

CLINICAL REVIEW

Clinical Review Section

Study 205.115/205.128

except Bodily Pain were numerically (although not generally statistically) better in the tiotropium group during treatment. The "Physical Health Summary" scores were statistically higher in the tiotropium group compared to the placebo group only on the last test day (Day 344) [U99-3170-01.pdf/p100]. Statistical differences between groups were uncommon in the mental health domains. There was essentially no difference between groups on the "Mental Health Summary" scores [U99-3170-01.pdf/p101]. The study report does not describe analyses of a total SF-36 score, combining all of the domains.

Analysis of "Rebound"

Following the end of the treatment period, patients were followed for an additional 3 weeks. During this period patients recorded PEFs and albuterol use. In addition, quality of life questionnaires, COPD symptoms, and Physician's Global Evaluation data were collected [U99-3169.pdf/139-146]. *Note: It is not entirely clear from the protocol, but this period was presumably not blinded [U99-3169.pdf/p310]. In addition, the protocol does not state that information from this period would be assessed for the purposes of identifying a "rebound" effect [U99-3169.pdf/p313].* Only patients who had a valid baseline measurement, completed the trial, and had at least some post-treatment data were included in the analyses. No statistical tests were applied to the data. The Applicant states that there was no evidence of rebound effect.

Reviewer's Comment: The post-treatment pattern of decline in morning and evening PEF, and increase in supplemental albuterol use did not suggest a "rebound" effect. In addition, analysis of the SGRQ, SF-36, COPD Symptoms, Physician's Global Evaluation, and the Energy Fatigue Questionnaire scores did not suggest a rebound effect [U99-3170-01.pdf/p.119-26].

Pharmacoeconomic Variables

Pharmacoeconomic data included the number of patients hospitalized, the number of days spent in ICU, the number of days patients were able to do a majority of their usual daily activities, the number of days patients had unscheduled visits to a Physician, the number of days patients had unscheduled visits to an "other" healthcare provider, and the number of patients who changed their employment status by each visit. These data will not be discussed in this review.

Pharmacokinetic Data

This study did not include pharmacokinetic assessments.

Reviewer's Comments on Efficacy

This study compared the effects of tiotropium bromide inhalation powder (18mcg, once daily) and placebo in 451 patients with COPD. Using a 2:1 randomization scheme, a total of 271 patients were assigned to active drug and 180 patients were assigned to placebo. Although the total treatment period was 49 weeks, the primary efficacy determination was made at 13 weeks. The study population was almost exclusively white (97%), with a mean smoking history of 59.3 pack-years, and a mean age of 65 years. The baseline FEV₁ was approximately 1 liter, or 45% of the predicted normal value.

The study demonstrated that tiotropium was superior to placebo on the pre-specified primary efficacy endpoint: trough FEV₁ response after 13 weeks of treatment. The 13-week trough FEV₁

CLINICAL REVIEW

Clinical Review Section

Study 205.115/205.128

(defined as the mean of two pre-dose values) increased from baseline by 0.13 liters in the tiotropium group and decreased by 0.01 liter in the placebo group ($p=0.0001$). This effect size is considered meaningful, particularly for an end-of-dosing-interval comparison. Three-hour serial spirometry performed on six test days throughout the 49-weeks of active treatment also demonstrated that tiotropium was statistically superior to placebo in terms of the trough, average, and peak FEV₁ responses. The Day 1 mean post-dose FEV₁ in the tiotropium group increased by ≤ 200 ml (depending on how the baseline was defined). Customarily a change of $\geq 12\%$ and ≥ 200 ml is considered to be a clinically significant bronchodilator effect. Of note, the mean peak FEV₁ change from baseline exceeded 200ml on all test days. Study 205.114/205.117 revealed similar findings, suggesting that the time to peak response may differ among patients. A second observation, which was also seen in Study 205.114/205.117, is that the treatment effect was lower on Day 1 than on other test days, suggesting that multiple dosing is required to achieve optimum effect.

Efficacy was also supported by statistically significant improvements in numerous secondary spirometry variables including trough, mean, and peak FVC responses during the 3-hour serial spirometry on all test days. Statistically significant improvements were also demonstrated for the weekly mean morning and evening PEF_R, for each of the weeks of treatment except one.

The results of various patient- and physician-reported outcome variables generally provided supportive evidence of efficacy. The table below divides the various non-spirometric variables into those for which statistical significance was demonstrated and those for which it was not.

Note that for many of these endpoints, the clinical significance of the effect size is not clear.

Non-Spirometric Secondary Efficacy Variables (Study 205.115/205.128)	
Statistically Significant Benefit Demonstrated	Statistically Significant Benefit NOT Demonstrated
<ul style="list-style-type: none"> ▪ Physician's Global Evaluation (all test days) ▪ Mahler TDI Focal Score (all test days)^a ▪ COPD symptom^b: Shortness of Breath (15/17 test days) ▪ COPD symptom^b: Wheeze (9/17 test days) ▪ Total SGRQ score (all test days)^c ▪ SGRQ "Impacts" domain score (all test days) 	<ul style="list-style-type: none"> ▪ Energy Fatigue Questionnaire ▪ COPD symptom^b: Cough ▪ COPD symptom^b: Tightness in Chest ▪ COPD Exacerbations (all analyses) ▪ Nocturnal Awakenings
<p>^aEffect size surpassed the Applicant's proposed threshold for minimal clinically important change at 9 and 12 months only.</p> <p>^bAssessed by the Investigator</p> <p>^cEffect size did surpassed the accepted threshold for minimal clinically important change at 6 and 12 months only.</p>	

Analyses of several variables during a 3-week post-treatment period did not suggest a "rebound" effect after withdrawal of active drug. It is not clear from the protocol whether this period was blinded.

d. Safety Review

The safety findings from this study, along with the safety data from the other placebo-controlled studies, will be reviewed in depth in the Integrated Review of Safety section of this Medical Officer Review. Brief observations from this study are described below.

All 451 patients who received at least one dose of test drug were included in the safety analysis [U99-3170-01.pdf/p131]. A total of 234 patients received tot for more than 6 months and 145

CLINICAL REVIEW

Clinical Review Section

Study 205.115/205.128

patients received tiotropium for more than 330 days. The table below outlines the extent of exposure to study drug.

Extent of Exposure, Study 205.115/205.128		[U99-3170-01.pdf/p131]
	Tiotropium N (%)	Placebo N (%)
Total Treated Maximum Exposure (Days)	271	180
1	2 (0.7)	1 (0.6)
2-7	1 (0.4)	9 (5.0)
8-60	17 (6.3)	17 (9.4)
61-100	9 (3.3)	9 (5.0)
101-200	8 (3.0)	4 (2.2)
201-330	89 (32.8)	52 (28.9)
>330	145 (53.5)	88 (48.9)
Median (days)	337	326
Range (days)	5 -398	1 - 363

During the course of the study, the great majority of patients in both the tiotropium and the placebo treatment groups experienced at least one adverse event (87.5% and 86.1%, respectively) [U99-3170-01.pdf/p133]. Dry mouth was reported more frequently in the tiotropium group (19.6%) than in the placebo group (2.8%). Other AEs occurring more commonly in the tiotropium group included: Upper Respiratory Disorders (53.1% vs. 47.2%), and the specific AEs of chest pain (7.4% vs. 6.1%), accidents (13.6% vs. 11.1%), dependent edema (4.4% vs. 3.9%), influenza-like symptoms (10.3% vs. 7.8%), dizziness (5.5% vs. 5.0%), abdominal pain (3.7% vs. 3.3%), gastroesophageal reflux (3.0% vs. 0.6%), arthritis (4.4% vs. 3.9%), myalgia (4.4% vs. 2.8%), infection (4.1% vs. 3.3%), epistaxis (4.4% vs. 1.7%), pharyngitis (10.0% vs. 8.9%), rhinitis (5.5% vs. 5.0%), sinusitis (11.4% vs. 6.1%), rash (3.0% vs. 1.7%), and urinary tract infection (8.1% vs. 4.4%) [U99-3170-01.pdf/p135-6].

Serious adverse events (SAEs) were reported by 15.5% of patients in the tiotropium group and 19.4% of patients in the placebo group [U99-3170-01.pdf/p139]. None of the serious adverse events were considered by the investigator to be related to the study drug. Withdrawal from the trial due to adverse events occurred in 11.1% of the tiotropium treatment group and 13.9% of the placebo group [U99-3170-01.pdf/p143].

A total of 6 patients died during the course of the study, 4 (1.5%) on tiotropium, and 2 (1.1%) on placebo [U99-3170-01.pdf/p137]. None were considered by the investigator to be related to study medication. Deaths in the tiotropium group were attributed to: unknown; suicide; cardiac arrest; and cardiomyopathy. Deaths in the placebo group were attributed to lung cancer in one and cor pulmonale and cardiac insufficiency in the other.

CLINICAL REVIEW

Clinical Review Section
Study 205.130

B. Six-Month Placebo- and Active-Controlled Studies

1. Study 205.130: "A multiple dose comparison of tiotropium inhalation capsules, salmeterol inhalation aerosol, and placebo in a six-month, double-blind, double-dummy, safety and efficacy study in patients with chronic obstructive pulmonary disease (COPD)"

a. Study Description

The results of Study 205.130 are provided in Study Report #U01-1236-1, dated February 20, 2001. The final study protocol is dated September 14, 1998 [U01-1236-1.pdf/p281]. The study was performed during the period of February, 1999 and May, 2000 [U01-1236-1.pdf/p9]. The final protocol was amended once, in a document dated October 13, 2000 [U01-1236-1.pdf/p378]. This amendment was issued in order to change the primary efficacy endpoint of the study to include an assessment of dyspnea as well as bronchodilation. The protocol amendment also dictated an increase in sample size from approximately 150 patients per arm to approximately 170 patients per arm [U01-1236-1.pdf/p384]. *Of note, the study was already complete, although not yet un-blinded, when the protocol was amended to change the sample size.*

Study Design

This was a randomized, double-blind, double-dummy, placebo- and active-controlled, parallel group study.

Duration

The treatment period was six months. This was preceded by a two-week baseline period, and was followed by a three-week washout period.

Study Centers

The study was performed in 39 centers in 12 countries (Australia, Belgium, Canada, Denmark, Germany, Italy, Netherlands, New Zealand, South Africa, Spain, United Kingdom, United States) [U01-1236-1.pdf/p73]. In the US, five centers randomized a total of 78 subjects.

