study. There were no statistically significant differences among the treatment groups in the demographic and baseline characteristics in both studies. Patients were approximately 64 years

old, and most (73.7% and 72.0% in Trial 5 and Trial 6, respectively) were male. The majority of patients were white (69.5% and 72.5%, respectively) or Asian (25.0% and 25.6%, respectively). All patients were either smokers (37.5% and 36.4%, respectively) or ex-smokers (62.5% and 63.6%, respectively). The mean duration from COPD diagnosis to trial enrolment ranged from 6.5 years to 6.6 years. Screening spirometry and severity of lung function impairment were comparable across treatment groups within each trial and consistent between the two trials (Data not shown here). The number of African Americans who participated in the trials was 75 patients overall.

Table 4 Patients Demographics and Baseline Characteristics (Trial 5, Treated Set)

	Olo 5 N=528	Tio 2.5 N=525	Tio 5 N=527	T+O 2.5/5 N=522	T+O 5/5 N=522	Total N=2624
Sex, N (%)						
Male	386 (73.1)	392 (74.7)	383 (72.7)	389 (74.5)	384 (73.6)	1934 (73.7)
Female	142 (26.9)	133 (25.3)	144 (27.3)	133 (25.5)	138 (26.4)	690 (26.3)
Age(years), N	528	525	527	522	522	2624
Mean (SD)	63.7 (8.0)	64.2 (8.6)	64.2 (8.5)	64.1 (8.0)	64.8 (8.2)	64.2 (8.3)
Range	40-86	41-89	40-89	43-85	42-85	40-89
Age class, N(%)						
<65	278 (52.7)	264 (50.3)	268 (50.9)	269 (51.5)	240 (46.0)	1319 (50.3)
65 to <75	205 (38.8)	204 (38.9)	199 (37.8)	196 (37.5)	223 (42.7)	1027 (39.1)
75 to <85	43 (8.1)	54 (10.3)	59 (11.2)	56 (10.7)	58 (11.1)	270 (10.3)
>=85	2 (0.4)	3 (0.6)	1 (0.2)	1 (0.2)	1 (0.2)	8 (0.3)
Race						
white	358 (73.1)	388 (73.9)	356 (67.6)	364 (69.7)	357 (68.4)	1823 (69.5)
Asian	150 (28.4)	118 (22.5)	141 (26.8)	131 (25.1)	132 (25.3)	672 (25.6)
American Indian/Alaska Native	0	2 (0.4)	9 (1.7)	6 (1.1)	6 (1.1)	23 (0.9)
Black/African American	4 (0.8)	3 (0.6)	5 (0.9)	7 (1.3)	5 (1.0)	24 (0.9)
Native Hawaiian/Pacific	0	1 (0.2)	0	0	0	1 (0.0)
Missing	16 (3.0)	13 (2.5)	16 (3.0)	14 (2.7)	22 (4.2)	81 (3.1)
Region						
Western Europe	135 (25.6)	126 (24.0)	147 (27.9)	152 (29.1)	126 (24.1)	686 (26.1)
East Asia	132 (25.0)	102 (19.4)	123 (23.3)	121 (23.2)	121 (23.2)	599 (22.8)
Eastern Europe	89 (16.9)	114 (21.7)	86 (16.3)	86 (16.5)	94 (18.0)	469 (17.9)
North America	97 (18.4)	92 (17.5)	105 (19.9)	82 (15.7)	91 (17.4)	467 (17.8)
Latin America	52 (9.8)	65 (12.4)	44 (8.3)	62 (11.9)	71 (13.6)	294 (11.2)
India	18 (3.4)	15 (2.9)	17 (3.2)	10 (1.9)	9 (1.7)	69 (2.6)
Australia/NewZ/S.African	5 (0.9)	11 (2.1)	5 (0.9)	9 (1.7)	10 (1.9)	40 (1.5)
Smoking status, N (%)						
Ex-smoker	332 (62.9)	310 (59.0)	339 (64.3)	326 (62.5)	333 (63.8)	1640 (62.5)
Current smoker	196 (37.1)	215 (41.0)	188 (35.7)	196 (37.5)	189 (36.2)	984 (37.5)
Never smoked	0	0	0	0	0	0
Mean pack years (SD)	46.4(23.3)	44.7 (24.8)	47.1 (28.7)	46.6 (24.8)	47.4 (26.1)	46.4 (25.6)
COPD duration (years), N	528	524	527	522	522	2623
Mean (SD)	6.5(6.1)	6.4(5.8)	6.6(6.4)	6.2(5.1)	6.6(5.6)	6.5(5.8)
Range	0.0-45.3	0.0-42.0	0.0-43.0	0.0-31.0	0.1-40.0	0.0-45.3
COPD duration (years), N (%)						
<1	69 (13.1)	59 (11.2)	66 (12.5)	44 (8.4)	44 (8.4)	282 (10.7)
1 to <10	342 (64.8)	353 (67.2)	340 (64.5)	362 (69.3)	345 (66.1)	1742 (66.4)
10 to <20	92 (17.4)	94 (17.9)	98 (18.6)	100 (19.2)	118 (22.6)	502 (19.1)
>= 20	25 (4.7)	18 (3.4)	23 (4.4)	16 (3.1)	15 (2.9)	97 (3.7)
Missing	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

Source: Clinical Study Report, Trial 1237.5, Table 11.2.1:1 and Table 15.1.4:2 (with modifications in format)

Table 5 Patients Demographics and Baseline Characteristics (Trial 6, Treated Set)

	Olo 5 N=510	Tio 2.5 N=507	Tio 5 N=506	T+O 2.5/5 N=508	T+O 5/5 N=507	Total N=2538
Sex, N (%)						
Male	378 (74.1)	361 (71.2)	372 (73.5)	368 (72.4)	349 (68.8)	1828 (72.0)
Female	132 (25.9)	146 (28.8)	134 (26.5)	140 (27.6)	158 (31.2)	710 (28.0)
Age(years), N	510	507	506	508	507	2548
Mean (SD)	64.7 (8.3)	63.9 (8.7)	63.5 (8.7)	64.1 (7.6)	62.7 (8.4)	63.8 (8.4)
Range	43-87	40-87	40-97	42-83	40-82	40-97
Age class, N(%)						
<65	242 (47.5)	270 (53.3)	272 (53.8)	266 (52.4)	285 (56.2)	1335 (52.6)
65 to <75	203 (39.8)	175 (34.5)	184 (36.4)	194 (38.2)	184 (36.3)	940 (37.0)
75 to <85	64 (12.5)	61 (12.0)	47 (9.3)	48 (9.4)	38 (7.5)	258 (10.2)
>=85	1 (0.2)	1 (0.2)	3 (0.6)	0 (0.0)	0 (0.0)	5 (0.2)
Race						
white	371 (72.7)	356 (70.2)	358 (70.8)	379 (74.6)	375 (74.0)	1839 (72.5)
Asian	129 (25.3)	130 (25.6)	137 (27.1)	120 (23.6)	118 (23.3)	634 (25.0)
American Indian/Alaska Native	1 (0.2)	2 (0.4)	3 (0.6)	0	1 (0.2)	7 (0.3)
Black/African American	8 (1.6)	16 (3.2)	7 (1.4)	9 (1.8)	11 (2.2)	51 (2.0)
Native Hawaiian/Pacific	0	1 (0.2)	0	0	0	1
Missing	1 (0.2)	2 (0.4)	1 (0.2)	0	2 (0.4)	6 (0.2)
Region						
Western Europe	146 (28.6)	129 (25.4)	137 (27.1)	156 (30.7)	142 (28.0)	710 (28.0)
East Asia	106 (20.8)	113 (22.3)	120 (23.7)	106 (20.9)	107 (21.1)	552 (21.7)
Eastern Europe	80 (15.7)	77 (15.2)	73 (14.4)	78 (15.4)	83 (16.4)	391 (15.4)
North America	102 (20.0)	109 (21.5)	101 (20.0)	102 (20.1)	110 (21.7)	524 (20.6)
Latin America	36 (7.1)	37 (7.3)	36 (7.1)	35 (6.9)	38 (7.5)	182 (7.2)
India	23 (4.5)	15 (3.0)	16 (3.2)	14 (2.8)	10 (2.0)	78 (3.1)
Australia/NewZ/S.African	17 (3.3)	27 (5.3)	23 (4.5)	17 (3.3)	17 (3.4)	101 (4.0)
Smoking status, N (%)						
Ex-smoker	328 (64.3)	334 (65.9)	324 (64.0)	332 (65.4)	296 (58.4)	1614 (63.6)
Current smoker	182 (35.7)	173 (34.1)	182 (36.0)	176 (34.6)	211 (41.6)	924 (36.4)
Never smoked	0	0	0	0	0	0
Mean pack years (SD)	47.8 (27.0)	44.6 (22.7)	45.5 (26.5)	45.6 (25.4)	46.0 (25.0)	45.9 (25.4)
COPD duration (years), N	510	507	506	508	507	2538
Mean (SD)	7.1(6.2)	6.5(6.0)	6.2(5.7)	7.0(6.1)	6.1 (5.5)	6.6 (5.9)
Range	5.3- 40.0	5.0-42.0	5.0- 34.1	5.4-34.2	4.8-40.0	5.0-42.0
COPD duration (years), N (%)						
<1	49 (9.6)	72 (14.2)	74 (14.6)	60 (11.8)	65 (12.8)	320 (12.6)
1 to <10	317 (62.2)	311 (61.3)	314 (62.1)	304 (59.8)	335 (66.1)	1581 (62.3)
10 to <20	114 (22.4)	100 (19.7)	101 (20.0)	112 (22.0)	90 (17.8)	517 (20.4)
>= 20	30 (5.9)	24 (4.7)	17 (3.4)	32 (6.3)	17 (3.4)	120 (4.7)

Source: Clinical Study Report, Trial 1237.6, Table 11.2.1:1 and Table 15.1.4:2 (with modifications in format)

3.2.1.4 Results and Conclusions

3.2.1.4.1 Primary Endpoints

The applicant's efficacy assessment for both studies was based on the analyses of FEV_1 AUC_{0-3h} response and trough FEV_1 response assessed after 24 weeks of treatment (Table 4 and Table 5). According to the pre-specified hierarchical testing sequence, the primary endpoint comparisons for Tio+Olo 5/5 µg were tested first across endpoints and the comparisons for Tio+Olo 2.5/5 µg were tested thereafter. In all hypothesis tests, the Tio+Olo FDCs were superior to the respective individual components for both primary endpoints in both trials ($p<0.0001$ to $p=0.0231$). Additional analyses, using either an asymptotically consistent empirical 'sandwich' estimator approach or a pattern mixture model, both yielded consistent results.

Trial 5

The adjusted mean FEV_1 AUC_{0-3h} response after 24 weeks (Day 169) was statistically significantly greater for the Tio+Olo FDCs than for the respective individual components ($p<0.0001$ for all comparisons). For Tio+Olo 5/5 µg, the treatment difference in the adjusted mean FEV_1 AUC_{0-3h} response was 0.123 L compared with Olo 5 µg and 0.117 L compared with Tio 5 µg. For Tio+Olo 2.5/5 µg, the treatment difference in the FEV_1 AUC_{0-3h} response was 0.109 L compared with Olo 5 µg and 0.093 L compared with Tio 2.5 µg.

The adjusted mean trough FEV_1 response after 24 weeks (Day 170) was also statistically significantly greater for the Tio+Olo FDCs than for the respective individual components ($p<0.0001$ to $p=0.0174$). For Tio+Olo 5/5 µg, the treatment difference in trough FEV_1 response was 0.082 L compared with Olo 5 µg and 0.071 L compared with Tio 5 µg. For Tio+Olo 2.5/5 µg, the treatment difference in trough FEV_1 response was 0.058 L compared with Olo 5 µg and 0.029 L compared with Tio 2.5 µg.

Trial 6

The adjusted mean FEV_1 AUC_{0-3h} response after 24 weeks (Day 169) was statistically significantly greater for the Tio+Olo FDCs than for the respective individual components ($p<0.0001$ for all comparisons). For Tio+Olo 5/5 µg, the treatment difference in the adjusted mean FEV_1 AUC_{0-3h} response was 0.132 L compared with Olo 5 µg and 0.103 L compared with Tio 5 µg. For Tio+Olo 2.5/5 µg, the treatment difference in the FEV_1 AUC_{0-3h} response was 0.121 L compared with Olo 5 µg and 0.131 L compared with Tio 2.5 µg.

The adjusted mean trough FEV_1 response after 24 weeks (Day 170) was also statistically significantly greater for the Tio+Olo FDCs than for the respective individual components ($p<0.0001$ to $p=0.0231$). For Tio+Olo 5/5 µg, the treatment difference in trough FEV_1 response was 0.088 L compared with Olo 5 µg and 0.050 L compared with Tio 5 µg. For Tio+Olo 2.5/5 µg, the treatment difference in trough FEV_1 response was 0.067 L compared with Olo 5 µg and 0.062 L compared with Tio 2.5 µg.