Study Population

A total of 623 subjects were entered into the trial and randomized to: tiotropium (n = 209), salmeterol (n = 213), and placebo (n = 201).

Materials

The following materials were used [U01-1236-1.pdf/12, and Submission 4/12/02, p9]:

Tiotropium inhalation capsule	18mcg once daily	Batch No. 9806003
Salmeterol inhalation aerosol	50mcg once daily	Batch No. 8F 002
Placebo inhalation capsule		Batch No. 9806002
Placebo inhalation aerosol		Batch No. 701291

CLINICAL REVIEW

Clinical Review Section Study 205.130

The commercially approved product (Serevent® Inhalation Aerosol) was used for the salmeterol clinical supplies [Submission date 4/12/02, p9-11]. For blinding purposes, the commercially available product (canister + actuator) was fitted into a blinding device housing. The same housing device was used for all clinical supplies in the study. The Applicant states that, at the time of development, the blinding devices were evaluated to determine if they had any impact on the delivered dose, aerodynamic fine particle dose, weight loss, and valve delivery. The Applicant claims that these tests indicated that the housing device had no effect on these performance characteristics. Such testing was not performed on the actual clinical supplies for this study. The placebo MDIs were manufactured at Boehringer Ingelheim Pharma KG, Germany.

Objectives

The originally stated objectives of the study were changed in the protocol amendment. The primary efficacy objective of the study was to compare the bronchodilator efficacy and effect on dyspnea of tiotropium inhalation capsules and placebo in patients with COPD [U01-1236-1.pdf/p380]. The secondary objectives of the study were to: 1) compare the impact of tiotropium and salmeterol on "humanistic" and economic health outcomes, such as quality of life, patient preference, and health resource utilization; and 2) compare the safety of tiotropium inhalation capsules, salmeterol inhalation aerosol, and placebo [U01-1236-1.pdf/380].

Inclusion Criteria

Notable inclusion criteria were [U01-1236-1.pdf/p293-4]:

- Males or females, aged ≥ 40 years
- Current or past smokers with a smoking history of >10 pack-years
- Diagnosis of COPD, which is "relatively stable" (excludes patients with "frequent exacerbations which could be expected to interfere with the patient's ability to participate in the trial")
- $FEV_1 \leq 60\%$ predicted and $FEV_1 \leq 70\%$ of FVC

Exclusion Criteria

Notable exclusion criteria were [U01-1236-1.pdf/p295]:

- Significant disease other than COPD
- Clinically relevant abnormal baseline laboratory values if the abnormality defines a disease listed as an exclusion criterion
- SGOT or SGPT >80 , bilirubin >2.0 , creatinine >2.0
- Myocardial infarction within 1 year
- Cardiac arrhythmia requiring drug therapy
- Hospitalization for heart failure within the past 3 years
- Regular use of daytime oxygen for more than 1 hour per day and, in the investigator's opinion, will be unable to abstain from the use of oxygen therapy
- History of cancer within 5 years (basal cell carcinoma allowed)
- Cystic fibrosis or bronchiectasis
- History of thoracotomy with pulmonary resection
- Recent (6 weeks) upper respiratory infection

CLINICAL REVIEW

Clinical Review Section

Study 205.130

- Current or recent (6 weeks) participation in pulmonary rehabilitation program
- Known symptomatic prostatic hypertrophy or bladder neck obstruction
- Known narrow angle glaucoma
- Current use of cromolyn sodium, nedocromil sodium, or H₁ receptor antagonists
- Current use of oral corticosteroids at unstable doses (< 6 weeks on a stable dose) or at doses in excess of the equivalent of 10mg of prednisolone per day or 20mg of every other day
- History of asthma

Conduct

Following an initial screening, patients entered a two-week baseline period. During the baseline period patients measured and recorded PEFR. Patients who completed the baseline period were randomized into the 6-month double-blind treatment period, during which they received tiotropium, salmeterol, or placebo, in a double-dummy fashion. Visits were scheduled at the end of the baseline period (Visit 2), after 2 weeks, 4 weeks post randomization, and every 4 weeks for the remainder of the treatment period. A final visit was also scheduled 3 weeks after the treatment period. Pulmonary function testing was conducted at Visit 2, prior to the start of treatment at -60 minutes and -10 minutes (pre-dose) and at 30 minutes, 60 minutes, 2, 3, 4, 6, 8, 10, and 12 hours post dosing. Pulmonary function testing at the same intervals was performed after 2, 8, 16, and 24 weeks of therapy (Visits 3, 5, 7, and 9). A three-week follow-up period followed the treatment period.

In addition to the pulmonary function testing described above, the following efficacy assessments were made. The schedule for these assessments is outlined in the table below.

- Record of investigational drug and rescue medication use.
- PEFR, measured and recorded two times daily by the patients. The protocol specified that the AM measurement should be immediately upon arising (after "the patient has cleared out mucus") and the that the evening measurement should be at bedtime [U01-1236-1.pdf/p307]. The timing of PEFR measurements in relation to administration of study medication was not specified.
- Shuttle Walking Test, 15 minutes after the completion of the +3 hour pulmonary function test. Patients completed a modified Borg Dyspnea Rating Scale immediately before and immediately after the Shuttle Walking Test.
- COPD symptom scores (wheezing, shortness of breath, coughing, and tightness of chest) (these scores are based on the *investigator's* assessment of the patient's condition during the week just prior to the visit) [U01-1236-1.pdf/p307].
- Physician's Global Evaluation (made prior to pulmonary function testing, when applicable) A score of 1-8 [ranging from poor to excellent], was based on the need for concomitant medication, number and severity of exacerbations since the last visit, severity of cough, ability to exercise, amount of wheezing, "etc." Investigators reviewed their previous score before completing each new evaluation [U01-1236-1.pdf/p308].
- St. George's Respiratory Questionnaire (SGRQ) administered during the first 2 hours in the clinic.
- Mahler Baseline Dyspnea Index score (BDI, Visit 2) and Transition Dyspnea Index score (TDI, subsequent visits), administered during the first 2 hours in the clinic.

CLINICAL REVIEW

Clinical Review Section

Study 205.130

- Patient satisfaction with COPD medication questionnaire.
- Health resource utilization information including exacerbations of COPD, hospitalizations, concomitant medications, non-scheduled contacts with physicians and other health care providers, disability days, and employment status.

During the treatment period, each dose of tiotropium or its placebo was taken as one capsule, once daily in the morning (8 – 10 AM). Each dose of salmeterol or its placebo was taken as two inhalations twice daily (morning and evening). The evening dose was taken approximately 12 hours after the morning dose. Albuterol inhalation aerosol supplied by the Applicant was used as rescue medication.

Compliance with study medication was assessed using patient-reported Daily Patient Record forms, in which patients recorded each dose of investigational drug taken and the number of doses of salmeterol MDI taken [U01-1236-1.pdf/p304].

The table below summarizes the study procedures.

Study Procedures, Study 205.130											[U01-1236-1.pdf/p283]
Visit #:	1	2	3	4	5	6	7	8	9	10	
Weeks:		0	2	4	8	12	16	20	24	+3	
Day:	-14	1	15	29	57	85	113	141	169	+21	
Physical Examination	X								X		
Vital Signs (seated)	X	X	X		X		X		X		
Laboratory Tests (fasting)	X								X		
12-lead ECG	X								X		
Theophylline level ¹	X	X	X		X		X		X		
Issue Diary Cards	X	X	X	X	X	X	X	X	X		
Collect Diary Cards		X	X	X	X	X	X	X	X	X	
Dispense Drugs		X		X	X	X	X	X			
PFTs (FEV ₁ and FVC) ²	X	X	X		X		X		X		
Shuttle walking test		X			X		X		X	X	
Quality of Life		X			X		X		X	X	
Mahler Dyspnea Index (BDI or TDI, as appropriate)		X			X		X		X	X	
Patient Preference Questionnaire		X							X		
Health Resource Utilization		X	X	X	X	X	X	X	X	X	
Review of PEFV Records		X	X	X	X	X	X	X	X	X	
COPD Symptom Scores		X	X	X	X	X	X	X	X	X	
Global Evaluations		X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	
Concomitant Therapy		X	X	X	X	X	X	X	X	X	

¹Theophylline levels on all patients at Visit 1 and only on patients taking theophylline at subsequent test day visits
²Prior to drug administration and 30, 60 minutes, 2, 3, 4, 6, 8, 10, 12 hours post dose

Concomitant Medications

Albuterol inhalation aerosol was provided for as-needed use.

The following medications were allowed, if stabilized for at least 6 weeks and throughout the study period:

CLINICAL REVIEW

Clinical Review Section

Study 205.130

- Oral corticosteroids at a dose equivalent to ≤ 10 mg of prednisolone per day or 20 mg every other day
- Orally inhaled corticosteroids
- Theophylline preparations, excluding 24-hour preparations
- Mucolytic agents not containing bronchodilators

For control of acute COPD exacerbations, the following medications were allowed [U01-1236-1.pdf/p302]:

- Three increases in the dose of theophylline of up to 7 days (If the increases or additions occurred prior to pulmonary function testing days the testing was to be postponed for at least two, but not more than seven days after the last increased or additional dose is given.)
- Three increases in the dose, or addition of, oral steroids of up to 7 days. (If the increase or addition of oral corticosteroids occurred prior to pulmonary function testing days the testing was to be postponed for at least two, but not more than seven days after the last increased or additional dose is given.)
- The use of antibiotics was not restricted and could be used as medically necessary.

The use of anticholinergic drugs other than the study drug, and long-acting beta-adrenergic agonists were not allowed during the treatment period (but were allowed during the two week baseline/run-in period as well as the 3-week follow-up period) [U01-1236-1.pdf/p304].

Data Analysis

Efficacy Endpoints

The final protocol dated 9/14/98 indicated that the primary efficacy endpoint would be the trough FEV₁ response at the end of the six month study [U01-1236-1.pdf/p291]. Trough response was defined as the mean change from baseline at the end of the dosing interval (24 hours post dosing for tiotropium and 12 hours post dosing for salmeterol). Baseline was defined as the mean of two pre-treatment measurements at Visit 2, which was the day of the first dose of study medication.

The protocol amendment changed the primary efficacy endpoints to the trough FEV₁ response, AND the focal score from the Mahler Transition Dyspnea Index (TDI) at the end of the six-month study (co-primary endpoints) [U01-1236-1.pdf/p380]. The focal score is the sum of the three components of the transition dyspnea index, functional impairment, magnitude of task, and magnitude of effort. The superiority of tiotropium over placebo for trough FEV₁ response was to be established first, then the TDI scores would be compared.

Secondary efficacy variables were:

- Mahler Transition Dyspnea (TDI) (focal score) on other test days
- Average and peak FEV₁ response on each test day
- Trough, average and peak FVC measured at the same times as FEV₁ on each test day
- Individual FEV₁ and FVC measurements at each time point

CLINICAL REVIEW

Clinical Review Section Study 205.130

- Mean weekly AM and PM PEFr (measured by the patients at home twice daily)
- Rescue medication
- St. George's Respiratory Questionnaire (SGRQ) (total score [U01-1236-1.pdf/p383])
- Physician's Global Evaluation
- COPD symptom scores (wheezing, shortness of breath, coughing, and tightness of chest)
- Number and length of COPD exacerbations, defined as a complex of respiratory events reported as adverse events with a duration of ≥ 3 days
- Number of patients with at least one COPD exacerbation during treatment period
- Number and length of hospitalizations for respiratory disease
- Number of patients with at least one hospitalization for respiratory disease during treatment period
- Mahler Baseline Dyspnea Index (BDI) and TDI components
- Health resource utilization (hospitalization, physician and other health care providers)
- Patient preference measures
- Shuttle walking test and Borg Dyspnea Rating Scale

Statistical Model

The statistical model for the FEV₁ comparison was an analysis of covariance, with terms for treatment and center and baseline FEV₁ [U01-1236-1.pdf/p381]. The statistical model for the TDI comparison was logistic regression with terms for treatment, center, and BDI focal score. Both analyses were to include all three treatment groups. Centers with less than 12 evaluable patients were pooled.

The statistical model was changed in the protocol amendment [U01-1236-1.pdf/p381]. The hypotheses were tested in a stepwise manner. First, the superiority of tiotropium over placebo in trough FEV₁ was to be established. The null hypothesis is that there is no difference in the mean trough FEV₁ response between tiotropium and placebo. The alternative hypothesis is that the mean trough FEV₁ response is greater than placebo (two-tailed test at 0.05 level of significance).

If the superiority of tiotropium over placebo in trough FEV₁ response is established, the two treatment groups will be compared in TDI focal score. The null hypothesis is that there is no difference in proportion of patients with TDI focal score greater than or equal to 1 unit between tiotropium and placebo. The alternative hypothesis is that the proportion of patients with TDI focal score greater than or equal to 1 unit is different in those treated with tiotropium compared to those treated with placebo (two-tailed test at 0.05 level of significance).

The protocol amendment also stipulated a secondary comparison for non-inferiority of tiotropium versus salmeterol in trough FEV₁. The null hypothesis for this comparison is that the mean trough FEV₁ response for tiotropium is inferior to the mean trough FEV₁ response for salmeterol by at least 50 ml after 24 weeks of treatment. The alternative hypothesis is that the mean trough FEV₁ response for tiotropium is not 50 ml less than the mean trough FEV₁ response for salmeterol.

CLINICAL REVIEW

Clinical Review Section Study 205.130

If non-inferiority of tiotropium in comparison with salmeterol is established, the following superiority test of tiotropium will be performed with no penalty for multiple comparison. The null hypothesis for this comparison is that the trough FEV₁ response for tiotropium is less than or equal to the mean trough FEV₁ response for salmeterol. The alternative hypothesis is that the mean trough FEV₁ response for tiotropium is greater than the mean trough FEV₁ response for salmeterol (one-tailed test at 0.025 level of significance).

Reviewer's Comment: Emphasis on a direct comparison between tiotropium and salmeterol on trough FEV₁ would be inappropriate in comparing the overall efficacy of these two drugs. Superiority on this endpoint would primarily reflect differences in pharmacodynamics.

Missing Data

All randomized patients with at least baseline (pre-treatment at Visit 2) and trough FEV₁ after 2 weeks of randomized treatment were used for the efficacy analysis. If a patient discontinued the study early due to unexpected worsening of the disease under study, the missing data were estimated by the least favorable data observed prior to discontinuation. The missing data for patients who miss a visit due to other reasons were estimated by their last observed data. Linear interpolation between the two adjacent measurements was used to estimate random, middle, missing spirometry measurements. For values at the end of the serial spirometry that are missing because rescue medication was taken, the minimum observed FEV₁ value on that test day (even if it is pre-dose) was used as the estimate. The last available value was used as the estimate for data that were missing for reasons unrelated to the patient's response to treatment.

Sample Size

The final protocol indicated that a sample of 450 patients (150 per treatment group) would detect a 0.065 liters difference in mean trough FEV₁ response between tiotropium and salmeterol at 5% level of significance with at least 80% power using a two-tailed t-test. This calculation was based on the assumption of a standard deviation for trough FEV₁ of 0.20 liters. **Reviewer's Note: The original power calculations focused on the comparison of tiotropium to salmeterol. The protocol was subsequently amended to establish the primary comparison as that of tiotropium versus placebo and to add the co-primary TDI comparison. The protocol amendment indicated that, while still blinded, approximately 170 patients per group were actually randomized [U01-1236-1.pdf/p384]. As discussed above, the amendment specified a (co-) primary analysis of the TDI. A sample size of 170 per group was determined to have a 80% power to detect the same magnitude of difference between tiotropium and placebo that was seen in the prior studies (50% increase over placebo, combined data), at a 5% level of significance [U01-1236-1.pdf/p70 and 384].**

b. Patient Disposition

A total of 39 centers in 12 countries recruited 833 subjects, who were screened and signed the informed consent. Of these, a total of 623 subjects were randomized as follows: tiotropium (209 subjects), salmeterol (213 subjects), and placebo (201 subjects) [U01-1236-1.pdf/p73]. Of the 623 randomized patients, 506 (81.2%) completed all nine study visits. This included 88% of the tiotropium group, 83% of the salmeterol group, and 72.1% of the placebo group. Fewer subjects

CLINICAL REVIEW

Clinical Review Section

Study 205.130

in the tiotropium group (5.7%) failed to complete the study because of adverse events compared with salmeterol (13.6%) and placebo (19.4%). The table below summarizes the patient disposition and reasons for withdrawal.

Patient Disposition and Reasons for Withdrawal, Study 205.130				[U01-1236-1.pdf/p74]
	Tiotropium	Salmeterol	Placebo	Total
Randomized	209	213	201	623
Completed the Trial	184 (88%)	177 (83.1%)	145 (72.1%)	506 (81.2%)
Adverse Event Total	12 (5.7%)	29 (13.6%)	39 (19.4%)	80 (12.8%)
Worsening of Disease Under Study	7 (3.3%)	22 (10.3%)	30 (14.9%)	59 (9.5%)
Worsening of Other Pre-existing Disease	0 (0.0)	2 (0.9%)	0 (0.0)	2 (0.3%)
Other Adverse Event	5 (2.4%)	5 (2.3%)	9 (4.5%)	19 (3.0%)
Administrative	11 (5.3%)	7 (3.3%)	14 (7.0%)	32 (5.1%)
Non-compliant with Protocol	3 (1.4%)	1 (0.5%)	4 (2.0%)	8 (1.3%)
Lost to Follow-up	0 (0.0)	1 (0.5%)	0 (0.0)	1 (0.2%)
Consent Withdrawn	8 (3.8)	5 (2.3%)	10 (5.0)	23 (3.7%)
Other	2 (1.0)	0 (0.0)	3 (1.5%)	5 (0.8%)

The mean age of the patients in this study was 64.9 years [U01-1236-1.pdf/p77]. The majority (74.6%) were men, and 99.5% were caucasian. The mean FEV₁ was 1.08 L (mean 38% of predicted). As shown in the table below, the baseline features were comparable across treatment groups.

Demographics and Baseline Characteristics, Study 205.130				[U01-1236-1.pdf/p78-9]
	Tiotropium N (%)	Salmeterol N (%)	Placebo N (%)	Total N (%)
Total Treated	209	213	201	623
Sex				
Male (%)	154 (73.7)	160 (75.1)	151 (75.1)	465 (74.6)
Race				
White	209 (100)	213 (100)	198 (98.5)	620 (99.5)
Black	0 (0.0)	0 (0.0)	2 (1)	2 (0.3)
Asian	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Age				
Mean	64.5	64.6	65.6	64.9
Range	45 - 84	43 - 82	41 - 83	41 - 84
Smoking History (pack years)				
Mean	46.89	48.29	45.54	46.93
Range	10 - 170	10 - 160	10 - 132	10 - 170
Duration of COPD (years)				
Mean	9.2	10.4	9.7	9.8
Range	0 - 53	0 - 49	0 - 44	0 - 53
Screening FEV ₁ (L)				
Mean	1.11	1.07	1.06	1.08
Range	0.33 - 2.05	0.26 - 2.23	0.44 - 2.14	0.26 - 2.23
FEV ₁ /FVC x 100				
Mean	43.64	42.02	41.32	42.34
Range	22.0 - 69.3	22.4 - 68.4	22.6 - 64.1	22.0 - 69.3

CLINICAL REVIEW

Clinical Review Section

Study 205.130

Concomitant medications taken any time during the two-week baseline period were similar between treatment groups [U01-1236-1.pdf/p80]. Of the entire group, 53.1% used an anticholinergic drug, 66.5% used inhaled corticosteroids, 20.7% used theophylline preparations, 5.5% used oral steroids, and 1.1% used oxygen.

c. Efficacy Review

Data Sets Analyzed

The ITT data set was defined as all randomized patients who had baseline data and “adequate” post-treatment data [U01-1236-1.pdf/p76]. The Applicant states that decisions regarding the adequacy of post-treatment data “as well as other exclusions from the ITT data set” were determined at a blinded “report planning meeting” prior to opening the treatment codes.

For the analysis of spirometry data, all randomized patients with baseline (pre-treatment on test day 1 [Visit 2]) and trough FEV₁ on test-day 15 (Visit 3) after 2 weeks of randomized treatment were included in the ITT data set.