Table 6 FEV_1 AUC_{0-3h} response and trough FEV_1 response after 24 weeks – FAS

	Trial 5		Trial 6	
Parameter **Treatment**	**N**	**Response** **Adjusted Mean (SE)**	**N**	**Response** **Adjusted Mean (SE)**
FEV1 AUC_{0-3h} (Day 169)				
Olo 5	525	0.133 (0.008)	507	0.136 (0.009)
Tio 2.5	524	0.148 (0.008)	504	0.125 (0.009)
Tio 5	526	0.139 (0.008)	500	0.165 (0.009)
T+O 2.5/5	521	0.241 (0.008)	506	0.256 (0.009)
T+O 5/5	522	0.256 (0.008)	502	0.268 (0.009)
Trough FEV_1 (Day 170)				
Olo 5	519	0.054 (0.009)	503	0.057 (0.009)
Tio 2.5	519	0.083 (0.008)	499	0.062 (0.009)
Tio 5	520	0.065 (0.008)	498	0.096 (0.009)
T+O 2.5/5	518	0.111 (0.008)	500	0.125 (0.009)
T+O 5/5	521	0.136 90.008)	497	0.145 (0.009)

Source: Clinical Study Report, Trial 1237.5, Table 11.4.1.1.1:1 and Table 11.4.1.1.1:2 (with modifications in format)

Table 7 Treatment comparisons for FEV_1 AUC $_{0-3h}$ response and trough FEV_1 response after 24 weeks – FAS

		Trial 5			Trial 6		
		Treatment Difference			Treatment Difference		
Parameter	**Treatment comparison**	**Adjusted Mean**	**95% CI**	**P-value**	**Adjusted Mean**	**95% CI**	**P-value**
Test	**FEV1 AUC0-3h (Day 169)**						
1	T+O 5/5 ---Olo 5	0.123	0.100, 0.146	<0.0001	0.132	0.108, 0.157	<0.0001
2	T+O 5/5 ---Tio 5	0.117	0.094, 0.140	<0.0001	0.103	0.078, 0.127	<0.0001
5	T+O 2.5/5 ---Olo 5	0.109	0.086, 0.132	<0.0001	0.121	0.096, 0.145	<0.0001
6	T+O 2.5/5 ---Tio 2.5	0.093	0.070, 0.116	<0.0001	0.131	0.106, 0.155	<0.0001
9	T+O 2.5/5 --- Tio 5	0.102	0.080, 0.125	<0.0001	0.091	0.066, 0.115	<0.0001
	Trough FEV1 (Day 170)						
3	T+O 5/5 ---Olo 5	0.082	0.059, 0.106	<0.0001	0.088	0.063, 0.113	<0.0001
4	T+O 5/5 ---Tio 5	0.071	0.047, 0.094	<0.0001	0.050	0.024, 0.075	0.0001
7	T+O 2.5/5 ---Olo 5	0.058	0.034, 0.081	<0.0001	0.067	0.042, 0.092	<0.0001
8	T+O 2.5/5 ---Tio 2.5	0.029	0.005, 0.052	0.0174	0.062	0.037, 0.087	<0.0001
10	T+O 2.5/5 --- Tio 5	0.046	0.023, 0.070	0.0001	0.029	0.004, 0.054	0.0231

Source: Clinical Study Report, Trial 1237.6, Table 11.4.1.1.1:1 and Table 11.4.1.1.1:2 (with modifications in format)

3.2.1.4.2 Selected Secondary and Further Efficacy Endpoints

3.2.1.4.2.1 FEV_1 AUC $_{0\text{-}3h}$ response [L] on Days 1, 85, and 365

Adjusted mean FEV_1 $AUC_{0\text{-}3h}$ response over the 52-week treatment period is illustrated for the 5 treatment groups in Figure 1 for Trial 5 and Figure 2 for Trial 6, respectively.

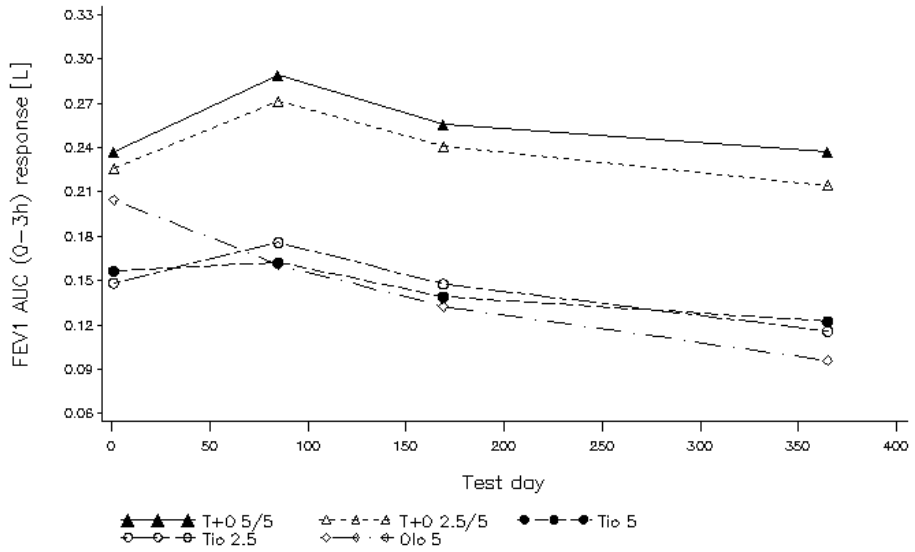
Trial 5

For Tio+Olo 5/5 µg, the increase in adjusted mean FEV_1 $AUC_{0\text{-}3h}$ response vs. Olo 5 µg was 0.033 L on Day 1 (p=0.0067), 0.128 L on Day 85 (p<0.0001), and 0.141 L on Day 365 (p<0.0001); increases in adjusted mean FEV_1 $AUC_{0\text{-}3h}$ response vs. Tio 5 µg ranged from 0.081 L to 0.126 L (p<0.0001 for all comparisons). For Tio+Olo 2.5/5 µg, the increase in adjusted mean FEV_1 $AUC_{0\text{-}3h}$ response vs. Olo 5 µg was 0.022 L on Day 1 (p=0.0746), 0.111 L on Day 85 (p<0.0001), and 0.119 L on Day 365 (p<0.0001). Increases in adjusted mean FEV_1 $AUC_{0\text{-}3h}$ response vs. Tio 2.5 µg ranged from 0.078 L to 0.099 L, while increases vs. Tio 5 µg ranged from 0.070 L to 0.109 L (p<0.0001 for all comparisons).

Study 6

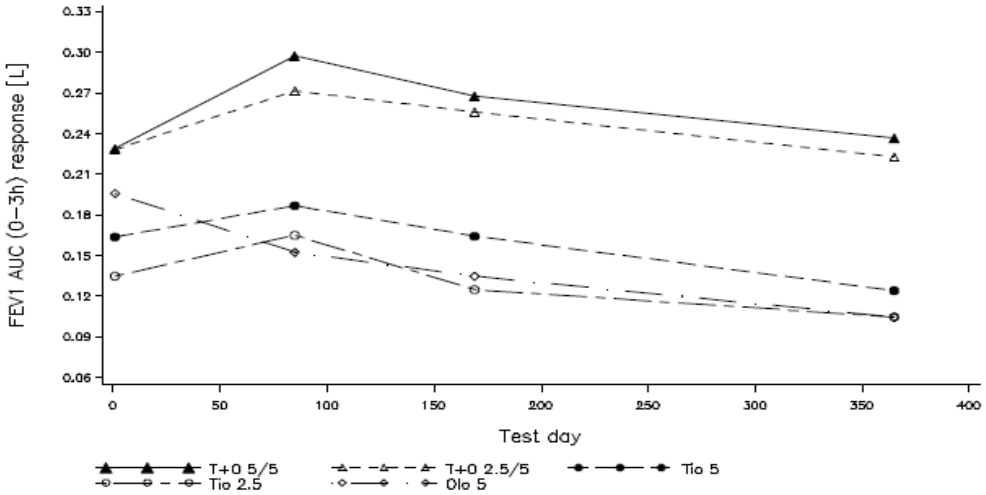
For Tio+Olo 5/5 µg, the increase in adjusted mean FEV_1 $AUC_{0\text{-}3h}$ response vs. Olo 5 µg was 0.033 L on Day 1 (p=0.0095), 0.145 L on Day 85 (p<0.0001), and 0.133 L on Day 365 (p<0.0001); increases in adjusted mean FEV_1 $AUC_{0\text{-}3h}$ response vs. Tio 5 µg ranged from 0.065 L to 0.112 L (p<0.0001 for all comparisons). For Tio+Olo 2.5/5 µg, the increase in adjusted mean FEV_1 $AUC_{0\text{-}3h}$ response vs. Olo 5 µg was 0.033 L on Day 1 (p=0.0112), 0.119 L on Day 85 (p<0.0001), and 0.118 L on Day 365 (p<0.0001). Increases in FEV_1 $AUC_{0\text{-}3h}$ response vs. Tio 2.5 µg ranged from 0.093 L to 0.118 L, while increases vs. Tio 5 µg ranged from 0.064 L to 0.098 L (p<0.0001 for all comparisons). There was a consistent separation in FEV_1 $AUC_{0\text{-}3h}$ response Tio+Olo 5/5 µg and Tio+Olo 2.5/5 µg throughout the 52-week treatment period, ranging from 0.001 L to 0.026 L (nominal p-values ranging from p=0.0470 to 0.9514).

Figure 1 Adjusted mean FEV_1 $AUC_{0\text{-}3h}$ response [L] over 52 weeks –Trial 5



Source: Clinical Study Report, Trial 1237.5, Figure 11.4.1.2.1:1

Figure 2 Adjusted mean FEV_1 $AUC_{0\text{-}3h}$ response [L] over 52 weeks –Trial 6



Source: Clinical Study Report, Trial 1237.6, Figure 11.4.1.2.1:1

3.2.1.4.2.2 Trough FEV_1 response [L] on Days 15, 43, 85, 169, and 365

Adjusted mean trough FEV_1 response over the 52-week treatment period is illustrated for the 5 treatment groups in Figure 3 for Trial 5 and Figure 4 for Trial 6, respectively.

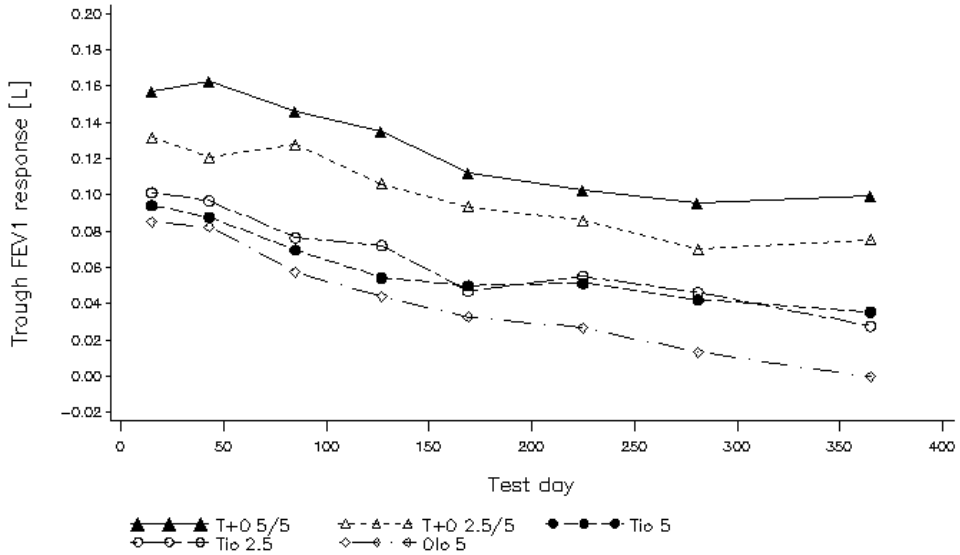
Study 5

For Tio+Olo 5/5 µg, increases in adjusted mean trough FEV_1 response vs. Olo 5 µg ranged from 0.072 L and 0.100 L, while increases vs. Tio 5 µg ranged from 0.062 L to 0.076 L ($p<0.0001$ for all comparisons). For Tio+Olo 2.5/5 µg, increases in adjusted mean in trough FEV_1 response vs. Olo 5 µg ranged from 0.038 L to 0.076 L ($p<0.0001$ to $p=0.0018$); increases vs. Tio 2.5 µg ranged from 0.024 L to 0.051 L ($p<0.0001$ to $p=0.0517$), and increases vs. Tio 5 µg ranged from 0.033 L to 0.058 L ($p<0.0001$ to $p=0.0072$).

Study 6

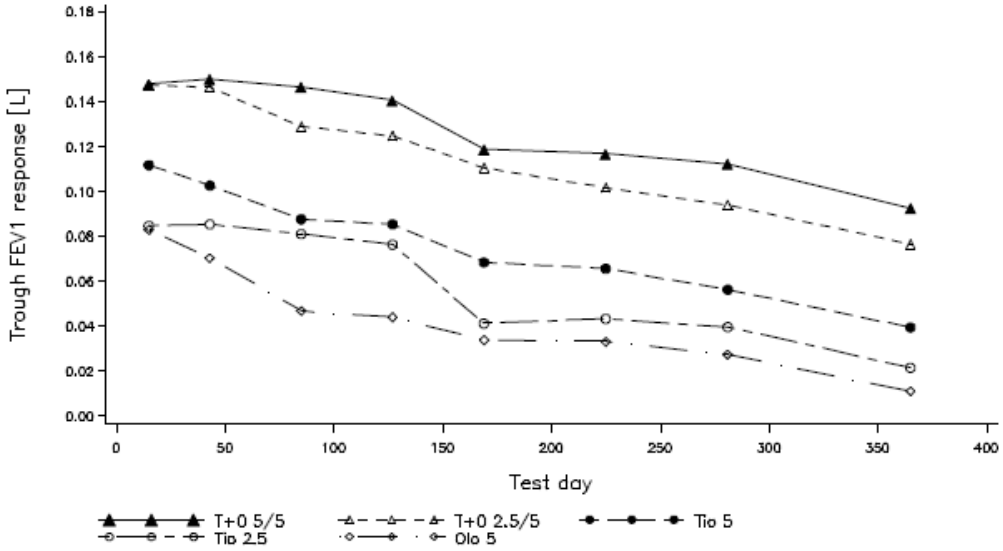
For Tio+Olo 5/5 µg, increases in adjusted mean trough FEV_1 response vs. Olo 5 µg ranged from 0.065 L to 0.100 L ($p<0.0001$ for all comparisons); while increases vs. Tio 5 µg ranged from 0.036 L to 0.059 L ($p<0.0001$ to $p=0.0050$). For Tio+Olo 2.5/5 µg, increases in adjusted mean trough FEV_1 response vs. Olo 5 µg ranged from 0.064 L to 0.082 L ($p<0.0001$ for all comparisons), while increases vs. Tio 2.5 µg ranged from 0.048 L to 0.069 L ($p<0.0001$ to $p=0.0002$), and increases vs. Tio 5 µg ranged from 0.036 L to 0.044 L ($p=0.0007$ to $p=0.0057$).