For the analysis of daily record data, all randomized patients with baseline data as well as data for two weeks on treatment with at least four observations each week were included in the ITT data set. Daily record card data during steroid and theophylline bursts for COPD exacerbations were excluded. Also, weekly summary data from the daily record card were set to missing if the summary was based on less than four observations in a week. The Applicant indicates that the last two provisions were made in response to FDA recommendations made at the End-of-Phase 2 meeting. However, these specific recommendations are not captured in the meeting minutes.

The table below provides the numbers of subjects included in the data sets for the TDI ITT analysis, the PFT ITT analysis, and the safety analyses. *Note that 53 of the 201 subjects randomized to placebo were excluded from the TDI analysis*.*

Number of subjects in various data sets (Study 205.130)				[U01-1236-1.pdf/p77]
Data Set	Tiotropium	Salmeterol	Placebo	Total
Safety	209	213	201	623
TDI ITT	184	179	148*	511
PFT ITT	202	203	179	584

Primary Endpoints

The two co-primary endpoints were the trough FEV₁ response and the TDI focal score, both evaluated on test-day 169 (Week 24) of randomized treatment. These were analyzed in a step-wise fashion. The primary comparison was tiotropium versus placebo. The numbers of patients included in the analyses of these two endpoints are provided in the table above.

CLINICAL REVIEW

Clinical Review Section
Study 205.130

Reviewer's Note: In regard to the composition of the ITT data sets, the protocol stated that all randomized patients with at least baseline and trough FEV₁ after two weeks of treatment would be used for the efficacy analysis [U01-1236-1.pdf/p322]. (This was not altered in the protocol amendment). The study report states that the determination of the ITT populations (i.e. the definitions of "adequate" post-treatment data and "other exclusions from the ITT data set") were made at a blinded report planning meeting, which occurred after the completion of the study and prior to "opening of the treatment codes" [U01-1236-1.pdf/p76]. As shown in the table above, considerable numbers of randomized subjects were excluded from the ITT data sets. For example, the ITT data set used to analyze the TDI co-primary endpoint included only 511 of the 623 randomized subjects. The placebo group for this comparison included only 148 of the 201 randomized subjects. This issue was discussed with the Biometrics Reviewer (Dr. Gebert). The decreased size of the ITT population was due to subjects who dropped out prior to Day 57 (the first day the TDI was administered) or for whom there was insufficient data to calculate the BDI or TDI focal scores. Thus, further analyses using the ITT as defined in the protocol would not be possible.

There were 26 subjects who were excluded from all efficacy analyses because they had no data following multiple administration of trial medication (tiotropium 4, salmeterol 5, placebo 17) [U01-1236-1a.pdf/p458]. The reasons for failure to obtain adequate on-treatment data included consent withdrawn, worsening of the disease under study, non-compliance with protocol, and other adverse events.

Tiotropium was statistically superior to placebo for the trough FEV₁ on test-day 169 ($p < 0.001$) [U01-1236-1.pdf/p92]. The magnitude of the effect size (0.14 liters) is considered clinically significant.

The primary analysis of the TDI focal score was a "responder" analysis, comparing the proportion of subjects with a TDI focal score of ≥ 1 unit in the tiotropium and placebo groups at test-day 169. Tiotropium was shown to be statistically superior to placebo in this analysis ($p < 0.01$) [U01-1236-1.pdf/p100]. On test-day 169, 42% of patients in the tiotropium group, 26% of patients in the placebo group, and 35% of patients in the salmeterol group had a TDI focal score ≥ 1 unit. The comparison of tiotropium to salmeterol was not statistically significant.

Reviewer's Note: There are two difficulties with this type of analysis. First, the magnitude of change representing a clinically meaningful "response" must be established. The Division has previously informed the Applicant of this important requirement (See meeting minutes of 7/24/00 and letter dated 10/11/00). The Applicant has asserted that a change of ≥ 1 unit should be considered to be a clinically meaningful "response." The second difficulty is that there is no customary or accepted minimally clinically significant effect size for proportion of responders. The Applicant was also informed of the need to provide justification of the clinical significance of any difference demonstrated in the percentages of responders in each

CLINICAL REVIEW

Clinical Review Section
Study 205.130

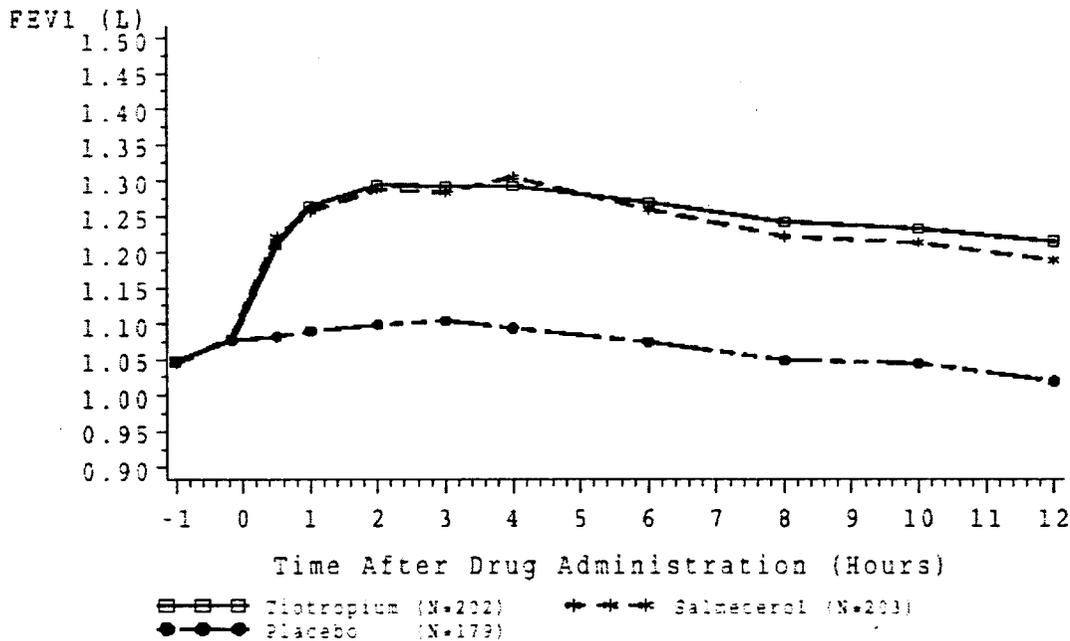
group. The adequacy of the justifications of both the definition of clinical response (i.e. ≥ 1 unit) and the significance of the observed effect size are to be discussed in the Integrated Summary of Efficacy section of this Medical Officer Review.

Secondary Endpoints

Pulmonary Function Endpoints

Serial spirometry was performed on the first day of dosing, and after 2, 8, 16, and 24 weeks of treatment. Measures were made 60 minutes and 10 minutes prior to dosing, and 30 minutes, 60 minutes, and 2, 3, 4, 6, 8, 10, and 12 hours after dosing. The mean FEV_1 was statistically superior to placebo at all individual timepoints on all test days ($p < 0.001$) (with the exception of the pre-dose measures on the first day of treatment) [U01-1236-1.pdf/p87-91]. The mean FEV_1 for tiotropium and salmeterol were not statistically different on the first day of treatment. However, the FEV_1 response for tiotropium was statistically superior to salmeterol at all timepoints on all other test days (except the -60 minute timepoint at Week 2 and Week 8). The figures below illustrate the mean FEV_1 at Day 1 and Week 24.

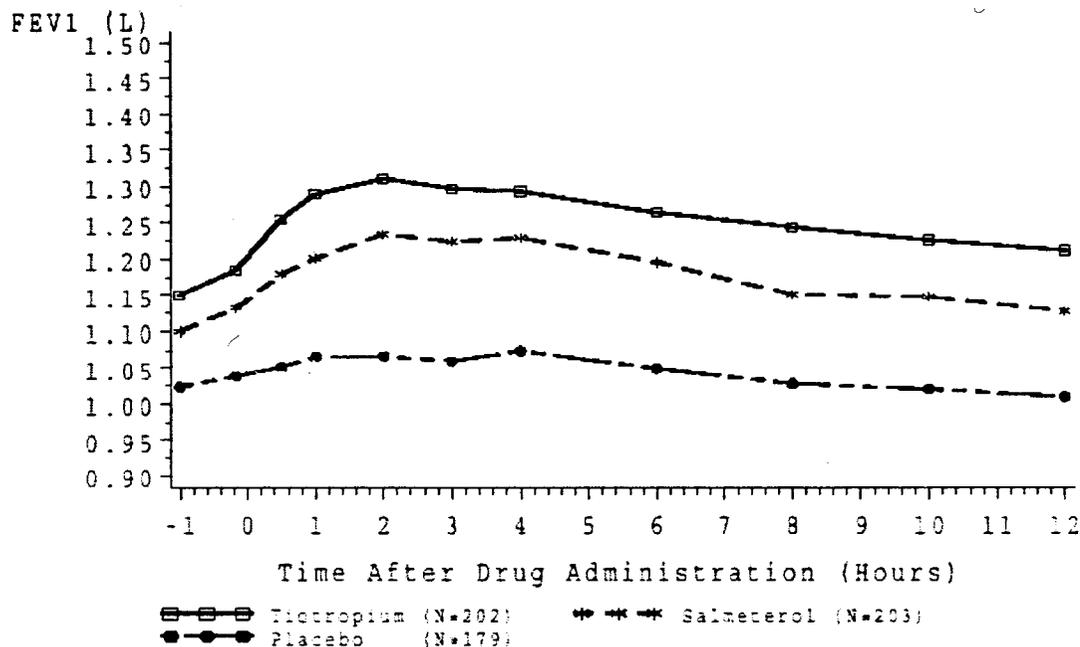
Mean FEV_1 , Day 1 (ITT data set, Study 205.130) [U01-1236-1.pdf/p82]



CLINICAL REVIEW

Clinical Review Section
Study 205.130

Mean FEV₁, Week 24 (ITT data set, Study 205.130) [U01-1236-1.pdf/p86]



The trough FEV₁ response in the tiotropium group was statistically superior to placebo on all test days ($p < 0.001$; absolute difference = 0.14 – 0.15L) and was statistically superior to salmeterol ($p < 0.05$; absolute difference 0.03 – 0.05L) on all test days except Week 2 [U01-1236-1.pdf/p93]. Note that the absolute difference between tiotropium and salmeterol, while statistically significant, is quite small.

The average FEV₁ response over the 12-hour post-dosing period in the tiotropium group was also statistically superior to placebo at each test day. The difference between tiotropium and placebo was 0.19L on the first treatment day, and ranged from 0.21 – 0.23L during the remainder of the treatment period [U01-1236-1.pdf/p98]. Tiotropium was not superior to salmeterol on this endpoint on the first treatment day. On subsequent days, although tiotropium was statistically superior to salmeterol on this endpoint ($p < 0.001$), the magnitude of the difference was small (0.06 – 0.08L) [U01-1236-1.pdf/p98].

The peak FEV₁ response over the 12-hour post-dosing period in the tiotropium group was statistically superior to placebo on all test days. The mean peak FEV₁ response in the tiotropium group on test day 1 was 0.31 liters. The difference between tiotropium and placebo was 0.19L

CLINICAL REVIEW

Clinical Review Section

Study 205.130

on the first treatment day and ranged from 0.23 to 0.26L during the remainder of the treatment period [U01-1236-1.pdf/p98]. Tiotropium was not superior to salmeterol on this endpoint on the first treatment day. On subsequent days, tiotropium was statistically superior to salmeterol on this endpoint ($p < 0.001$), although the magnitude of the difference was small (0.01 – 0.09L) [U01-1236-1.pdf/p98].

The individual, trough, average, and peak FVC responses in the tiotropium group were also statistically superior to placebo at each test day (except the pre-dose values on the first treatment day) [U01-1236-1.pdf/p116-120, 121, 127].

Subjects measured their PEFR twice daily and recorded the values in their diaries. The mean morning PEFRs during the baseline period were slightly higher for the tiotropium (238 L/min) and salmeterol (236 L/min) groups, compared to placebo (224 L/min) [U01-1236-1.pdf/p129]. The daily morning PEFR (averaged weekly) in the tiotropium group was statistically superior to placebo throughout the treatment period ($p < 0.001$) [U01-1236-1.pdf/p131-2]. The difference between tiotropium and placebo ranged from 19 L/min (during Week 1) and 27 L/min. The difference between tiotropium and salmeterol was not statistically significant at any treatment week.

The mean evening PEFRs during the baseline period were slightly higher for the tiotropium (248 L/min) and salmeterol (248 L/min) groups, compared to placebo (240 L/min) [U01-1236-1.pdf/p133]. The daily evening PEFR (averaged weekly) in the tiotropium group was statistically superior to placebo throughout the treatment period ($p < 0.001$) [U01-1236-1.pdf/p135-6]. The difference between tiotropium and placebo ranged from 30 - 33 L/min. The difference between tiotropium and salmeterol ranged from 7 – 19 L/min, and was statistically significant at all Weeks except Week 6.

Patient Reported Outcomes

The Mahler Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) are comprised of three components: the Functional Impairment, the Magnitude of Task, and the Magnitude of Effort scales. The focal score is the sum of the three individual components. The BDI is utilized as a baseline measure. The TDI, which was administered at Weeks 8, 16, and 24, is used to assess change from baseline. For the TDI, each component is scored on a scale of –3 (major deterioration) to 3 (major improvement). At baseline, the BDI, individual components and focal score was comparable between groups [U01-1236-1.pdf/p100, 104].

The proportion of subjects with a TDI focal score of ≥ 1 unit was statistically greater in the tiotropium group than the placebo group at Week 8 (40% vs. 24%) and Week 16 (43% vs. 27%) [U01-1236-1.pdf/p103]. Tiotropium, while numerically superior, was not statistically superior to salmeterol on this parameter at either Week 8 (40% vs. 34%), or Week 16 (43% vs. 34%).

CLINICAL REVIEW

Clinical Review Section Study 205.130

The Applicant also analyzed the mean TDI focal score at Weeks 8, 16, and 24. On this analysis, tiotropium was statistically superior to placebo on each test day. The mean difference between groups exceeded 1 unit at Week 8 and Week 24 [U01-1236-1.pdf/p109]. The mean difference between tiotropium and salmeterol was statistically significant only at Week 24. However, the magnitude of the difference was less than 1 unit.

In regard to the individual components of the TDI, tiotropium was statistically superior to placebo for all three components on all test days except Week 16 for Functional Impairment, and Week 24 for Magnitude of Effort [U01-1236-1.pdf/p104].

The SGRQ consists of 50 questions comprising three domains (Activities, Impacts, and Symptoms). A lower score indicates lesser impairment. In the existing medical literature, a change of 4 units in the SGRQ has been generally considered to be the minimally clinically meaningful difference. The SGRQ was administered at baseline, and after 8, 16, and 24 weeks of treatment. At baseline, the total SGRQ score and the scores for the individual domains were comparable among the treatment groups. The total SGRQ scores in the tiotropium group were statistically superior to placebo at Weeks 8 and 24 ($p=0.0495$ and $p=0.0374$, respectively), but not at Week 16. However, the numerical differences between groups (2.24 at Week 8, 1.83 at Week 16, and 2.71 at Week 24) did not reach the threshold of a clinically meaningful difference (4 units) on any test day. The comparisons between tiotropium and salmeterol and between salmeterol and placebo were not statistically different on any test day [U01-1236-1.pdf/p149].

The Applicant also performed a “responder analysis” on the SGRQ total score data, defining response as a change of more than 4 units. *However, this analysis was not pre-specified in either the protocol or the protocol amendment.* The number of responders was numerically greater in the tiotropium group compared to the placebo group on all three test days. This difference reached statistical significance only at Week 24 (51% versus 42%, Odds ratio = 1.605, $p<0.05$) [U01-1236-1.pdf/p151].

In regard to the individual SGRQ domains, tiotropium was statistically superior to placebo for Symptoms score on all three test days, and for Impacts score at Week 24. No statistical difference was seen for Activities score on any test day. The absolute change that constitutes a clinically meaningful change is not well established for the individual domains of the SGRQ.

At each visit during the treatment and post-treatment period, *the investigator* completed the COPD symptom score evaluation. The scores were based on the *investigator's* assessment of the patient's condition during the week just prior to the visit and were completed prior to pulmonary function testing [U01-1236-1.pdf/p307; 416]. The specific symptoms rated were wheezing, shortness of breath, coughing, and tightness of chest. The scoring ranged from 0 – 3, corresponding to “not present”, “mild”, “moderate”, and “severe,” respectively. The baseline scores were comparable among the three treatment groups (Wheezing 0.87 – 0.93; Shortness of breath 1.44 – 1.47; Coughing 0.98 – 1.05; and Tightness of Chest 0.64 – 0.68) [U01-1236-1.pdf/p157]. Tiotropium was statistically superior to placebo ($p<0.05$) for Wheezing, Shortness of Breath, and Tightness of Chest on all test days except test day 113 for wheezing [U01-1236-1.pdf/p162-4]. The effect sizes were 0.13 – 0.31 for Wheezing, 0.27 – 0.36 for Shortness of

CLINICAL REVIEW

Clinical Review Section Study 205.130

Breath, and 0.14 – 0.23 for Tightness of Chest. Tiotropium was not statistically superior to placebo for coughing, except on test day 169 (effect size 0.17). Salmeterol was statistically superior to placebo ($p < 0.05$) for Wheezing, Shortness of Breath, and Tightness of Chest on all test days except test days 85, 113, and 169 for wheezing [U01-1236-1.pdf/p162-4]. Salmeterol was not statistically superior to placebo for coughing, except on test days 15 and 57 (effect size 0.13 and 0.17, respectively). The only statistically significant comparisons between tiotropium and salmeterol were the Day 57, 85, and 169 Shortness of Breath scores, all of which favored tiotropium. However, the difference between groups was small (0.14 – 0.19).

Subjects also completed Patient Satisfaction and Patient Preference Questionnaires on the first day of treatment and at the end of the treatment period [U01-1236-1.pdf/p210-212; 360-4]. The Patient Satisfaction questionnaire included ratings for satisfaction with: current medication, side effects, “how COPD medication makes you feel,” “how quickly medication starts to work,” “COPD medication on your sleep,” control of COPD symptoms, and current dosing schedule (first treatment visit only). These were rated on a 1-7 scale. There were no significant differences between the tiotropium and the placebo groups on these questions at the end of treatment. The difference in mean scores between treatment groups did not reach 1 for any question. The Patient Preference questionnaire addressed the following: which treatment preferred, “how often do you prefer to take an inhaler?”, “how important is the number of times/day you take inhalers?”, and “does treatment frequency affect compliance?” Interestingly, the median responses in all groups indicated a preference for twice-a-day inhalers, and a belief that the recommended dosing frequency has “no impact” on compliance.

COPD Exacerbations and Hospitalizations

There were statistically fewer COPD exacerbations in the tiotropium group compared to placebo. The number of COPD exacerbations per 100 patient-years was 104 in the tiotropium group, 134 in the salmeterol group, and 165 in the placebo group (tiotropium vs. placebo, $p = 0.022$) [U01-1236-1.pdf/p175]. There were statistically fewer exacerbation days in the tiotropium group compared to the placebo group. The number of “event days” per 100 patient-years was 1767 in the tiotropium group, 2757 in the salmeterol group, and 2948 in the placebo group (tiotropium vs. placebo, $p = 0.0278$). There was no statistically significant difference between groups in regard to the number of subjects with at least one COPD exacerbation during the six-month study (34%, 37%, and 43% in the tiotropium, salmeterol, and placebo groups, respectively).

Hospitalizations for COPD exacerbation were infrequent. There were no notable differences between treatment groups regarding the number of patients with at least one hospitalization for COPD exacerbation (3%, 5%, and 6%), number of hospitalizations for COPD exacerbation (8 per 100 patient-years in the tiotropium group compared with 19 and 17 in the salmeterol and placebo groups, respectively), or number of hospitalization days for COPD exacerbation (86 event-days per 100 patient years in the tiotropium group compared with 111 and 264 in the salmeterol and placebo groups, respectively) [U01-1236-1.pdf/p175]. The percentages of subjects with hospitalization (all cause) were also similar among the treatment groups (9-10%).