Figure 3 Adjusted mean trough FEV_1 response [L] over 52 weeks − Trial 5



Source: Clinical Study Report, Trial 1237.5, Figure 11.4.1.2.1:2

Figure 4 Adjusted mean trough FEV_1 response [L] over 52 weeks − Trial 6

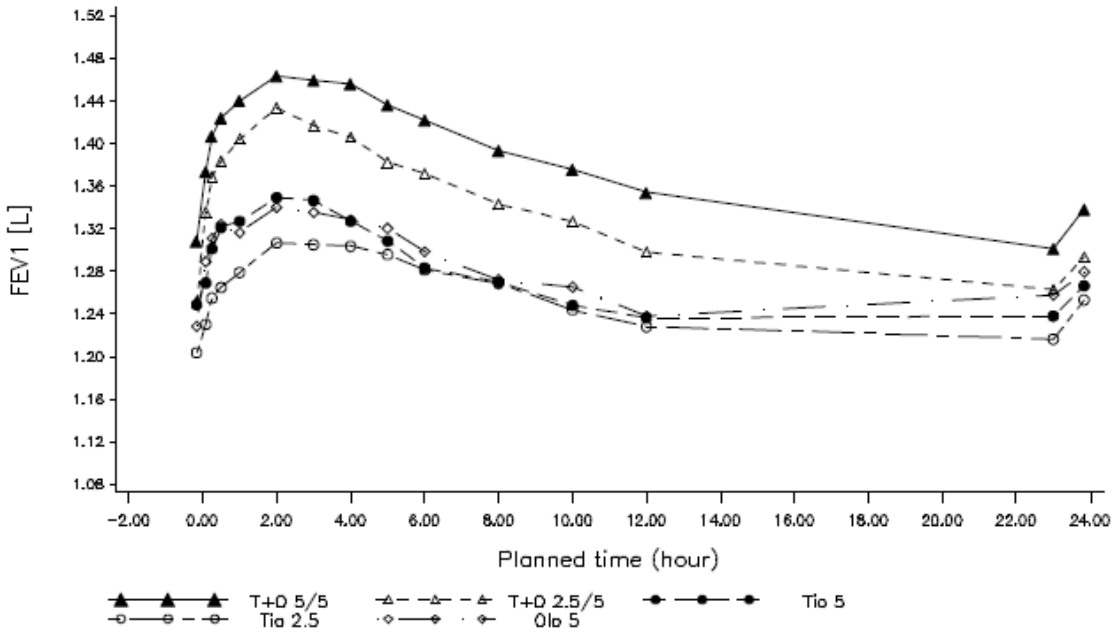


Source: Clinical Study Report, Trial 1237.6, Figure 11.4.1.2.1:2

3.2.1.4.2.3 FEV1 analysis in the subset of patients with 12-h PFT

In a subgroup of patients in both Trial 5 and Trial 6, pulmonary function tests were continued up to 12 hours post-dose on Day 169 which provided further characterization of the bronchodilating profile of Tio+Olo FDC. The time course of the mean FEV_1 measurements after 24 Weeks (on Day 169) in the combined dataset is presented in Figure 5. Both FDCs demonstrated increased bronchodilator efficacy compared with the monotherapies up to 12 hours post-dose on Day 169.

Figure 5 Adjusted mean FEV_1 [L] over 24 hours post-dose after 24 weeks − 12-h PFT set (Trials 5 and 6 Combined)



Source: Clinical Study Report, Summary of Clinical Efficacy, Module 2.7.3, Figure 5

The adjusted mean responses and comparisons of each FDC to monotherapies for FEV1 AUC_{0-12h} and FEV_1 AUC_{0-24h} responses on Day 169 are given in Tables 8 and 9. The difference between Tio+Olo FDCs and the respective individual components were all statistically significant (p<0.0001 to 0.0136).

Table 8 FEV_1 AUC_{0-12h} response [L] and FEV_1 AUC_{0-24h} response [L] at Week 24 (12-hour PFT set, Trials 5 and 6 Combined)

Parameter Treatment	N	Response Adjusted Mean (SE)
FEV1 AUC_{0-12h}		
Olo 5	194	0.131 (0.015)
Tio 2.5	185	0.109 (0.016)
Tio 5	160	0.127 (0.017)
T+O 2.5/5	178	0.202 (0.016)
T+O 5/5	167	0.250 (0.016)
FEV1 AUC_{0-24h}		
Olo 5	194	0.108 (0.014)
Tio 2.5	185	0.083 (0.015)
Tio 5	160	0.100 (0.016)
T+O 2.5/5	178	0.159 (0.015)
T+O 5/5	167	0.206 (0.015)

Source: Clinical Study Report, Trial 1237.9991, Table11.4.1.2.2

Table 9 Treatment comparisons for FEV_1 AUC 0-12h response and FEV_1 AUC $_{0-24h}$ response at Week 24 (12-hour PFT set, Trials 5 and 6 Combined)

	Treatment Difference		
Parameter **Treatment comparison**	**Adjusted Mean**	**95% CI**	**P-value**
FEV1 AUC_{0-12h}			
T+O 5/5 ---Olo 5	0.118	0.074, 0.162	<0.0001
T+O 5/5 ---Tio 5	0.123	0.077, 0.169	<0.0001
T+O 2.5/5 ---Olo 5	0.071	0.028, 0.114	0.0012
T+O 2.5/5 ---Tio 2.5	0.094	0.050, 0.137	<0.0001
T+O 2.5/5 --- Tio 5	0.076	0.031, 0.121	0.0010
FEV1 AUC_{0-24h}			
T+O 5/5 ---Olo 5	0.098	0.057, 0.139	<0.0001
T+O 5/5 ---Tio 5	0.106	0.063, 0.149	<0.0001
T+O 2.5/5 ---Olo 5	0.051	0.010, 0.091	0.0136
T+O 2.5/5 ---Tio 2.5	0.075	0.035, 0.116	0.0003
T+O 2.5/5 --- Tio 5	0.059	0.016, 0.101	0.0065

Source: Clinical Study Report, Trial 1237.9991, Table11.4.1.2.2

3.2.1.4.3 Missing Data Impact

The overall discontinuation rate at the primary analysis time point, Week 24 or Day 169, was relatively low ranging from 4% to 12% in Trial 5 and from 7% to 12% in Trial 6, respectively. Thus the differences in the discontinuation rates at Week 24 among the treatment groups had minimal impact on the comparisons of the primary efficacy endpoints between treatment groups. Nevertheless, the proportion of patient who discontinued before week 24 are described in Table 10 and a continuous responder analysis, incorporating patient who discontinued the study as failures are provided in Figures 6 and 7. This type of utility analysis is considered an appropriate reflection of the efficacy of the study treatment in that subject(s) who are unable or unwilling to continue study treatment cannot be expected to gain efficacy from that treatment. This is in contrast to the assumption of "missing at random" which is required for inferential methods such as MMRM which aim to provide a hypothetical estimate of efficacy in a world where all subject adhere. We also note that these sensitivity utility analyses are consistent with the protocol specified primary analysis method for the primary efficacy endpoints in these studies since to some extent, the pre-specified analysis was a similar type of utility analysis (reader is referred to missing data imputation description in section 3.2.1.2 of this document).

Table 10 Number of Patients Discontinued before Week 24 (Day 169)

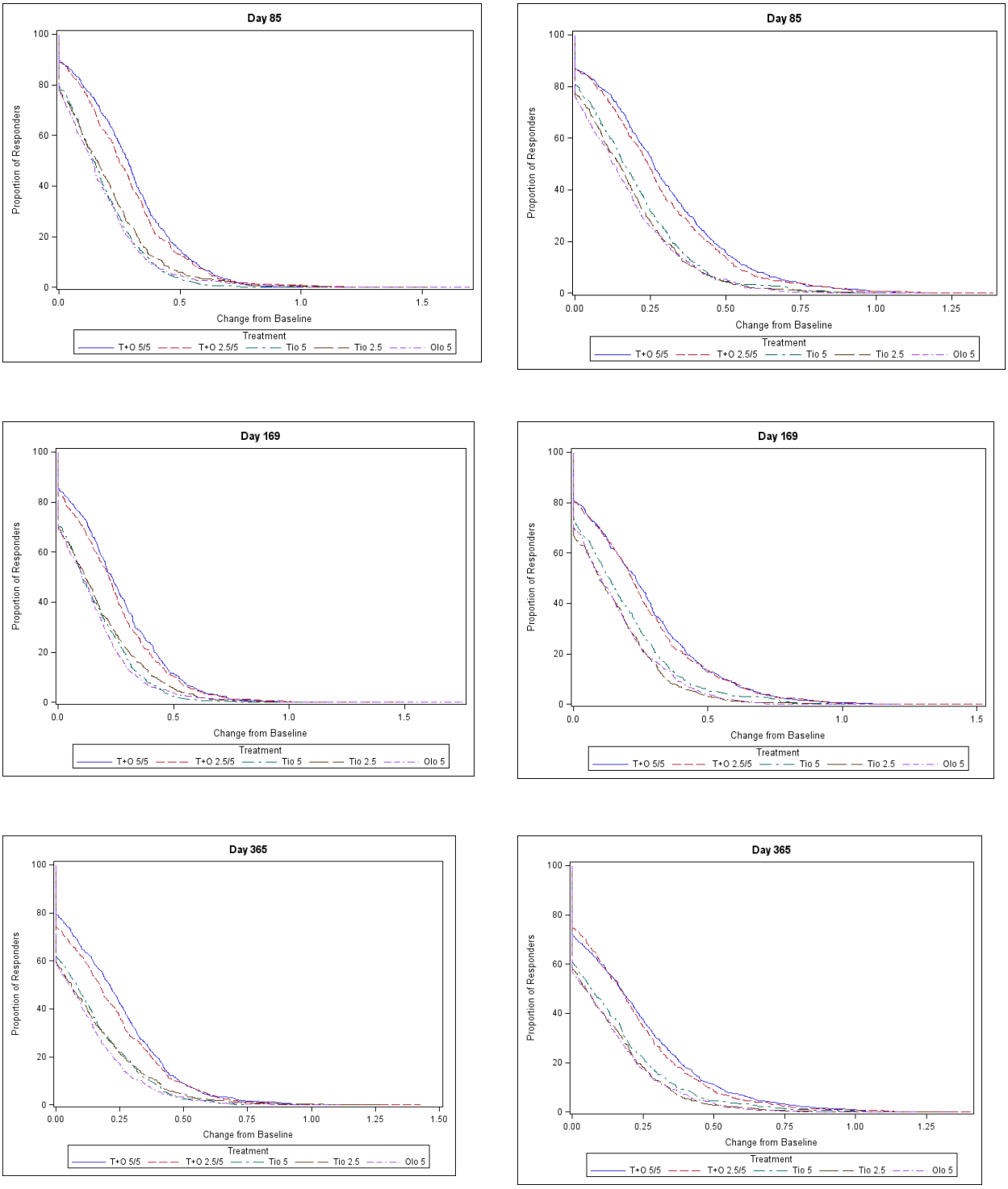
	Trial 5					Trial 6				
	Olo 5 N (%)	Tio 2.5 N (%)	Tio 5 N (%)	T+O 2.5/5 N (%)	T+O 5/5 N (%)	Olo 5 N (%)	Tio 2.5 N (%)	Tio 5 N (%)	T+O 2.5/5 N (%)	T+O 5/5 N (%)
Treated on Day 1	528	525	527	522	522	510	507	506	508	507
Discontinued before Visit										
Day 43	15	15	11	5	6	13	18	11	9	11
Day 85	22	8	18	5	7	14	9	18	8	12
Day 127	11	8	6	9	7	17	22	16	10	9
Day 169	15	7	9	4	9	16	9	10	7	5
Overall	63 (11.9)	38 (7.2)	44 (8.3)	23 (4.4)	29 (5.6)	60 (11.7)	58 (11.4)	55 (10.9)	34 (6.7)	37 (7.3)

Source: Reviewer.

A further exploration of FEV_1 $AUC_{0\text{-}3h}$ response and trough FEV_1 response was conducted by this reviewer utilizing the continuous responder analyses (Figure 6 and Figure 7, respectively). In these plots, patients who discontinued from the study regardless of reason are considered non-responders. The worst value is imputed to missing post-baseline observations. These figures provide a visual display of the relative benefit of Tio+Olo FDC across the entire range of response, as well over the period of double-blind treatment. The x-axis shows change from baseline in FEV_1 $AUC_{0\text{-}3h}$ or Trough FEV_1 and the y-axis shows the corresponding percentage of patients achieving that level of response. From the plots for FEV_1 $AUC_{0\text{-}3h}$ response and trough FEV_1 response there is clear evidence that a higher proportion of patients treated with Tio+Olo FDC responded better compared to monotherapy throughout the entire 52 weeks.