Other Secondary Endpoints

CLINICAL REVIEW

Clinical Review Section Study 205.130

A “shuttle walk test” (SWT) was performed after the first dose of study medication and on Days 57, 113, and 169. The SWT is a standardized test in which subjects walk at a steady pace on a 10-meter course until they are unable to maintain the required speed “without becoming unduly breathless” [U01-1236-1.pdf/p338-41]. The Modified Borg Dyspnea Scale was administered before and after each SWT. The Modified Borg scale ranges from 0 (“nothing at all”) to 10 (“maximal”). Of note, a score of 5 indicates “severe” dyspnea, with higher scores indicating “very severe” and “very, very severe” dyspnea. After the first dose of study medication there were no differences between groups in regard to the pre- or post-exercise Borg Dyspnea scores [U01-1236-1.pdf/p151-2]. The pre-and post-exercise Borg Dyspnea scores were numerically lower in the tiotropium group as compared to the placebo group on all subsequent test days. However, this numerical difference reached statistical significance only on test day 57, when the absolute difference between tiotropium and placebo was 0.24 (pre-exercise) and 0.32 (post-exercise). The Applicant does not state what magnitude of difference is considered clinically meaningful. There was no difference between groups in regard to the walking distance, and the walking distance did not increase during the study in any group [U01-1236-1.pdf/p153].

At each visit during the treatment and post-treatment periods, the investigator completed the Physician’s Global Evaluation. This evaluation was made prior to pulmonary function testing, (when applicable) and was scored on a scale of 1-8 [ranging from poor to excellent], based on the need for concomitant medication, number and severity of exacerbations since the last visit, severity of cough, ability to exercise, amount of wheezing, “etc.” Investigators reviewed their previous score before completing each new evaluation [U01-1236-1.pdf/p308]. The baseline scores were comparable among the groups (mean score 4.49 – 4.60) [U01-1236-1.pdf/p154]. Both the tiotropium and the salmeterol groups had statistically greater improvement than placebo on all test days ($p < 0.01$) [U01-1236-1.pdf/p156]. The absolute difference between the tiotropium group and the placebo group in mean score ranged from 0.48 to 0.59.

During the treatment period all subjects were provided with albuterol for use as a rescue medication as needed. Subjects recorded the number of puffs of albuterol used in their daily diaries. Weekly means were computed for total number of puffs taken per day for each subject. During the baseline period the use of albuterol was similar between groups (tiotropium = 3.34 puffs/day; salmeterol = 3.96 puffs/day; placebo = 3.24 puffs/day). Throughout the 24-week treatment period, the use of albuterol was statistically lower ($p < 0.01$) for both the tiotropium group and the salmeterol group, as compared with placebo. During the last week of treatment (Week 24), subjects in both the tiotropium group and the salmeterol group used a mean of 3.00 puffs of albuterol per day, compared with 4.45 puffs per day in the placebo group [U01-1236-1.pdf/p143].

The protocol also specified that “pharmacoeconomic data” would be analyzed as a secondary endpoint. This was to include the number of subjects hospitalized, the number of days spent in the ICU, the number of days the subjects were unable to perform the majority of their daily activities, the number of days subjects had unscheduled visits to a physician, the number of days subjects had an unscheduled visit to an other healthcare provider, and the number of subjects who changed their employment status at each visit. The Applicant states that these data were comparable across the treatment groups [U01-1236-1.pdf/p174].

CLINICAL REVIEW

Clinical Review Section
Study 205.130

Analysis of Washout Period

Following the active treatment period, subjects were followed for 3 additional weeks. Analyses of various data from the washout period (PEFRs, rescue medication use, patient reported outcomes, shuttle walk test, physicians global evaluation, and COPD symptoms) were performed. These analyses include only those subjects who completed the study and had at least some post-treatment data. The TDI focal score decreased by 0.82 in the tiotropium group from the end of treatment period to the end of the washout period. Interestingly, the TDI focal score in the placebo group increased by 0.31 during this period. The mean weekly AM PEFR in the tiotropium group decreased from 29.74 L/min above baseline at the end of the treatment period to 20.41 L/min above baseline during the third week of the washout period [U01-1236-1.pdf/p165]. In keeping with the TDI data from the washout period, the mean weekly PEFR in the placebo group actually improved during the washout period (from 8.42 L/min greater than baseline at the end of the treatment period to 18.4 L/min during the last week of the washout period) [U01-1236-1.pdf/p166]. PM PEFR values followed a similar pattern during the washout period. These data, and the remainder of the washout period data do not suggest a "rebound" effect related to discontinuation of tiotropium [U01-1236-1.pdf/p167-73]. The failure of the PEFR to return to baseline values in the tiotropium group may indicate continued effect of the drug. Alternatively, patients may not have been at their true baseline at the time of enrollment.

Pharmacokinetic Data

This study did not include pharmacokinetic assessments.

Reviewer's Comments on Efficacy

The efficacy analyses utilized an ITT data set, defined as all randomized patients who had baseline data and "adequate" post-treatment data. Decisions regarding the adequacy of the data as well as other exclusions from the ITT data set were made at a "blinded report planning meeting." As discussed above, the ITT data set for the TDI comparison excluded a large number of subjects (112), particularly in the placebo group.

The amended protocol established two co-primary endpoints, the trough FEV₁ response and the TDI focal score, both evaluated on test day 169 (Week 24). Tiotropium was statistically and clinically superior to placebo on the trough FEV₁ endpoint (p<0.001; effect size 0.14 liters). The trough FEV₁ endpoint helps to establish the duration of action of tiotropium. However, the threshold for a "clinically relevant" effect at the trough timepoint is not as well established as for the peak timepoint. At peak, one might consider a change of 12% (and at least 200ml) to be clinically relevant. The effect size seen in this study in regard to the trough FEV₁ is less than that, but is still considered to be clinically relevant. One further point regarding the trough FEV₁ endpoint is that comparisons to other drugs based on this endpoint would not be wholly appropriate. Differences on this endpoint may reflect differences in pharmacodynamic profiles, and miss other, perhaps more relevant performance characteristics.

The TDI comparison was specified to be a "responder analysis", with a pre-defined change of 1 unit being considered to represent a meaningful response. A statistically greater percentage of subjects in the tiotropium group, as compared to the placebo group, demonstrated a response on

CLINICAL REVIEW

Clinical Review Section Study 205.130

test day 169 (42% versus 26%). Thus, tiotropium was statistically superior to placebo on each of the two co-primary endpoints. However, the study report does not address two important issues in regard to the TDI analysis. The first issue is whether the observed effect size (i.e. 42% versus 26%) is clinically meaningful. The second issue is whether the pre-specified responder definition (1 unit) is appropriate.

The secondary endpoints generally support the efficacy of tiotropium as a bronchodilator. Secondary endpoints for which tiotropium was statistically superior to placebo included: individual FEV₁ and FVC measurements on all test days; morning and evening PEFR; TDI "responder analyses" at Weeks 8 and 16; physician's assessment of COPD symptoms of wheezing, shortness of breath, and tightness of chest (but not coughing); physician's global evaluation; COPD exacerbations (number of events and number of event days, but not number of subjects with at least one exacerbation); and rescue medication. It must be noted that the clinical significance of the observed effects on some of these endpoints is not clear. Secondary endpoints that did not establish superiority of tiotropium over placebo include the SGRQ (for which the differences between tiotropium and placebo did not reach the minimal threshold representing a clinically meaningful change); patient satisfaction questionnaire; shuttle walk test/ Borg Dyspnea scale; and hospitalizations for COPD exacerbation.

In summary, the analyses of the primary and secondary endpoints of this study establish the efficacy of tiotropium as a bronchodilator in this patient population. The data may support the effect of tiotropium on the symptom of dyspnea; however, this depends on the determination as to whether a change in the TDI score of 1 unit is demonstrated to be clinically meaningful. In addition, the significance of the observed effect size must be considered.

d. Safety Review

Safety evaluations in this study were: adverse events, pulse and blood pressure (measured at the same time intervals as the spirometry testing, for the first three hours post-dose), fasting laboratory tests (screening and at the end of treatment), ECGs (screening and at the end of treatment; interpreted by the investigator), and physical examination (screening and at the end of treatment).

The safety data from this study, combined with the data from Study 205.137, will be discussed in detail in the Integrated Review of Safety section of this document. The following is a brief summary of the salient safety findings of this study.

A total of 623 subjects were randomized and received at least one dose of study medication (tiotropium = 209, salmeterol = 213, and placebo = 201). Of these, 117 subjects withdrew from the study prior to completion (tiotropium = 25, salmeterol = 36, and placebo = 56). The table below summarizes the duration of exposure, by treatment group.

Extent of Exposure, Study 205.130			[U01-1236-1.pdf/p179]
	Tiotropium N (%)	Salmeterol N (%)	Placebo N (%)
Total Treated	209 (100)	213 (100)	201 (100)
1	1 (0.5)	2 (0.9)	6 (3.0)

CLINICAL REVIEW

Clinical Review Section Study 205.130

Extent of Exposure, Study 205.130		[U01-1236-1.pdf/p179]	
	Tiotropium N (%)	Salmeterol N (%)	Placebo N (%)
2-7	1 (0.5)	1 (0.5)	8 (4.0)
8-60	11 (5.3)	18 (8.5)	26 (12.9)
61-100	7 (3.3)	5 (2.3)	6 (3.0)
101-168	58 (27.8)	51 (23.9)	42 (20.9)
169-200	130 (62.2)	136 (63.8)	113 (56.2)
201-330	1 (0.5)	0 (0.0)	0 (0.0)
Mean (days)	156.8	152.7	135.5
Median (days)	169	169	169
Range (days)	1-210	1-190	1-183

Adverse events were reported by 79.5% of the subjects. The incidence of adverse events was similar among the treatment groups (tiotropium = 80.9%, salmeterol = 76.5%, and placebo = 81.1% [U01-1236-1.pdf/p180]). The most frequent adverse events were categorized as lower respiratory system disorders (tiotropium = 45.9%, salmeterol = 48.4%, and placebo = 55.2%). However, the distinction between upper and lower respiratory disorders is not made in the adverse event classification system used in this study (the Boehringer Ingelheim- World Health Organization- Adverse Reaction Terminology List). This distinction was made by the BI clinical monitor for this study [U01-1236-1.pdf/p179]. Upper respiratory system disorders were actually more common in the tiotropium group (32.5%) than in the salmeterol group (28.2%) and the placebo group (26.4%). The most frequent specific AE was COPD exacerbation, which occurred slightly less commonly in the tiotropium group as compared to the placebo group (tiotropium = 36.8%, salmeterol = 38.5%, and placebo = 45.8%). Common (incidence \geq 3%) adverse events occurring more frequently in the tiotropium group as compared to the placebo group were: upper respiratory tract infection (20.1% vs. 15.9%), mouth dry (10.0% vs. 3.5%), influenza-like symptoms (9.6% vs. 4.5%), headache (8.6% vs. 5.5%), coughing (5.7% vs. 3.5%), pharyngitis (5.3% vs. 4.5%), accident household (4.8% vs. 2.5%), chest pain (4.3% vs. 4.0%), sinusitis (3.8% vs. 2.5%), dyspepsia (3.3% vs. 1.5%), and nausea (3.3% vs. 3.0%) [U01-1236-1.pdf/p182].

The number of subjects experiencing serious adverse events (SAEs) was similar in the treatment groups (tiotropium = 10%, salmeterol = 12.7%, and placebo = 13.9%) [U01-1236-1.pdf/p180].

Fewer subjects in the tiotropium group discontinued the study due to adverse events (5.7%) compared with the salmeterol group (13.6%) and the placebo group (17.9%).

There were 7 deaths in the study, 3 in the salmeterol group and 4 in the placebo group.

CLINICAL REVIEW

Clinical Review Section
Study 205.137

2. Study 205.137: “A multiple dose comparison of tiotropium inhalation capsules, salmeterol inhalation aerosol, and placebo in a six-month, double-blind, double-dummy, safety and efficacy study in patients with chronic obstructive pulmonary disease (COPD)”

a. Study Description

This study was performed under a protocol that was identical to the protocol for Study 205.130. The only notable difference between the two protocols is that in study 205.137 spirometry was performed before dosing (-60 and -10 minutes) and for 3 hours post-dosing (30 minutes, and 1, 2, and 3 hours post-dosing), whereas, in Study 205.130 post-dose spirometry was performed for 12 hours after dosing [U01-1231-1.pdf/p11]. The reader is referred to the description of the protocol discussed in the section above. This study was performed between February, 1999 and May, 2000 [U01-1231-1.pdf/p11]. The study was performed in 50 centers in 15 countries (48 centers actually recruited subjects) [U01-1231-1.pdf/p40-1]. The countries were: Australia, Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, South Africa, United Kingdom, and the US. A total of 584 subjects were included, 193 assigned to tiotropium, 192 assigned to salmeterol, and 199 assigned to placebo. In the US, four study centers randomized a total of 31 patients [U01-1231-1.pdf/p74].

The test product (tiotropium inhalation capsules) was from batch number 9806003. The reference active product was commercially available salmeterol (Glaxo batch number 8F 002). The two reference placebo products were manufactured by Boehringer Ingelheim Pharma KG and are identified as batch number 9806002 (placebo inhalation capsule) and 701291 (placebo inhalation aerosol).

b. Patient Disposition

A total of 48 centers in 15 countries recruited and screened 772 subjects, of whom 771 signed the informed consent. Of these, a total of 584 subjects were randomized as follows: tiotropium (199 subjects), salmeterol (192 subjects), and placebo (199 subjects) [U01-1231-1.pdf/p74]. Of the 584 randomized patients, 460 (78.8%) completed all nine study visits. This included 80.8% of the tiotropium group, 79.2% of the salmeterol group, and 76.4% of the placebo group. Fewer subjects in the tiotropium group (9.3%) failed to complete the study because of adverse events compared with salmeterol (16.1%) and placebo (14.1%). The table below summarizes the patient disposition and reasons for withdrawal.

Patient Disposition and Reasons for Withdrawal, Study 205.137 [U01-1231-1.pdf/p75]				
	Tiotropium	Salmeterol	Placebo	Total
Randomized	193	192	199	584
Completed the Trial	156 (80.8%)	152 (79.2%)	152 (76.4%)	460 (78.8%)
Adverse Event Total	18 (9.3%)	31 (16.1%)	28 (14.1%)	77 (13.2%)
Worsening of Disease Under Study	13 (6.7%)	19 (9.9%)	15 (7.5%)	47 (8.0%)
Worsening of Other Pre-existing Disease	0 (0.0)	1 (0.5%)	5 (2.5%)	6 (1.0%)
Other Adverse Event	5 (2.6%)	11 (5.7%)	8 (4.0%)	24 (4.1%)

CLINICAL REVIEW

Clinical Review Section Study 205.137

	Tiotropium	Salmeterol	Placebo	Total
Administrative	15 (7.8%)	8 (4.2%)	13 (6.5%)	36 (6.2%)
Non-compliant with Protocol	10 (5.2%)	2 (1.0%)	3 (1.5%)	15 (2.6%)
Lost to Follow-up	0 (0.0%)	1 (0.5%)	2 (1.0%)	3 (0.5%)
Consent Withdrawn	5 (2.6%)	5 (2.6%)	8 (4.0%)	18 (3.1%)
Other	4 (2.1%)	1 (0.5%)	6 (3.0%)	11 (1.9%)

The mean age of the patients in this study was 63.4 years [U01-1231-1.pdf/p78]. The majority (77.9%) were men, and 99.5% were caucasian. The mean FEV₁ was 1.11 L (mean 39% of predicted). As shown in the table below, the baseline features were comparable across treatment groups.

	Tiotropium N (%)	Salmeterol N (%)	Placebo N (%)	Total N (%)
Total Treated	193	192	199	584
Sex				
Male (%)	157 (81.3)	144 (75.0)	154 (77.4)	455 (77.9)
Race				
White	191 (99.0)	192 (100)	198 (99.5)	581 (99.5)
Black	2 (1.0)	0 (0.0)	0 (0.0)	2 (0.3)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age				
Mean	63.0	63.5	63.7	63.4
Range	41 - 80	42 - 81	39 - 87	39 - 87
Smoking History (pack years)				
Mean	41.09	40.82	39.16	40.34
Range	10 - 144	10 - 147	10 - 126	10 - 147
Duration of COPD (years)				
Mean	8.9	9.4	9.9	9.4
Range	0 - 36	0 - 40	0 - 45	0 - 45
Screening FEV ₁ (L)				
Mean	1.14	1.06	1.13	1.11
Range	0.37 - 2.51	0.35 - 2.06	0.37 - 2.30	0.35 - 2.51
FEV ₁ /FVC x 100				
Mean	43.67	42.30	43.19	43.05
Range	13.7 - 67.3	21.9 - 67.5	21.1 - 67.5	13.7 - 67.5

Concomitant medications taken any time during the two-week baseline period were similar between treatment groups [U01-1231-1.pdf/p81-2]. Of the entire group, 48.8% used an anticholinergic drug, 66.4% used inhaled corticosteroids, 33.6% used theophylline preparations, 7.5% used oral steroids, and 0.3% used oxygen.

c. Efficacy Review

Data Sets Analyzed

The ITT data set was defined as all randomized subjects who had baseline data and "adequate" post-treatment data [U01-1231-1.pdf/p77]. As discussed in the review of Study 205.130,

CLINICAL REVIEW

Clinical Review Section Study 205.137

decisions regarding the adequacy of the post-treatment data “as well as other exclusions from the ITT data set” were determined at a blinded “report planning meeting” prior to opening of the treatment codes. For the analysis of the spirometry data, all randomized subjects with baseline (pre-treatment on test day 1) and trough FEV₁ on test-day 15 after 2 weeks of randomized treatment were included in the ITT data set. An additional “per-protocol” data set was also analyzed. The per-protocol analyses will not be discussed in this document.

The table below provides the numbers of subjects included in the data sets for the TDI ITT analysis, the PFT ITT analysis, and the safety analyses. As seen in Study 205.130, a greater number of subjects were excluded from the TDI ITT data set than from the PFT ITT data set.

Number of subjects in various data sets (Study 205.137)				[U01-1231-1.pdf/p78]
Data Set	Tiotropium	Salmeterol	Placebo	Total
Safety	193	192	199	584
TDI ITT	164	161	161	486
PFT ITT	184	185	183	552

Primary Endpoint

The two co-primary endpoints were the trough FEV₁ response and the TDI focal score, both evaluated on test-day 169 (Week 24) of randomized treatment. These were analyzed in a step-wise fashion. The primary comparison was tiotropium versus placebo. The numbers of patients included in the analyses of these two endpoints are provided in the table above.

Reviewer’s Note: In regard to the composition of the ITT data sets, the protocol stated that all randomized patients with at least baseline and trough FEV₁ after two weeks of treatment would be used for the efficacy analysis [U01-1231-1.pdf/p307]. (This was not altered in the protocol amendment). The study report states that the determination of the ITT populations (i.e. the definitions of “adequate” post-treatment data and “other exclusions from the ITT data set”) were made at a blinded report planning meeting, which occurred after the completion of the study and prior to “opening of the treatment codes” [U01-1231-1.pdf/p77]. As shown in the table above, considerable numbers of randomized subjects were excluded from the TDI ITT data set. This issue was discussed with the Biometrics Reviewer (Dr. Gebert). The decreased size of the ITT population was due to subjects who dropped out prior to Day 57 (the first day the TDI was administered) or for whom there was insufficient data to calculate the BDI or TDI focal scores. Thus, further analyses using the ITT as defined in the protocol would not be possible.

Tiotropium was statistically superior to placebo for the trough FEV₁ on test-day 169 ($p < 0.001$) [U01-1231-1.pdf/p92]. The magnitude of the effect size (0.11 liters) is considered clinically significant.

The primary analysis of the TDI focal score was a “responder” analysis, comparing the proportion of subjects with a TDI focal score of ≥ 1 unit in the tiotropium and placebo groups at test-day 169. Tiotropium was shown to be statistically superior to placebo in this analysis

CLINICAL REVIEW

Clinical Review Section
Study 205.137

($p < 0.05$) [U01-1231-1.pdf/p99]. On test-day 169, 45% of patients in the tiotropium group, 48% of subjects in the salmeterol group, and 33% of patients in the placebo group had a TDI focal score ≥ 1 unit. The comparison of salmeterol versus placebo was also statistically significant ($p < 0.01$).