Figure 6 FEV_1 $AUC_{0\text{-}3h}$ Response Profile by Visits

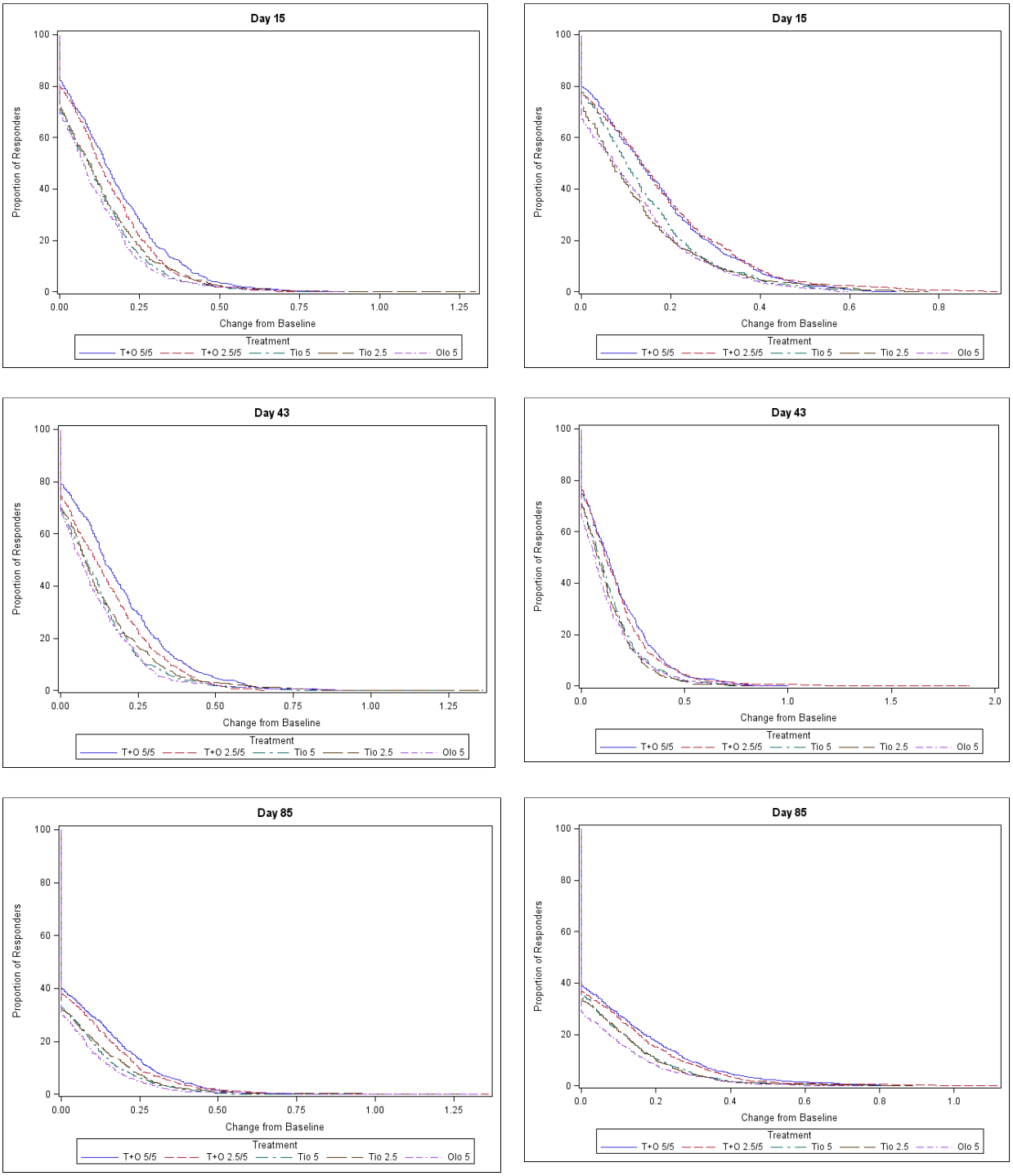
Trial 5 **Trial 6**



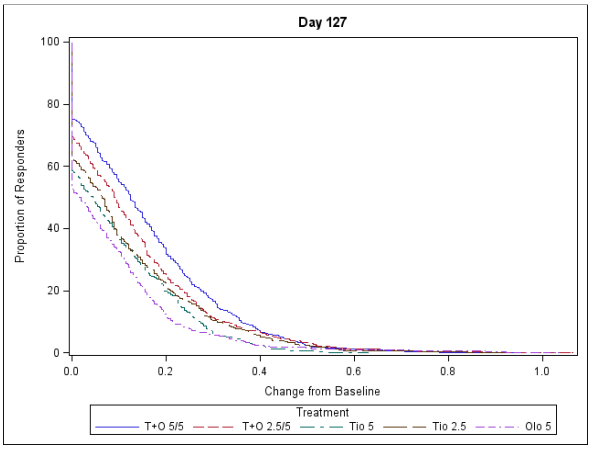
Source: Reviewer

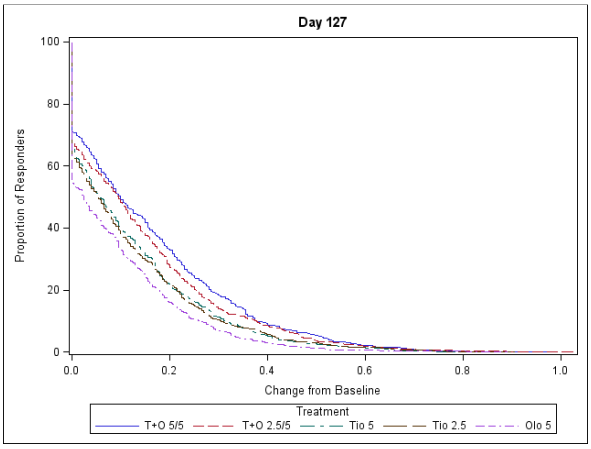
Figure 7 Trough FEV_1 Response Profile by Visits

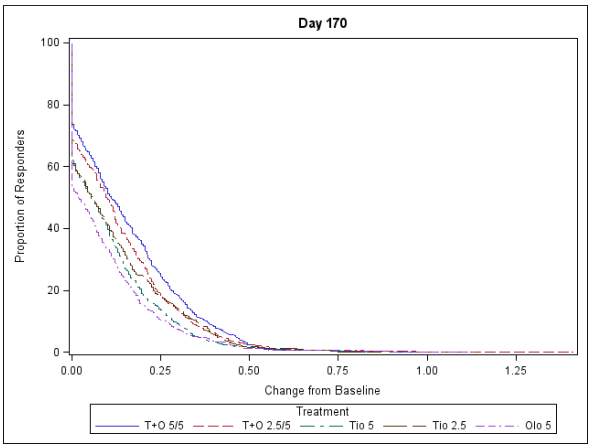
Trial 5 **Trial 6**

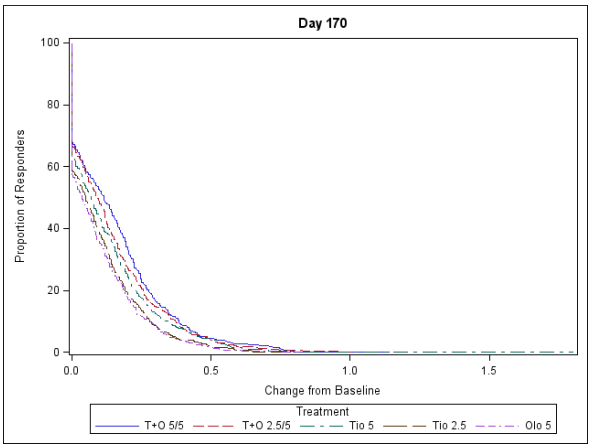


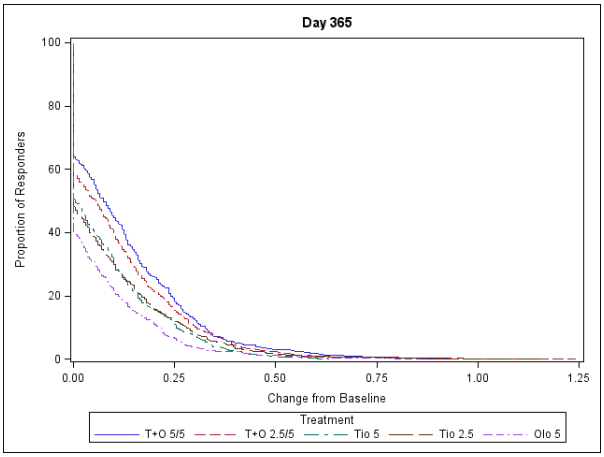
Trial 5 **Trial 6**

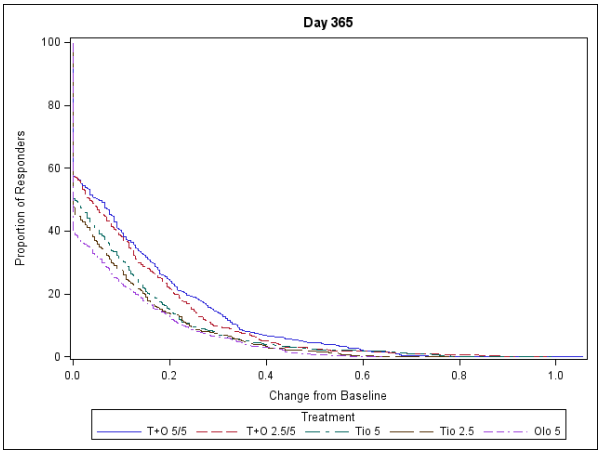












Source: Reviewer

3.2.2 Trial 20

3.2.2.1 Study Design and Endpoints

Trial 20 was part of the phase III registration program for Tio+Olo FDC and was complimentary to the replicate pivotal studies, Trial 5 and Trial 6. It was a phase III multi-center, multi-national, randomized, double-blind, placebo-controlled, 6 treatment, 4 period, crossover trial. The primary objective was to characterize the 24-hour lung function profiles with once daily orally inhaled tiotropium+olodaterol fixed dose combination (T+O 5/5 µg; T+O 2.5/5 µg), and compare with the profiles of once daily orally inhaled tiotropium (2.5 µg and 5 µg) [tiotropium 2.5 µg (Tio 2.5); tiotropium 5 µg (Tio 5)], olodaterol 5 µg (Olo 5), and placebo in patients with COPD after 6 weeks of treatment in a rigorous assessment. The 6-week treatment periods were separated by 3-week washout periods. There were 30 treatment sequences, each of which consisted of 4 treatments in predefined order. Eligible patients were randomly assigned to one of 30 treatment sequences such that the 6 treatments were distributed equally in each treatment period. There were 10 scheduled visits including screening, randomization, Weeks 6, 9, 15, 18, 24, 27, and 33 as well as 21 days after the final dose of study medication. Trial 20 was conducted in 29 centers in 7 countries from 3/27/2012 to 8/12/2013.

The primary endpoint was the forced expiratory volume in 1 second (FEV_1) $AUC_{0\text{-}24h}$ response [L] after 6-weeks of treatment. FEV_1 $AUC_{0\text{-}24h}$ was calculated as the area under the FEV_1-time curve from 0 to 24 h post-dose using the trapezoidal rule, divided by the duration (24 h) to report in liters. Response was defined as the change from patient baseline which was the mean of non-missing period baselines for each patient. Period baseline was defined as the value in the morning of the start of each treatment period, just prior to administration of the morning dose of randomized treatment. Key secondary endpoints included $FEV_1AUC_{0\text{-}12h}$ response and FEV_1 $AUC_{12\text{-}24h}$ response after 6 weeks of treatment.

3.2.2.2 Statistical Methodologies

The following analysis datasets of interest were defined in the protocol:

- Randomized set (RS): included all randomized patients, regardless of whether they received treatment or not.
- Treated set (TS): included all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.
- Full analysis set (FAS): included patients in the TS who had any period baseline and any evaluable post-dose data for the primary efficacy endpoint at any Week 6 visits.
- Per protocol set (PPS): included patients who complied with the protocol sufficiently. If any important protocol violation (IPV) related to efficacy occurred in any treatment period the whole patient was to be excluded from the PPS.

The primary efficacy analysis was testing superiority of Tio+Olo FDC compared with the individual components (Tio, Olo) with respect to $FEV_1AUC_{0\text{-}24h}$ response. Comparisons between treatment groups were analyzed using a restricted maximum likelihood (REML)-based mixed

effects model for repeated measures (MMRM) approach. This model included patient as a random effect, treatment and period as fixed effects, and period baseline as well as patient baseline as covariates. Compound symmetry was used as a covariance structure for within patient variation and the Kenward-Roger approximation was used to estimate for denominator degrees of freedom. The primary analysis and analysis of key secondary endpoints was performed on the FAS. If the number of patients in the PPS was less than 90% of the number of patients in the FAS, the primary analysis was also to be performed on the PPS for the primary endpoint. There is no interim analysis.

A hierarchical testing scheme, each at the 5% level of significance (2-sided), was employed to protect the overall type I error. The primary efficacy endpoint, FEV_1 $AUC_{0\text{-}24h}$ response, was analyzed in the following order:

1) Tio+Olo 5/5 vs placebo
2) Tio+Olo 5/5 vs Olo 5
3) Tio+Olo 5/5 vs Tio 5
4) Tio+Olo 2.5/5 vs placebo
5) Tio+Olo 2.5/5 vs Olo 5
6) Tio+Olo 2.5/5 vs Tio 5

A hypothesis test in this chain was only considered confirmatory if all previous hypothesis tests were statistically significant at the 2-sided 5% level and the treatment effect favored Tio+Olo FDC; if a test failed, all results from subsequent tests were considered descriptive. The same order was applied when testing key secondary endpoint, first $FEV_1AUC_{0\text{-}12h}$ response and then $FEV_1AUC_{12\text{-}24h}$ response, after 6 weeks.

According to the trial Statistical Analysis Plan and for the purpose of primary efficacy analysis, missing data were handled as follows:

- Data for a visit during a period when there is no study medication given for the period (most likely this will be the beginning-of-period visit) will be set to missing and will not be imputed.
- Missing data at a given visit will be imputed by the available data from the patient at that visit.
- Data obtained after intake of rescue medication will be considered missing. Post-dosing data missing due to worsening of COPD (e.g. exacerbation or need of rescue medication) will be replaced by the worst prior observation on that test day (least favorable value within visit/period). The patient must have received at study drug in the respective period.
- Post-dosing data missing at random for which there are data from that visit both before and after will be linearly interpolated using the pre-dose value if necessary. If there are no subsequent non-missing values for that visit, the last valid observation is carried forward (LOCF within visit/period). The patient must have received study drug in the respective period.
- Completely random missing data were handled through the statistical model.

An alternative analysis was to be performed by considering patient as a fixed effect instead of a random effect. This alternative analysis model included patient, treatment, and period as fixed effects, and only period baseline as a covariate.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 11 shows disposition of patients in Trial 20. A total of 219 were randomized into the trial; all received at least one dose of study medication and were included in the treated set. Overall, 193 patients (88.1%) completed all four treatment periods. Trial medication was most often discontinued during placebo treatment. Discontinuations of trial medication during placebo treatments were mostly due to COPD worsening or other AEs. The FAS dataset excluded 7 patients who had no period baseline or no evaluable post-dose data at any Week 6 visits for the primary endpoint. A further 4 patients with important protocol violation related to efficacy were excluded from the PPS, leading to 208 patients in the PPS set which is >90% of the number of patients in the FAS.

Table 11 Number of subjects and disposition in Trial 20

	Total N (%)
Entered/Randomized	219
Complete all 4 treatment period	193 (88.1%)
Prematurely discontinued trial medication	26 (11.9%)
Analysis Datasets	
Treated Set (TS)	219
Full analysis set (FAS)	212 (96.8)
Patients with no baseline or post-dose data excluded from FAS	7
Per protocol set (PPS)	208 (95.0)
Patients with important protocol violation related to efficacy analysis and excluded from PPS	4

Source: Clinical Study Report, Trial 1237.020, Table 10.1:1 and 11.1:1 (with modification in format)

Selected demographic features and baseline covariates were presented in Table 12. Patients were approximately 61 years old, 58.9% of them were male, and 99.1% were White. All patients were either smokers (62.6%) or ex-smokers (37.4%), with a mean smoking history of 44.4 pack-years. The mean duration from COPD diagnosis to study enrollment was 7.8 years, with 63.5% of the patients having COPD in the range of 1 to less than 10 years.

Table 12 Patient Demographics and Baseline Characteristics (Trial 20, Treated Set)

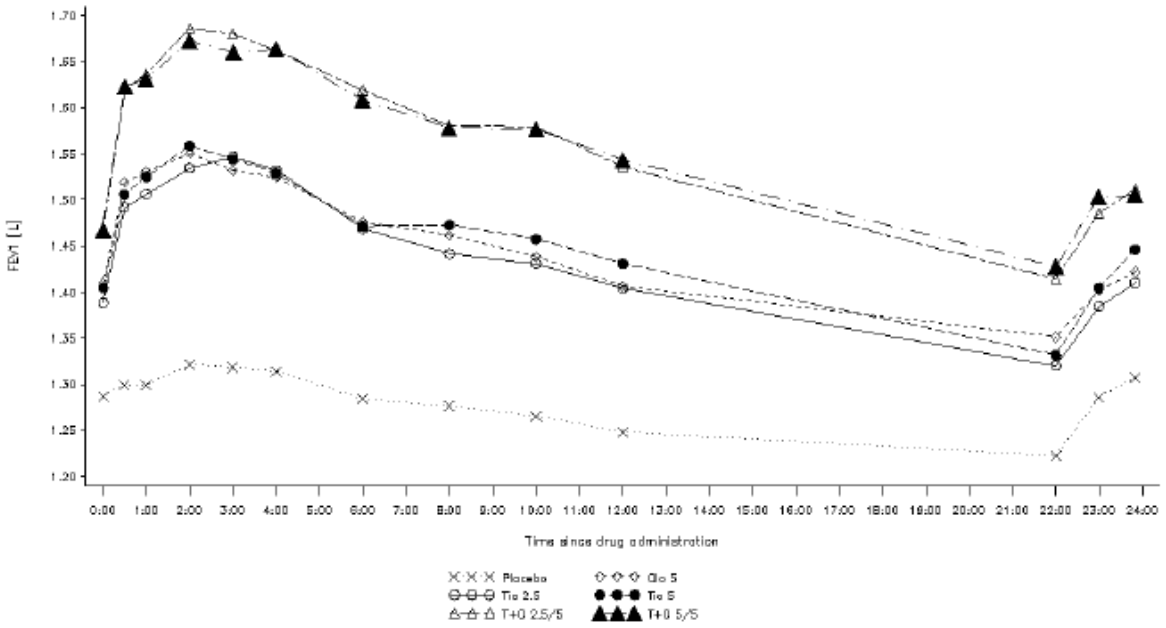
	Total
Treated Patients	219 (100.0)
Sex, N (%)	
Male	129 (58.9)
Female	90 (41.1)
Age(years), N	219
Mean (SD)	61.1 (7.7)
Range	41 – 78
Age class, N(%)	
<65	146 (66.7)
65 to <75	61 (27.9)
75 to <85	12 (5.5)
Race	
white	217 (99.1)
Asian	2 (0.9)
Region	
Eastern Europe	20 (9.1)
North America	50 (22.8)
Western Europe	149 (68.0)
Smoking status, N (%)	
Ex-smoker	82 (37.4)
Current smoker	137 (62.6)
Mean pack years (SD)	44.4 (19.5)
COPD duration (years), N	219
Mean (SD)	7.8 (5.8)
Range	0 – 37.5
COPD duration(years), N (%)	
<1	12 (5.5)
1 to <10	139 (63.5)
10 to <20	57 (26.0)
>= 20	11 (5.0)

Source: Clinical Study Report, Trial 1237.020, Table 11.2.1:1 and 15.1.4:2 (with modification in format)

3.2.2.4 Primary Efficacy Results

Figure 8 displays the adjusted mean FEV_1 [L] over 24 hours post-dose after 6 weeks of treatment in Trial 20. Placebo showed a slight deterioration in $FEV_1AUC_{0\text{-}24h}$ response after 6 weeks of treatment (-0.037 L) while the monotherapies yielded an improvement from baseline of 0.117 to 0.133 L. Both combination therapies showed a larger improvement from baseline of about 0.240 L.

Figure 8 Adjusted mean FEV1 [L] over 24 hours post-dose after 6 weeks of treatment-treated set



Source: Clinical Study Report, Trial 1237.020, Figure 11.4.1:1

The applicant's efficacy assessment was based on the analyses of FEV_1AUC_{0-24h} response after 6 weeks of treatment (Table 4 and Table 5). According to the pre-specified hierarchical testing sequence, the primary endpoint comparisons for Tio+Olo 5/5 µg were tested first followed by the comparisons for Tio+Olo 2.5/5 µg. In all hypothesis tests in Trial 20, the Tio+Olo FDCs were superior to placebo and the respective individual components (all p<0.0001). For Tio+Olo 5/5 µg, there was a 0.280 L improvement compared with placebo, a 0.115 L improvement compared with Olo 5 µg and a 0.110 L improvement compared with Tio 5 µg. For Tio+Olo 2.5/5 µg, there was a 0.277 L improvement compared with placebo, a 0.111 L improvement compared with Olo 5 µg and a 0.124 L improvement compared with Tio 2.5 µg.

Table 13 FEV_1 AUC_{0-24h} response [L] after 6 weeks -- FAS

Treatment	N	Adjusted Mean (SE)
Placebo	132	-0.037 (0.014)
Olo 5	136	0.129 (0.013)
Tio 2.5	136	0.117 (0.013)
Tio 5	135	0.133 (0.014)
T+O 2.5/5	135	0.241 (0.014)
T+O 5/5	138	0.244 (0.013)

Source: Clinical Study Report, Trial 1237.020, Table 11.4.1.1.1:1 (with modification in format)

Table 14 Treatment comparisons for FEV_1 AUC_{0-24h} response [L] after 6 weeks -- FAS

Treatment comparison	Adjusted Mean difference	95% CI	P-value
T+O 5/5 --- Placebo	0.280	0.252, 0.309	<0.0001
T+O 5/5 --- Olo 5	0.115	0.087, 0.143	<0.0001
T+O 5/5 --- Tio 5	0.110	0.082, 0.139	<0.0001
T+O 2.5/5 --- Placebo	0.277	0.249, 0.306	<0.0001
T+O 2.5/5 --- Olo 5	0.111	0.083, 0.140	<0.0001
T+O 2.5/5 --- Tio 2.5	0.124	0.096, 0.152	<0.0001

Source: Clinical Study Report, Trial 1237.020, Table 11.4.1.1.1:2 (with modification in format)

An alternative analysis considering patient as a fixed effect, treatment, period, and period baseline as a covariate, yielded results very similar to the primary analysis. As less than 10% of patients in the FAS were excluded from the PPS, a sensitivity analysis based on the PPS was not performed.

3.2.2.5 Key Secondary Efficacy Results

Tables 15 and 16 show results for key secondary endpoints, FEV_1 AUC_{0-12h} response and FEV_1 AUC_{12-24h} response, which were consistent with the primary analysis of FEV_1 AUC_{0-24h}. Furthermore, responses were higher in all active treatment groups for FEV_1 AUC_{0-12h} response compared with FEV_1 AUC_{12-24h}. Treatment differences between the Tio+Olo FDCs and placebo or the monotherapies were greater when only the first 12 h after dosing were analyzed (FEV_1 AUC_{0-12h}) and smaller when only the last 12 h of the 24-h dosing period were analyzed.

Treatment differences remained statistically significant in favor of the Tio+Olo FDCs for both time periods and for all treatment comparisons (all p<.0001).

Table 15 FEV_1 AUC_{0-12h} response and FEV_1 AUC_{12-24h} response [L] after 6 weeks -- FAS

Parameter	N	Response Adjusted Mean (SE)
FEV_1 AUC_{0-12h}		
Placebo	132	-0.013 (0.015)
Olo 5	136	0.179 (0.015)
Tio 2.5	136	0.171 (0.015)
Tio 5	135	0.186 (0.015)
T+O 2.5/5	135	0.310 (0.015)
T+O 5/5	138	0.305 (0.015)
FEV_1 AUC_{12-24h}		
Placebo	132	-0.060 (0.014)
Olo 5	136	0.079 (0.013)
Tio 2.5	136	0.062 (0.013)
Tio 5	135	0.081 (0.014)
T+O 2.5/5	135	0.172 (0.014)
T+O 5/5	138	0.182 (0.013)

Source: Clinical Study Report, Trial 1237.020, Table 11.4.1.2.1:1 (with modification in format)

Table 16 Treatment comparisons for FEV_1 AUC_{0-12h} response and FEV_1 AUC_{12-24h} response [L] -- FAS

Parameter Comparisons	Adjusted Mean Difference	95% CI	P-value
FEV_1 AUC_{0-12h}			
T+O 5/5 --- Placebo	0.319	0.289, 0.349	<0.0001
T+O 5/5 ---Olo 5	0.126	0.096, 0.156	<0.0001
T+O 5/5 ---Tio 5	0.119	0.089, 0.149	<0.0001
T+O 2.5/5 --- Placebo	0.323	0.293, 0.354	<0.0001
T+O 2.5/5 ---Olo 5	0.131	0.101, 0.161	<0.0001
T+O 2.5/5 ---Tio 2.5	0.139	0.109, 0.169	<0.0001
FEV_1 AUC_{12-24h}			
T+O 5/5 --- Placebo	0.243	0.212, 0.273	<0.0001
T+O 5/5 ---Olo 5	0.103	0.074, 0.133	<0.0001
T+O 5/5 ---Tio 5	0.102	0.072, 0.132	<0.0001
T+O 2.5/5 --- Placebo	0.232	0.201. 0.262	<0.0001
T+O 2.5/5 ---Olo 5	0.093	0.063, 0.123	<0.0001
T+O 2.5/5 ---Tio 2.5	0.110	0.080, 0.140	<0.0001

Source: Clinical Study Report, Trial 1237.020, Table 11.4.1.2.1:2 (with modification in format)

3.3 EVALUATION OF SAFETY

Please refer to the review by Medical Officer, Dr. Robert Lim, for discussion of safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 TRIAL 5 AND TRIAL 6

Subgroup analyses were performed by the applicant for the combined dataset from Trials 5 and 6 to assess the consistency of treatment effects (Tio+Olo FDC vs. mono components) across demographic subgroups including gender, race, age, and region. This reviewer conducted subgroup analysis of primary lung function endpoints (FEV_1 AUC_{0-3h} response, trough FEV_1 response) separately for Trial 5 and Trial 6. The treatment effects were evaluated in each category of a subgroup using the same model as used for the primary analysis. Since these were descriptive analyses, overall type I error was not protected.

The conclusions were consistent with those from the study population as a whole. For each of the subgroups analyzed, both Tio+Olo FDCs demonstrated a treatment effect compared with the individual components for the primary endpoints of FEV_1 AUC_{0-3h} response and trough FEV_1 response after 24 weeks.

4.1.1 Gender, Race, and Age

The adjusted means and treatment comparisons for FEV_1 AUC_{0-3h} response [L] and trough FEV_1 response [L] after 24 weeks are summarized according to gender (Tables 11 and 12), race (Tables 13 and 14), and age categories (Tables 15 and 16), respectively.

As noted in Section 3.2.1.3, the number of male patients was about 3 times that of female patients in both Studies 5 and 6. The majority of patients were White (69.5% to 72.5) or Asian (25.0% to 25.6%). Approximately half of the patients were less than 65 years old while 37% to 39% were between ages 65 to 75 and 10% were between age 75 and 85. With a few exceptions which were not statistically significant, improvements for both Tio+Olo FDCs compared to the individual components were evident across all demographic subgroups. Both Tio+Olo FDCs were superior to the respective individual components with regard to the primary endpoints FEV_1 AUC_{0-3h} response and trough FEV_1 response after 24 weeks. Note that in order to have adequate number of subjects in each subgroup, only White or Asian were included in the by-race analysis and the analysis by age group excluded 13 patients who were at least 85 years old.

Table 17 FEV_1 $AUC_{0\text{-}3h}$ response [L] and trough FEV_1 response [L] by Gender – FAS

		Trial 5		Trial 6	
Parameter	**Treatment**	**N**	**Response Adjusted Mean (SE)**	**N**	**Response Adjusted Mean (SE)**
FEV1 AUC0-3h (Day 169)					
Male	Olo 5	385	0.138 (0.010)	375	0.140 (0.011)
	Tio 2.5	391	0.147 (0.010)	360	0.127 (0.011)
	Tio 5	382	0.142 (0.010)	367	0.170 (0.011)
	T+O 2.5/5	389	0.250 (0.010)	367	0.269 (0.011)
	T+O 5/5	384	0.260 (0.010)	347	0.267 (0.011)
Female	Olo 5	140	0.118 (0.014)	132	0.124 (0.015)
	Tio 2.5	133	0.153 (0.014)	144	0.121 (0.015)
	Tio 5	144	0.129 (0.014)	133	0.153 (0.015)
	T+O 2.5/5	132	0.215 (0.014)	139	0.222 (0.015)
	T+O 5/5	138	0.244 (0.014)	155	0.271 (0.014)
Trough FEV1(Day 170)					
Male	Olo 5	380	0.053 (0.010)	373	0.055 (0.011)
	Tio 2.5	389	0.083 (0.010)	357	0.069 (0.011)
	Tio 5	379	0.069 (0.010)	366	0.096 (0.011)
	T+O 2.5/5	387	0.120 (0.010)	365	0.129 (0.011)
	T+O 5/5	383	0.140 (0.010)	342	0.145 (0.011)
Female	Olo 5	139	0.055 (0.014)	130	0.063 (0.016)
	Tio 2.5	130	0.083 (0.015)	142	0.046 (0.015)
	Tio 5	141	0.056 (0.014)	132	0.096 (0.015)
	T+O 2.5/5	131	0.084 (0.014)	135	0.111 (0.015)
	T+O 5/5	138	0.122 (0.014)	155	0.146 (0.014)

Source: Reviewer

Table 18 Treatment Comparisons for FEV_1 AUC_{0-3h} response [L] and trough FEV_1 response [L] by Gender – FAS

	Trial 5			Trial 6		
	Treatment Difference			Treatment Difference		
Parameter Treatment comparison	**Adjusted Mean**	**95% CI**	**P-value**	**Adjusted Mean**	**95% CI**	**P-value**
FEV1 AUC0-3h (Day 169)						
Male						
T+O 5/5 ---Olo 5	0.122	0.093, 0.150	<0.0001	0.127	0.097, 0.157	<0.0001
T+O 5/5 ---Tio 5	0.118	0.090, 0.145	<0.0001	0.097	0.066, 0.127	<0.0001
T+O 2.5/5 ---Olo 5	0.112	0.084, 0.140	<0.0001	0.129	0.099, 0.159	<0.0001
T+O 2.5/5 ---Tio 2.5	0.104	0.076, 0.131	<0.0001	0.141	0.111, 0.171	<0.0001
T+O 2.5/5 --- Tio 5	0.108	0.080, 0.136	<0.0001	0.099	0.069, 0.128	<0.0001
Female						
T+O 5/5 ---Olo 5	0.125	0.087, 0.163	<0.0001	0.147	0.106, 0.187	<0.0001
T+O 5/5 ---Tio 5	0.114	0.076, 0.152	<0.0001	0.118	0.078, 0.158	<0.0001
T+O 2.5/5 ---Olo 5	0.097	0.058, 0.135	<0.0001	0.098	0.056, 0.140	<0.0001
T+O 2.5/5 ---Tio 2.5	0.062	0.023, 0.102	0.0020	0.102	0.061, 0.142	<0.0001
T+O 2.5/5 --- Tio 5	0.086	0.047, 0.124	<0.0001	0.069	0.028, 0.111	<0.0001
Trough FEV1 (Day 170)						
Male						
T+O 5/5 ---Olo 5	0.088	0.059, 0.117	<0.0001	0.090	0.059, 0.121	<0.0001
T+O 5/5 ---Tio 5	0.071	0.043, 0.100	<0.0001	0.050	0.019, 0.081	0.0018
T+O 2.5/5 ---Olo 5	0.068	0.039, 0.096	<0.0001	0.074	0.044, 0.105	<0.0001
T+O 2.5/5 ---Tio 2.5	0.037	0.009, 0.065	0.0103	0.061	0.030, 0.091	0.0001
T+O 2.5/5 --- Tio 5	0.051	0.023, 0.080	0.0004	0.034	0.003, 0.064	0.0296
Female						
T+O 5/5 ---Olo 5	0.067	0.029, 0.106	0.0007	0.083	0.041, 0.125	<0.0001
T+O 5/5 ---Tio 5	0.066	0.028, 0.105	0.0008	0.050	0.009, 0.091	0.0175
T+O 2.5/5 ---Olo 5	0.029	-0.010, 0.069	0.1448	0.048	0.005, 0.091	0.0291
T+O 2.5/5 ---Tio 2.5	0.001	-0.039, 0.042	0.9440	0.065	0.023, 0.107	0.0024
T+O 2.5/5 --- Tio 5	0.028	-0.011, 0.068	0.1576	0.015	-0.028, 0.058	0.4862

Source: Reviewer

Table 19 FEV_1 $AUC_{0\text{-}3h}$ response [L] and trough FEV_1 response [L] by Race – FAS

		Trial 5		Trial 6	
Parameter	**Treatment**	**N**	**Response Adjusted Mean (SE)**	**N**	**Response Adjusted Mean (SE)**
FEV1 AUC0-3h (Day 169)					
Asian	Olo 5	150	0.108 (0.015)	128	0.105 (0.015)
	Tio 2.5	118	0.154 (0.017)	130	0.155 (0.015)
	Tio 5	141	0.140 (0.015)	135	0.160 (0.015)
	T+O 2.5/5	131	0.247 (0.016)	120	0.220 (0.016)
	T+O 5/5	132	0.263 (0.016)	118	0.249 (0.016)
White	Olo 5	355	0.145 (0.010)	369	0.148 (0.011)
	Tio 2.5	387	0.147 (0.010)	354	0.119 (0.011)
	Tio 5	355	0.141 (0.010)	355	0.166 (0.011)
	T+O 2.5/5	363	0.247 (0.010)	377	0.269 (0.011)
	T+O 5/5	357	0.256 (0.010)	372	0.277 (0.011)
Trough FEV1(Day 170)					
Asian	Olo 5	149	0.035 (0.015)	127	0.037 90.016)
	Tio 2.5	117	0.072 (0.017)	130	0.074 (0.016)
	Tio 5	139	0.074 90.015)	134	0.098 (0.016)
	T+O 2.5/5	131	0.123 (0.016)	119	0.088 (0.017)
	T+O 5/5	131	0.162 (0.016)	115	0.134 (0.017)
White	Olo 5	350	0.064 (0.011)	366	0.065 (0.011)
	Tio 2.5	383	0.086 (0.010)	349	0.062 (0.011)
	Tio 5	351	0.062 (0.011)	353	0.096 (0.011)
	T+O 2.5/5	360	0.117 (0.010)	372	0.137 (0.011)
	T+O 5/5	357	0.126 (0.010)	368	0.152 (0.011)

Source: Reviewer

Table 20 Treatment Comparisons for FEV_1 $AUC_{0\text{-}3h}$ response [L] and trough FEV_1 response [L] by Race – FAS

	Trial 5			Trial 6		
	Treatment Difference			Treatment Difference		
Parameter **Treatment comparison**	**Adjusted Mean**	**95% CI**	**P-value**	**Adjusted Mean**	**95% CI**	**P-value**
FEV1 AUC0-3h (Day 169)						
Asian						
T+O 5/5 ---Olo 5	0.155	0.112, 0.198	<0.0001	0.144	0.100, 0.188	<0.0001
T+O 5/5 ---Tio 5	0.123	0.079, 0.166	<0.0001	0.089	0.046, 0.132	<0.0001
T+O 2.5/5 ---Olo 5	0.139	0.095, 0.182	<0.0001	0.115	0.072, 0.159	<0.0001
T+O 2.5/5 ---Tio 2.5	0.093	0.047, 0.139	<0.0001	0.066	0.023, 0.109	0.0027
T+O 2.5/5 --- Tio 5	0.106	0.063, 0.150	<0.0001	0.060	0.018, 0.103	0.0056
White						
T+O 5/5 ---Olo 5	0.111	0.082, 0.139	<0.0001	0.130	0.100, 0.159	<0.0001
T+O 5/5 ---Tio 5	0.115	0.087, 0.143	<0.0001	0.112	0.082, 0.142	<0.0001
T+O 2.5/5 ---Olo 5	0.101	0.073, 0.129	<0.0001	0.121	0.091, 0.151	<0.0001
T+O 2.5/5 ---Tio 2.5	0.099	0.072, 0.126	<0.0001	0.150	0.120, 0.180	<0.0001
T+O 2.5/5 --- Tio 5	0.106	0.078, 0.134	<0.0001	0.103	0.073, 0.133	<0.0001
Trough FEV1 (Day 170)						
Asian						
T+O 5/5 ---Olo 5	0.127	0.084, 0.170	<0.0001	0.098	0.051, 0.144	<0.0001
T+O 5/5 ---Tio 5	0.088	0.044, 0.131	<0.0001	0.036	-0.010, 0.082	0.1238
T+O 2.5/5 ---Olo 5	0.088	0.045, 0.131	<0.0001	0.051	0.006, 0.097	0.0277
T+O 2.5/5 ---Tio 2.5	0.051	0.006, 0.097	0.0279	0.014	-0.031, 0.060	0.5321
T+O 2.5/5 --- Tio 5	0.048	0.005, 0.092	0.0283	-0.010	-0.055, 0.035	0.6569
White						
T+O 5/5 ---Olo 5	0.062	0.033, 0.091	<0.0001	0.087	0.057, 0.118	<0.0001
T+O 5/5 ---Tio 5	0.064	0.036, 0.093	<0.0001	0.057	0.026, 0.087	0.0003
T+O 2.5/5 ---Olo 5	0.053	0.024, 0.082	0.0004	0.072	0.042, 0.102	<0.0001
T+O 2.5/5 ---Tio 2.5	0.030	0.002, 0.059	0.0345	0.075	0.045, 0.106	<0.0001
T+O 2.5/5 --- Tio 5	0.055	0.026, 0.084	0.0002	0.041	0.011, 0.072	0.0077

Source: Reviewer

Table 21 FEV_1 $AUC_{0\text{-}3h}$ response [L] and trough FEV_1 response [L] by Age – FAS

		Trial 5		Trial 6	
Parameter	**Treatment**	**N**	**Response Adjusted Mean (SE)**	**N**	**Response Adjusted Mean (SE)**
FEV1 AUC0-3h (Day 169)					
<65 yr	Olo 5	278	0.136 (0.012)	241	0.133 (0.014)
	Tio 2.5	263	0.161 (0.013)	268	0.123 (0.013)
	Tio 5	268	0.148 (0.012)	267	0.183 (0.013)
	T+O 2.5/5	268	0.252 (0.012)	266	0.288 (0.013)
	T+O 5/5	240	0.289 (0.013)	282	0.282 (0.013)
65 - <75 yr	Olo 5	203	0.138 (0.013)	201	0.150 (0.012)
	Tio 2.5	204	0.139 (0.012)	174	0.122 (0.013)
	Tio 5	198	0.132 (0.013)	183	0.138 (0.013)
	T+O 2.5/5	196	0.240 (0.012)	193	0.217 (0.012)
	T+O 5/5	223	0.223 (0.012)	183	0.261 (0.013)
75 - <85 yr	Olo 5	42	0.094 (0.023)	64	0.101 (0.0180
	Tio 2.5	54	0.131 (0.020)	61	0.151 (0.019)
	Tio 5	59	0.123 (0.020)	47	0.156 (0.020)
	T+O 2.5/5	56	0.202 (0.020)	47	0.237 (0.020)
	T+O 5/5	58	0.244 (0.020)	37	0.192 (0.023)
Trough FEV1(Day 170)					
<65 yr	Olo 5	276	0.050 (0.013)	239	0.043 (0.015)
	Tio 2.5	262	0.083 (0.013)	266	0.052 (0.014)
	Tio 5	264	0.058 (0.013)	265	0.094 (0.014)
	T+O 2.5/5	266	0.101 (0.013)	262	0.144 (0.014)
	T+O 5/5	240	0.146 (0.014)	280	0.147 (0.013)
65 - <75 yr	Olo 5	200	0.064 (0.013)	199	0.080 (0.013)
	Tio 2.5	202	0.082 (0.013)	172	0.069 (0.014)
	Tio 5	197	0.067 (0.013)	183	0.085 (0.013)
	T+O 2.5/5	195	0.125 (0.013)	192	0.101 (0.013)
	T+O 5/5	222	0.126 90.012)	182	0.145 (0.013)
75 - <85 yr	Olo 5	41	0.031 (0.024)	64	0.047 (0.019)
	Tio 2.5	52	0.094 (0.021)	60	0.094 (0.020)
	Tio 5	58	0.096 (0.021)	47	0.134 (0.021)
	T+O 2.5/5	56	0.110 (0.021)	46	0.115 (0.021)
	T+O 5/5	58	0.138 (0.021)	35	0.123 (0.025)

Source: Reviewer

Table 22 Treatment Comparisons for FEV_1 AUC_{0-3h} response [L] and trough FEV_1 response [L] by Age – FAS

	Trial 5			Trial 6		
	Treatment Difference			Treatment Difference		
Parameter Treatment comparison	**Adjusted Mean**	**95% CI**	**P-value**	**Adjusted Mean**	**95% CI**	**P-value**
FEV1 AUC0-3h (Day 169)						
<65 yr						
T+O 5/5 ---Olo 5	0.154	0.119, 0.189	<0.0001	0.148	0.111, 0.186	<0.0001
T+O 5/5 ---Tio 5	0.142	0.106, 0.177	<0.0001	0.099	0.062, 0.135	<0.0001
T+O 2.5/5 ---Olo 5	0.116	0.082, 0.150	<0.0001	0.155	0.117, 0.194	<0.0001
T+O 2.5/5 ---Tio 2.5	0.091	0.056, 0.126	<0.0001	0.165	0.128, 0.202	<0.0001
T+O 2.5/5 --- Tio 5	0.104	0.069, 0.138	<0.0001	0.105	0.068, 0.143	<0.0001
65- <75 yr						
T+O 5/5 ---Olo 5	0.085	0.051, 0.119	<0.0001	0.111	0.076, 0.147	<0.0001
T+O 5/5 ---Tio 5	0.091	0.057, 0.125	<0.0001	0.123	0.087, 0.159	<0.0001
T+O 2.5/5 ---Olo 5	0.102	0.068, 0.137	<0.0001	0.067	0.032, 0.101	0.0002
T+O 2.5/5 ---Tio 2.5	0.101	0.066, 0.135	<0.0001	0.095	0.059, 0.131	<0.0001
T+O 2.5/5 --- Tio 5	0.108	0.074, 0.143	<0.0001	0.078	0.043, 0.113	<0.0001
75 - <85 yr						
T+O 5/5 ---Olo 5	0.150	0.090, 0.209	<0.0001	0.091	0.033, 0.149	0.0023
T+O 5/5 ---Tio 5	0.121	0.066, 0.176	<0.0001	0.036	-0.024, 0.097	0.2422
T+O 2.5/5 ---Olo 5	0.108	0.048, 0.167	0.0004	0.136	0.082, 0.189	<0.0001
T+O 2.5/5 ---Tio 2.5	0.071	0.016, 0.126	0.0111	0.086	0.031, 0.141	0.0024
T+O 2.5/5 --- Tio 5	0.079	0.023, 0.134	0.0053	0.081	0.025, 0.137	0.0048
Trough FEV1 (Day 170)						
<65 yr						
T+O 5/5 ---Olo 5	0.096	0.060, 0.133	<0.0001	0.105	0.066, 0.144	<0.0001
T+O 5/5 ---Tio 5	0.088	0.051, 0.124	<0.0001	0.053	0.016, 0.091	0.0056
T+O 2.5/5 ---Olo 5	0.052	0.016, 0.087	0.0047	0.101	0.062, 0.141	<0.0001
T+O 2.5/5 ---Tio 2.5	0.019	-0.018, 0.055	0.3150	0.092	0.054, 0.131	<0.0001
T+O 2.5/5 --- Tio 5	0.043	0.007, 0.079	0.0193	0.050	0.012, 0.088	0.0109
65- <75 yr						
T+O 5/5 ---Olo 5	0.062	0.028, 0.096	0.0004	0.065	0.028, 0.102	0.0005
T+O 5/5 ---Tio 5	0.059	0.026, 0.093	0.0006	0.060	0.023, 0.097	0.0015
T+O 2.5/5 ---Olo 5	0.061	0.026, 0.096	0.0006	0.021	-0.015, 0.057	0.2488
T+O 2.5/5 ---Tio 2.5	0.043	0.008, 0.078	0.0155	0.032	-0.005, 0.068	0.0918
T+O 2.5/5 --- Tio 5	0.058	0.024, 0.093	0.0011	0.016	-0.020, 0.052	0.3841
75 - <85 yr						
T+O 5/5 ---Olo 5	0.108	0.045, 0.170	0.0008	0.075	0.014, 0.137	0.0156
T+O 5/5 ---Tio 5	0.042	-0.015, 0.100	0.1502	-0.011	-0.075, 0.052	0.7256
T+O 2.5/5 ---Olo 5	0.080	0.017, 0.143	0.0133	0.068	0.012, 0.124	0.0177
T+O 2.5/5 ---Tio 2.5	0.017	-0.042, 0.075	0.5727	0.021	-0.037, 0.079	0.4826
T+O 2.5/5 --- Tio 5	0.015	-0.044, 0.073	0.6235	-0.019	-0.078, 0.040	0.5281

Source: Reviewer

4.1.2 Other Special/Subgroup Population

Trials 5 and 6 were conducted in over 80 centers in a wide geographic region including North America, Latin America, Europe, Asia Pacific, and Israel/South Africa. When FEV_1 $AUC_{0\text{-}3h}$ response [L] after 24 weeks is considered, treatment by Tio+Olo FDCs showed improved efficacy over monotherapy by individual components across all regions (Tables 23 and 24). The superiority of Tio+Olo FDCs to individual components was also observed for trough FEV_1 response [L] after 24 weeks in all regions except for a few cases in Eastern Europe and Latin America. Note this analysis didn't include patients from India or from Australia, New Zealand or South African which accounted for less than 5% of the patient population.

Table 23 FEV_1 $AUC_{0\text{-}3h}$ response [L] and trough FEV_1 response [L] by Region – FAS

		Trial 5		Trial 6	
Parameter	**Treatment**	**N**	**Response Adjusted Mean (SE)**	**N**	**Response Adjusted Mean (SE)**
FEV1 AUC0-3h (Day 169)					
Western Europe	Olo 5	135	0.134 (0.017)	146	0.163 (0.018)
	Tio 2.5	126	0.182 (0.017)	127	0.108 (0.020)
	Tio 5	147	0.123 (0.016)	135	0.163 (0.019)
	T+O 2.5/5	152	0.259 (0.015)	156	0.276 (0.017)
	T+O 5/5	126	0.263 (0.017)	141	0.292 (0.018)
Eastern Europe	Olo 5	88	0.171 (0.022)	80	0.115 (0.025)
	Tio 2.5	114	0.144 (0.019)	77	0.113 (0.025)
	Tio 5	86	0.153 (0.022)	73	0.142 (0.026)
	T+O 2.5/5	86	0.250 (0.022)	78	0.253 (0.025)
	T+O 5/5	94	0.268 (0.021)	81	0.262 (0.024)
East Asia	Olo 5	132	0.112 (0.016)	105	0.111 (0.017)
	Tio 2.5	102	0.148 (0.018)	113	0.137 (0.016)
	Tio 5	123	0.132 (0.016)	118	0.175 (0.016)
	T+O 2.5/5	121	0.247 (0.016)	106	0.224 (0.016)
	T+O 5/5	121	0.263 (0.016)	107	0.265 (0.017)
Latin America	Olo 5	51	0.124 (0.026)	36	0.141 (0.028)
	Tio 2.5	65	0.130 (0.023)	37	0.067 (0.028)
	Tio 5	44	0.123 (0.028)	36	0.153 (0.028)
	T+O 2.5/5	61	0.160 (0.024)	34	0.250 (0.029)
	T+O 5/5	71	0.214 (0.022)	38	0.209 (0.028)
North America	Olo 5	96	0.144 (0.019)	100	0.142 (0.019)
	Tio 2.5	91	0.119 (0.019)	108	0.132 (0.019)
	Tio 5	104	0.154 (0.018)	99	0.202 (0.019)
	T+O 2.5/5	82	0.239 (0.020)	101	0.276 (0.019)
	T+O 5/5	91	0.254 (0.019)	108	0.282 (0.019)
Trough FEV1(Day 170)					
Western Europe	Olo 5	133	0.039 (0.017)	143	0.060 (0.018)
	Tio 2.5	125	0.107 (0.018)	125	0.060 (0.020)
	Tio 5	145	0.041 (0.017)	135	0.075 (0.018)
	T+O 2.5/5	151	0.122 (0.016)	153	0.137 (0.017)
	T+O 5/5	126	0.144 (0.018)	140	0.146 (0.018)
Eastern Europe	Olo 5	88	0.079 (0.022)	80	0.048 (0.027)
	Tio 2.5	114	0.096 (0.019)	76	0.060 (0.027)
	Tio 5	86	0.053 (0.022)	73	0.084 (0.028)
	T+O 2.5/5	86	0.084 (0.022)	77	0.139 (0.027)
	T+O 5/5	94	0.114 (0.021)	81	0.139 (0.026)
East Asia	Olo 5	131	0.045 (0.016)	105	0.040 (0.017)
	Tio 2.5	101	0.069 (0.018)	113	0.061 (0.016)
	Tio 5	122	0.064 (0.016)	117	0.093 (0.016)
	T+O 2.5/5	121	0.122 (0.016)	105	0.097 (0.017)
	T+O 5/5	120	0.165 (0.016)	105	0.145 (0.017)
Latin America	Olo 5	50	0.078 (0.027)	36	0.089 (0.029)
	Tio 2.5	64	0.086 (0.023)	37	0.033 (0.028)
	Tio 5	43	0.067 (0.029)	36	0.109 (0.029)
	T+O 2.5/5	60	0.055 (0.024)	34	0.149 (0.029)
	T+O 5/5	71	0.100 (0.023)	37	0.125 (0.028)
North America	Olo 5	94	0.069 (0.020)	100	0.072 (0.020)
	Tio 2.5	90	0.042 (0.020)	106	0.052 (0.019)
	Tio 5	103	0.094 (0.019)	98	0.131 (0.020)
	T+O 2.5/5	81	0.135 (0.021)	100	0.133 (0.020)
	T+O 5/5	91	0.139 (0.020)	107	0.172 (0.019)

Source: Reviewer

Table 24 Treatment Comparisons for FEV_1 AUC_{0-3h} response [L] and trough FEV_1 response [L] by Region – FAS

	Trial 5			Trial 6		
	Treatment Difference			Treatment Difference		
Parameter Treatment comparison	Adjusted Mean	95% CI	P-value	Adjusted Mean	95% CI	P-value
FEV1 AUC0-3h (Day 169)						
Western Europe						
T+O 5/5 ---Olo 5	0.130	0.084, 0.176	<0.0001	0.129	0.078, 0.180	<0.0001
T+O 5/5 ---Tio 5	0.141	0.096, 0.185	<0.0001	0.129	0.078, 0.181	<0.0001
T+O 2.5/5 ---Olo 5	0.125	0.081, 0.170	<0.0001	0.113	0.063, 0.163	<0.0001
T+O 2.5/5 ---Tio 2.5	0.077	0.032, 0.122	0.0008	0.168	0.116, 0.220	<0.0001
T+O 2.5/5 --- Tio 5	0.136	0.093, 0.179	<0.0001	0.114	0.064, 0.164	<0.0001
Eastern Europe						
T+O 5/5 ---Olo 5	0.097	0.038, 0.156	0.0013	0.147	0.079, 0.215	<0.0001
T+O 5/5 ---Tio 5	0.115	0.056, 0.174	0.0002	0.121	0.052, 0.190	0.0007
T+O 2.5/5 ---Olo 5	0.078	0.018, 0.139	0.0107	0.137	0.069, 0.206	<0.0001
T+O 2.5/5 ---Tio 2.5	0.105	0.049, 0.162	0.0003	0.140	0.071, 0.209	<0.0001
T+O 2.5/5 --- Tio 5	0.097	0.036, 0.157	0.0018	0.111	0.041, 0.181	0.0019
East Asia						
T+O 5/5 ---Olo 5	0.150	0.106, 0.195	<0.0001	0.154	0.107, 0.200	<0.0001
T+O 5/5 ---Tio 5	0.131	0.086, 0.175	<0.0001	0.090	0.045, 0.135	<0.0001
T+O 2.5/5 ---Olo 5	0.135	0.090, 0.179	<0.0001	0.114	0.068, 0.160	<0.0001
T+O 2.5/5 ---Tio 2.5	0.099	0.051, 0.146	<0.0001	0.087	0.042, 0.132	<0.0001
T+O 2.5/5 --- Tio 5	0.115	0.070, 0.160	<0.0001	0.050	0.005, 0.094	0.0291
Latin America						
T+O 5/5 ---Olo 5	0.090	0.023, 0.158	0.0088	0.068	-0.010, 0.147	0.0874
T+O 5/5 ---Tio 5	0.091	0.021, 0.161	0.0112	0.057	-0.022, 0.135	0.1551
T+O 2.5/5 ---Olo 5	0.037	-0.033, 0.106	0.3026	0.109	0.030, 0.189	0.0071
T+O 2.5/5 ---Tio 2.5	0.031	-0.035, 0.096	0.3558	0.183	0.105, 0.262	<0.0001
T+O 2.5/5 --- Tio 5	0.037	-0.036, 0.110	0.3162	0.098	0.018, 0.177	0.0159
North America						
T+O 5/5 ---Olo 5	0.110	0.058, 0.163	<0.0001	0.141	0.088, 0.193	<0.0001
T+O 5/5 ---Tio 5	0.101	0.049, 0.152	0.0001	0.080	0.028, 0.133	0.0027
T+O 2.5/5 ---Olo 5	0.095	0.040, 0.149	0.0007	0.134	0.081, 0.187	<0.0001
T+O 2.5/5 ---Tio 2.5	0.120	0.065, 0.175	<0.0001	0.143	0.090, 0.196	<0.0001
T+O 2.5/5 --- Tio 5	0.085	0.032, 0.138	0.0019	0.074	0.020, 0.127	0.0068
Trough FEV1 AUC0-3h (Day 170)						
Western Europe						
T+O 5/5 ---Olo 5	0.105	0.056, 0.153	<0.0001	0.086	0.036, 0.137	0.0009
T+O 5/5 ---Tio 5	0.102	0.055, 0.150	<0.0001	0.071	0.021, 0.122	0.0060
T+O 2.5/5 ---Olo 5	0.083	0.036, 0.129	0.0005	0.076	0.027, 0.126	0.0024
T+O 2.5/5 ---Tio 2.5	0.014	-0.033, 0.062	0.5528	0.077	0.025, 0.128	0.0034
T+O 2.5/5 --- Tio 5	0.080	0.035, 0.126	0.0005	0.062	0.012, 0.111	0.0151
Eastern Europe						
T+O 5/5 ---Olo 5	0.035	-0.025, 0.095	0.2548	0.091	0.017, 0.164	0.0155
T+O 5/5 ---Tio 5	0.061	0.001, 0.122	0.0461	0.055	-0.020, 0.130	0.1504
T+O 2.5/5 ---Olo 5	0.005	-0.056, 0.066	0.8754	0.091	0.017, 0.165	0.0166
T+O 2.5/5 ---Tio 2.5	-0.011	-0.069, 0.046	0.6987	0.079	0.004, 0.154	0.0386
T+O 2.5/5 --- Tio 5	0.031	-0.030, 0.093	0.3161	0.055	-0.021, 0.131	0.1538
East Asia						
T+O 5/5 ---Olo 5	0.120	0.076, 0.164	<0.0001	0.104	0.057, 0.152	<0.0001
T+O 5/5 ---Tio 5	0.101	0.056, 0.145	<0.0001	0.052	0.006, 0.098	0.0255
T+O 2.5/5 ---Olo 5	0.077	0.033, 0.121	0.0007	0.056	0.010, 0.103	0.0177
T+O 2.5/5 ---Tio 2.5	0.053	0.006, 0.100	0.0269	0.036	-0.009, 0.082	0.1201
T+O 2.5/5 --- Tio 5	0.057	0.013, 0.102	0.0109	0.004	-0.041, 0.049	0.8587
Latin America						

T+O 5/5 ---Olo 5	0.023	-0.046, 0.092	0.5160	0.037	-0.043, 0.117	0.3688
T+O 5/5 ---Tio 5	0.033	-0.039, 0.105	0.3685	0.016	-0.064, 0.096	0.6957
T+O 2.5/5 ---Olo 5	-0.023	-0.094, 0.048	0.5293	0.060	-0.021, 0.142	0.1444
T+O 2.5/5 ---Tio 2.5	-0.032	-0.098, 0.035	0.3502	0.116	0.035, 0.196	0.0048
T+O 2.5/5 --- Tio 5	-0.013	-0.087, 0.062	0.7376	0.040	-0.041, 0.121	0.3360
North America						
T+O 5/5 ---Olo 5	0.070	0.016, 0.125	0.0118	0.100	0.046, 0.153	0.0003
T+O 5/5 ---Tio 5	0.045	-0.008, 0.099	0.0990	0.041	-0.013, 0.095	0.1368
T+O 2.5/5 ---Olo 5	0.066	0.010, 0.122	0.0216	0.061	0.007, 0.115	0.0280
T+O 2.5/5 ---Tio 2.5	0.093	0.036, 0.150	0.0014	0.081	0.027, 0.135	0.0034
T+O 2.5/5 --- Tio 5	0.041	-0.014, 0.096	0.1477	0.002	-0.053, 0.056	0.9459

Source: Reviewer

4.2 TRIAL 20

In Trial 20 the primary efficacy endpoint (FEV_1 $AUC_{0\text{-}24h}$ response after 6 weeks) was analyzed by demographic subgroups including gender, age, and region. The conclusions were consistent with those from the study population as a whole. For each of the subgroups analyzed, treatment with Tio+Olo FDCs showed statistically significant improvement in FEV_1 $AUC_{0\text{-}24h}$ response after 6 weeks compared with placebo and monotherapies.

4.2.1 Gender, Race, and Age

The adjusted means and treatment comparisons for FEV_1 $AUC_{0\text{-}24h}$ response [L] after 6 weeks are summarized according to gender (Tables 25 and 26) and age categories (Tables 27 and 28), respectively. Estimates by race are not provided as approximately 99% of subjects in these studies were white.

As noted in Section 3.2.2.3, Study 20 recruited 219 patients, out of which 58.9% were males, 66.7% were less than 65 years old, 27.9% were between age 65 and 75, and 5.5% were older than 75 years. All but 2 patients were White. In all demographic subgroups, FEV_1 $AUC_{0\text{-}24h}$ response after 6 weeks of treatment with Tio+Olo FDCs was statistically significantly higher compared with placebo and the comparator monotherapies. Due to small number of subjects, the subgroup analysis by race included only White patients and the subgroup analysis by age excluded those who were 75 years or older.

Table 25 FEV_1 AUC_{0-24h} response [L] after 6 weeks by Gender – FAS

	Male		Female	
Treatment	**N**	**Response Adjusted Mean (SE)**	**N**	**Response Adjusted Mean (SE)**
Placebo	69	-0.036 (0.020)	63	-0.046 (0.017)
Olo 5	76	0.166 (0.019)	60	0.082 (0.017)
Tio 2.5	83	0.139 (0.019)	53	0.086 (0.018)
Tio 5	77	0.166 (0.019)	58	0.088 (0.017)
T+O 2.5/5	80	0.277 (0.019)	55	0.189 (0.017)
T+O 5/5	82	0.274 (0.019)	56	0.205 (0.017)

Source: Reviewer

Table 26 Treatment Comparisons for FEV_1 AUC_{0-24h} response [L] after 6 weeks by Gender – FAS

	Treatment Difference		
Sex **Treatment comparison**	**Adjusted Mean**	**95% CI**	**P-value**
Male			
T+O 5/5 --- Placebo	0.309	0.268, 0.351	<0.0001
T+O 5/5 ---Olo 5	0.107	0.068, 0.148	<0.0001
T+O 5/5 ---Tio 5	0.107	0.067, 0.147	<0.0001
T+O 2.5/5 --- Placebo	0.313	0.271, 0.354	<0.0001
T+O 2.5/5 ---Olo 5	0.111	0.071, 0.151	<0.0001
T+O 2.5/5 ---Tio 2.5	0.137	0.098, 0.177	<0.0001
Female			
T+O 5/5 --- Placebo	0.250	0.212, 0.288	<0.0001
T+O 5/5 ---Olo 5	0.123	0.084, 0.161	<0.0001
T+O 5/5 ---Tio 5	0.116	0.078, 0.155	<0.0001
T+O 2.5/5 --- Placebo	0.235	0.197, 0.274	<0.0001
T+O 2.5/5 ---Olo 5	0.108	0.069, 0.147	<0.0001
T+O 2.5/5 ---Tio 2.5	0.104	0.063, 0.144	<0.0001

Source: Reviewer

Table 27 FEV_1 AUC_{0-24h} response [L] after 6 weeks by Age – FAS

	<65 Year		65 - <75 yr		75 - <85 yr	
Treatment	**N**	**Response Adjusted Mean (SE)**	**N**	**Response Adjusted Mean (SE)**	**N**	**Response Adjusted Mean (SE)**
Placebo	91	-0.047 (0.017)	37	-0.007 (0.024)	4	-0.018 (0.083)
Olo 5	90	0.142 (0.017)	41	0.098 (0.023)	5	0.102 (0.075)
Tio 2.5	92	0.125 (0.017)	39	0.087 (0.023)	5	0.091 (0.079)
Tio 5	92	0.139 (0.017)	36	0.112 (0.024)	7	0.143 (0.072)
T+O 2.5/5	93	0.249 (0.017)	36	0.224 (0.024)	6	0.224 (0.073)
T+O 5/5	96	0.253 (0.017)	35	0.222 (0.024)	7	0.259 (0.074)

Source: Reviewer

Table 28 Treatment Comparisons FEV_1 AUC_{0-24h} response [L] after 6 weeks by Age – FAS

	Treatment Difference		
Parameter **Treatment comparison**	**Adjusted Mean**	**95% CI**	**P-value**
<65 Year			
T+O 5/5 --- Placebo	0.299	0.265, 0.334	<0.0001
T+O 5/5 ---Olo 5	0.112	0.077, 0.146	<0.0001
T+O 5/5 ---Tio 5	0.114	0.079, 0.149	<0.0001
T+O 2.5/5 --- Placebo	0.296	0.261, 0.331	<0.0001
T+O 2.5/5 ---Olo 5	0.108	0.073, 0.143	<0.0001
T+O 2.5/5 ---Tio 2.5	0.125	0.089, 0.159	<0.0001
65 - <75 yr			
T+O 5/5 --- Placebo	0.229	0.176, 0.284	<0.0001
T+O 5/5 ---Olo 5	0.125	0.071, 0.178	<0.0001
T+O 5/5 ---Tio 5	0.110	0.054, 0.166	<0.0001
T+O 2.5/5 --- Placebo	0.232	0.177, 0.287	<0.0001
T+O 2.5/5 ---Olo 5	0.127	0.074, 0.179	<0.0001
T+O 2.5/5 ---Tio 2.5	0.137	0.082, 0.192	<0.0001

Source: Reviewer

4.2.2 Other Special/Subgroup Population

Trial 20 was conducted in 29 centers in North America, Eastern Europe and Western Europe. Table 29 and 30 present the adjustment mean and treatment comparisons for FEV_1 $AUC_{0\text{-}24h}$ response [L] after 6 weeks by geographic region. Consistent with the overall results, both Tio+Olo FDCs were superior to placebo and comparator monotherapies across all regions.

Table 29 FEV_1 $AUC_{0\text{-}24h}$ response [L] after 6 weeks by Region – FAS

	Eastern Europe		Western Europe		North America	
Treatment	**N**	**Response Adjusted Mean (SE)**	**N**	**Response Adjusted Mean (SE)**	**N**	**Response Adjusted Mean (SE)**
Placebo	13	-0.087 (0.046)	87	-0.024 (0.017)	32	-0.057 (0.024)
Olo 5	15	0.167 (0.043)	89	0.159 (0.016)	32	0.032 (0.024)
Tio 2.5	9	0.192 (0.055)	96	0.131 (0.016)	31	0.044 (0.024)
Tio 5	10	0.132 (0.052)	93	0.163 (0.016)	32	0.049 (0.024)
T+O 2.5/5	14	0.308 (0.044)	93	0.265 (0.016)	28	0.152 (0.025)
T+O 5/5	15	0.311 (0.045)	91	0.271 (0.016)	32	0.142 (0.024)

Source: Reviewer

Table 30 Treatment Comparisons for FEV_1 $AUC_{0\text{-}24h}$ response [L] after 6 weeks by Region – FAS

	Treatment Difference		
Parameter **Treatment comparison**	**Adjusted Mean**	**95% CI**	**P-value**
Eastern Europe			
T+O 5/5 --- Placebo	0.398	0.286, 0.510	<0.0001
T+O 5/5 ---Olo 5	0.144	0.039, 0.249	0.0079
T+O 5/5 ---Tio 5	0.179	0.056, 0.303	0.0053
T+O 2.5/5 --- Placebo	0.395	0.287, 0.504	<0.0001
T+O 2.5/5 ---Olo 5	0.141	0.037, 0.245	0.0089
T+O 2.5/5 ---Tio 2.5	0.116	-0.012, 0.244	0.0755
Western Europe			
T+O 5/5 --- Placebo	0.295	0.260, 0.329	<0.0001
T+O 5/5 ---Olo 5	0.112	0.078, 0.146	<0.0001
T+O 5/5 ---Tio 5	0.108	0.075, 0.142	<0.0001
T+O 2.5/5 --- Placebo	0.289	0.255, 0.323	<0.0001
T+O 2.5/5 ---Olo 5	0.105	0.072, 0.139	<0.0001
T+O 2.5/5 ---Tio 2.5	0.134	0.100, 0.167	<0.0001
North America			
T+O 5/5 --- Placebo	0.198	0.144, 0.253	<0.0001
T+O 5/5 ---Olo 5	0.109	0.054, 0.165	0.0001
T+O 5/5 ---Tio 5	0.092	0.038, 0.146	0.0009
T+O 2.5/5 --- Placebo	0.209	0.152, 0.266	<0.0001
T+O 2.5/5 ---Olo 5	0.120	0.062, 0.178	<0.0001
T+O 2.5/5 ---Tio 2.5	0.109	0.050, 0.167	0.0003

Source: Reviewer

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Trial 5 and Trial 6

This submission contains two replicate pivotal studies (Trial 5 and Trial 6) intended to evaluate the long term efficacy and safety of 2 doses of Tio+Olo (2.5/5 and 5/5 µg) versus the respective individual components in patients with COPD. In both of these pivotal trials, the primary lung function efficacy assessment was based on the results for two primary endpoints: FEV_1 AUC_{0-3h} response and trough FEV_1 response after 24 weeks of treatment. Since there were 2 different doses of Tio+Olo FDC and 3 individual components (Olo 5, Tio 2.5, and Tio 5), a sequence of hypothesis testing was used to first test the superiority of Tio+Olo 5/5 over respective components in FEV_1 AUC_{0-3h}, then Tio+Olo 5/5 over respective components in trough FEV_1 response, then Tio+Olo 2.5/5 over respective components in FEV_1 AUC_{0-3h}, and finally Tio+Olo 2.5/5 over respective components in trough FEV_1 response. This approach adequately controlled the Type I error inflation due to multiple endpoints and multiple doses.

Results from Trial 5 and Trial 6 are very similar. Both Tio+Olo FDCs were superior to the respective individual components in terms of spirometry function. FEV_1 AUC_{0-3h} response and trough FEV_1 response after 24 weeks of treatment with Tio+Olo 5/5 µg were statistically significantly higher compared with Olo 5 µg ($p<0.0001$) and Tio 5 µg ($p<0.0001$ to $p=0.0001$) which demonstrates the contribution of Olo 5 µg and Tio 5 µg within Tio+Olo 5/5 µg. For Tio+Olo 2.5/5 µg the response was also statistically significantly higher compared with Olo 5 µg ($p<0.0001$) and Tio 2.5 µg ($p<0.0001$ to $p=0.0174$), which demonstrate the contribution of Olo 5 µg and Tio 2.5 µg within Tio+Olo 2.5/5 µg.

In both trials, the lung function benefit of Tio+Olo FDCs over the individual components was maintained throughout the 24-h dosing interval. In Trial 5 for Tio+Olo 5/5 µg, the increase in adjusted mean FEV_1 AUC_{0-3h} response (Day 169) was 0.123 L vs. Olo 5 µg and 0.117 L vs. Tio 5 µg, while the increase in adjusted mean trough FEV_1 (Day 170) was 0.082 L vs. Olo 5 µg and 0.071 L vs. Tio 5 µg ($p<0.0001$ for each comparison). For Tio+Olo 2.5/5 µg, the increase in adjusted mean FEV_1 AUC_{0-3h} response was 0.109 L vs. Olo 5 µg and 0.093 L vs. Tio 2.5 µg ($p<0.0001$ for both comparisons), while the increase in adjusted mean trough FEV_1 response was 0.058 L vs. Olo 5 µg and 0.029 L vs. Tio 2.5 µg ($p<0.0001$ and $p=0.0174$, respectively). Likewise, in Trial 6 the improvements were maintained throughout the 24 h-dosing interval. For Tio+Olo 5/5 µg, the increase in adjusted mean FEV_1 AUC_{0-3h} response (Day 169) was 0.132 L vs. Olo 5 µg and 0.103 L vs. Tio 5 µg ($p<0.0001$ for both comparisons), while the increase in adjusted mean trough FEV_1 response (Day 170) was 0.088 L vs. Olo 5 µg ($p<0.0001$) and 0.050 L vs. Tio 5 µg ($p=0.0001$). For Tio+Olo 2.5/5 µg, the increase in adjusted mean FEV_1 AUC_{0-3h} response was 0.121 L vs. Olo 5 µg and 0.131 L vs. Tio 2.5 µg, while the increase in adjusted mean trough FEV1 response was 0.067 L vs. Olo 5 µg and 0.062 L vs. Tio 2.5 µg ($p<0.0001$ for all comparisons).

The efficacy of both doses of Tio+Olo over the monotherapies was present up to 52 weeks according to the analysis of FEV_1 AUC_{0-3h} responses and trough FEV_1 over the entire 52 treatment period.

The primary analyses were based on the MMRM with a spatial covariance structure. Alternative analyses using an asymptotically consistent empirical 'sandwich' estimator approach or a pattern mixture model yielded similar results.

Missing data for FEV_1 AUC_{0-3h} or trough FEV_1 were imputed with various techniques such worst-observation-carried forward and last-observation-carried forward. The overall discontinuation rate at Week 24 was relatively low, having minimal impact on the results. More than 90% of the patients in the full analysis dataset were also in the per protocol dataset, thus the primary analysis was not performed on the PPS. Consistent results were also obtained from a utility analysis incorporating subjects who discontinued the study as non-responders. This type of utility analysis is appropriate since subject(s) who are unable or unwilling to continue study treatment cannot be expected to gain efficacy from that treatment.

Analyses of other spirometry endpoints, such as FVC AUC_{0-3h} response and trough FVC response, generated consistent results and provided additional support for the lung function benefit of both doses of Tio+Olo compared to the monotherapies.

Trial 20

This submission also included a cross-over Phase III trial (Trial 20) intended to describe the average bronchodilator response over the 24 h dosing interval using the primary endpoint, FEV_1 AUC_{0-24h} response. Since there are 2 different doses of Tio+Olo FDC and 3 individual components (Olo 5, Tio 2.5, and Tio 5) as well as a placebo arm, a sequence of hypothesis testing was used to first test the superiority of Tio+Olo 5/5 over placebo, then Tio+Olo 5/5 over respective components, then Tio+Olo 2.5/5 over placebo, and finally Tio+Olo 2.5/5 over respective components. This approach adequately controlled the Type I error inflation due to multiple endpoints and multiple doses.

In all hypothesis tests based on treatment differences, the Tio+Olo FDCs were superior to the comparator treatments for FEV_1 AUC_{0-24h} ($p<.0001$). Treatment with Tio+Olo 5/5 µg resulted in a statistically significant increase in FEV_1 AUC_{0-24h} response compared to placebo (0.280 L), Olo 5 µg (0.115 L), and Tio 5 µg (0.110 L). Similarly, treatment with Tio+Olo 2.5/5 µg resulted in a statistically significant increase in FEV_1 AUC_{0-24h} response compared to placebo (0.277 L), Olo 5 µg (0.111 L), and Tio 2.5 µg (0.124 L). The results for the key secondary endpoints (FEV_1 AUC_{0-12h} response and FEV_1 AUC_{12-24h} response) and other secondary endpoints supported the results for the primary endpoint.

It should be noted, however, while the primary and secondary endpoints included spirometry AUC data from 0 to 24 hours, there were only three measured time-points (22, 23, and 23:50 hours post-dose) in the second 12 hour period (12-24 hours). As such, whether or not this can truly characterize the 24-hour spirometry profile is uncertain.

5.2 CONCLUSIONS AND RECOMMENDATIONS

The pivotal trials (Trial 5 and Trial 6) evaluated the efficacy of Tio+Olo 5/5 µg once daily in a broad population of patients with COPD. With respect to lung function measured by FEV_1 $AUC_{0\text{-}3h}$ response and trough FEV_1 response after 24 weeks, both trials confirmed the contribution of each component (Olo 5 µg, Tio 5 µg) within the combination product Tio+Olo 5/5 µg, and the contribution of each component (Olo 5 µg, Tio 2.5 µg) within the combination product Tio+Olo 2.5/5 µg. For both parameters, the FDC doses demonstrated a significantly greater bronchodilatory effect compared to their constituent monotherapy products. Specifically for the claimed dose of Tio+Olo 5/5 µg, the average benefit was 0.123 L to 0.132 L over Olo 5 µg and 0.103 L to 0.117 L over Tio 5 µg in FEV_1 $AUC_{0\text{-}3h}$ response on Day 169. The treatment effects were present at the end of the 24-hour dosing interval as demonstrated by the statistically significant improvements of 0.082 L to 0.088 L above Olo 5 µg and 0.050 L to 0.071 L above Tio 5 µg in trough FEV_1 response on Day 170. Furthermore, the improvements were present up to 52 weeks as shown by descriptively consistent spirometry data throughout the entire treatment period.

The bronchodilatory profile of Tio+Olo FDC was further confirmed in the supportive 6-week study (Trial 20), in which the mean FEV_1 improvements over 24 hours were superior to Tio 5 µg and Olo 5 µg.

Overall, the assessment of efficacy in the Phase III clinical program has demonstrated that Tio+Olo 5/5 µg provides incremental lung function benefit over the individual components, Tio 5 µg and Olo 5 µg. Tio+Olo 5/5 µg demonstrated statistically significant and clinically relevant benefit over the individual components in all primary and secondary endpoints.

5.3 LABELING REVIEW

The focus of the labeling review will be on Sections 14. Edits to the label are pending. Based on the preliminary review of the proposed label, we have the following general comments for consideration on Section 14.2 Confirmatory Trials:

- Add descriptions about actual treatment groups although not all arms are reported in the label
- Lung Function
  - Present mean for each group and treatment difference in Table 2
  - Remove (b) (4) and describe results in the text
  - Remove (b) (4) and describe results in the text

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/s/

LAN ZENG
01/23/2015

RUTHANNA C DAVI
01/23/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 206756 **Applicant: Boehringer Ingelheim** **Stamp Date: 5/22/4014**

Drug Name: tiotropium/olodaterol **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Studies to be reviewed: Trial 1237-0005, Trial 1237-0006, Trial 1237-0020

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician Date

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

LAN ZENG
08/04/2014

RUTHANNA C DAVI
08/05/2014