Reviewer's Note: There are two difficulties with this type of analysis. First, the magnitude of change representing a clinically meaningful "response" must be established. The Division has previously informed the Applicant of this important requirement (See meeting minutes of 7/24/00 and letter dated 10/11/00). The Applicant has asserted that a change of ≥ 1 unit should be considered to be a clinically meaningful "response." The second difficulty is that there is no customary or accepted minimally clinically significant effect size for proportion of responders. The Applicant was also informed of the need to provide justification of the clinical significance of any difference demonstrated in the percentages of responders in each group. The adequacy of the justifications of both the definition of clinical response (i.e. ≥ 1 unit) and the significance of the observed effect size are be discussed in the Integrated Summary of Efficacy section of this Medical Officer Review.

Secondary Endpoints

Pulmonary Function Endpoints

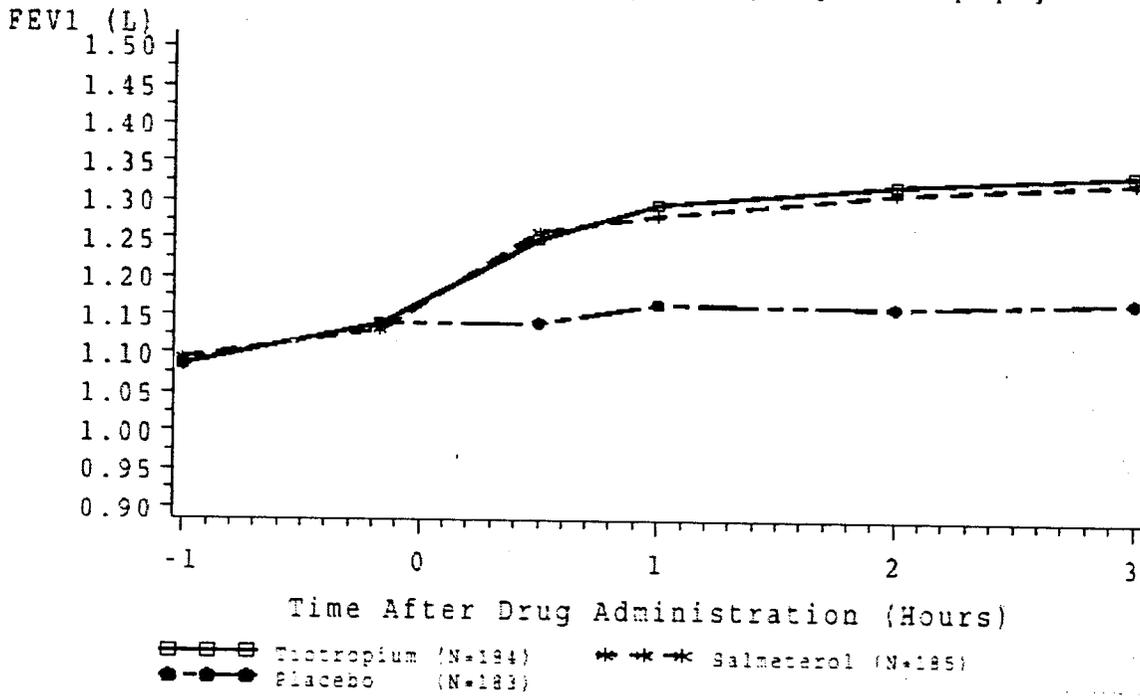
Serial spirometry was performed on the first day of dosing, and after 2, 8, 16, and 24 weeks of treatment. Measures were made 60 minutes and 10 minutes prior to dosing, and 30 minutes, 1, 2, and 3 hours after dosing. *The mean FEV₁ was statistically superior to placebo at all individual timepoints on all test days ($p < 0.001$) [U01-1231-1.pdf/p83].* The mean FEV₁ for tiotropium and salmeterol were not statistically different at any timepoint on any test day except Day 169 (and 1-hour post dose on test day 15). On test day 169, the mean FEV₁ in the tiotropium group was statistically superior to that of the salmeterol group at 1, 2, and 3 hours ($p < 0.05$), but the absolute difference was only 0.04 to 0.06 liters [U01-1231-1.pdf/p91]. The figures below illustrate the mean FEV₁ at Day 1 and Week 24.

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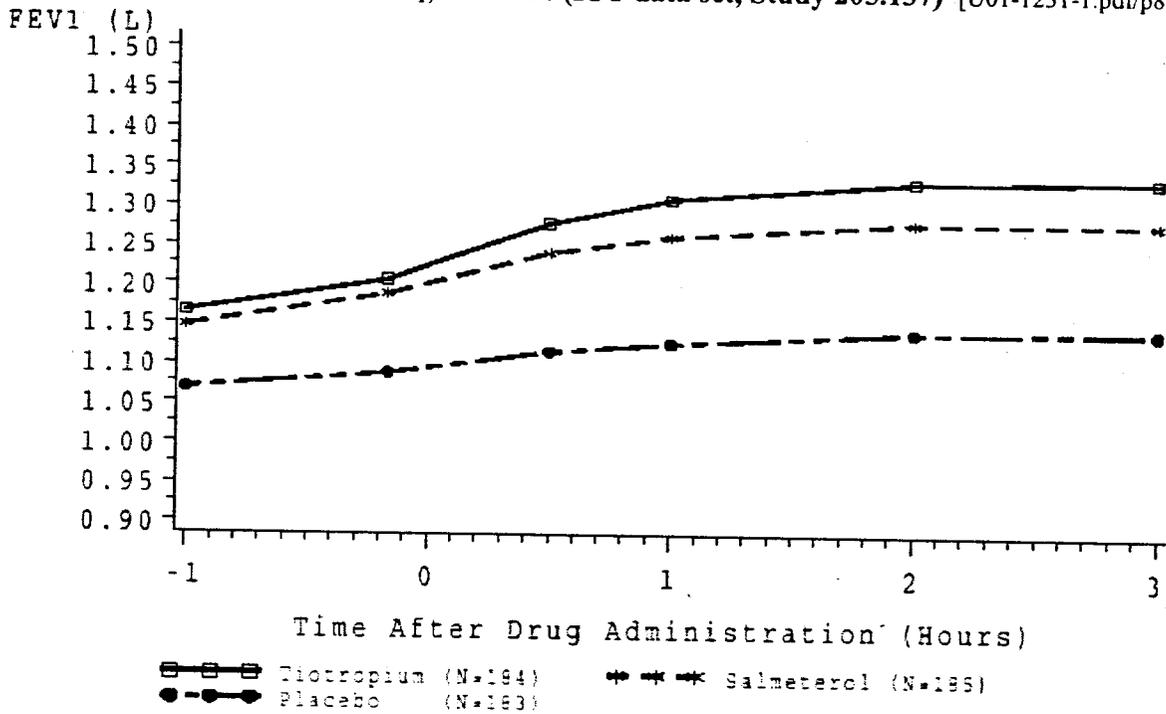
CLINICAL REVIEW

Clinical Review Section
Study 205.137

Mean FEV₁, Day 1 (ITT data set, Study 205.137) [U01-1231-1.pdf/p84]



Mean FEV₁, Week 24 (ITT data set, Study 205.137) [U01-1231-1.pdf/p88]



CLINICAL REVIEW

Clinical Review Section Study 205.137

The trough FEV₁ response in the tiotropium group was statistically superior to placebo on all test days ($p < 0.001$; absolute difference = 0.11 – 0.12L). The difference between tiotropium and salmeterol was not significant on any test day [U01-1231-1.pdf/p94].

The average FEV₁ response over the 3-hour post-dosing period in the tiotropium group was also statistically superior to placebo at each test day ($p < 0.001$). The difference between tiotropium and placebo was 0.13L on the first treatment day, and ranged from 0.18 – 0.20L during the remainder of the treatment period [U01-1231-1.pdf/p98]. Tiotropium was not statistically superior to salmeterol on any test day except Day 169 ($p = 0.0436$, absolute difference 0.05 L) [U01-1231-1.pdf/p98].

The peak FEV₁ response over the 3-hour post-dosing period in the tiotropium group was statistically superior to placebo on all test days ($p < 0.001$). The difference between tiotropium and placebo was 0.16L on the first treatment day (0.27L greater than baseline) and ranged from 0.19 to 0.21L during the remainder of the treatment period (0.27 – 0.30 L greater than baseline) [U01-1231-1.pdf/p96]. Tiotropium was statistically superior to salmeterol on this endpoint only on test days 15 and 169 ($p < 0.05$, absolute difference 0.05L and 0.07L, respectively) [U01-1231-1.pdf/p96].

The individual, trough, average, and peak FVC responses in the tiotropium group were also statistically superior to placebo at each test day (except the pre-dose values on the first treatment day) [U01-1231-1.pdf/p115-117, 119, 122].

Subjects measured their PEFr twice daily and recorded the values in their diaries. The mean morning PEFrs during the baseline period were similar among the treatment groups [U01-1231-1.pdf/p123]. The daily morning PEFr (averaged weekly) in the tiotropium group was statistically superior to placebo throughout the treatment period ($p \leq 0.01$) [U01-1231-1.pdf/p125-6]. The difference between tiotropium and placebo ranged from 14.9 L/min (during Week 1) and 21 L/min. The difference between tiotropium and salmeterol was not statistically significant at any treatment week.

The mean evening PEFrs during the baseline period were slightly higher for the placebo group (266 L/min) compared with the salmeterol (252 L/min) and the tiotropium (258 L/min) groups [U01-1231-1.pdf/p127]. The daily evening PEFr (averaged weekly) in the tiotropium group was statistically superior to placebo throughout the treatment period ($p < 0.001$) [U01-1231-1.pdf/p129-30]. The difference between tiotropium and placebo ranged from 21-28 L/min. The difference between tiotropium and salmeterol was statistically significant ($p < 0.05$) for weeks 3 and 4 only.

Patient Reported Outcomes

The Mahler Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) are comprised of three components: the Functional Impairment, the Magnitude of Task, and the Magnitude of Effort scales. The focal score is the sum of the three individual components. The BDI is utilized as a baseline measure. The TDI, which was administered at Weeks 8, 16, and 24, is used to

CLINICAL REVIEW

Clinical Review Section

Study 205.137

assess change from baseline. For the TDI, each component is scored on a scale of -3 (major deterioration) to 3 (major improvement). At baseline, the BDI, individual components and focal score was comparable between groups [U01-1231-1.pdf/p99, 103].

The proportion of subjects with a TDI focal score of ≥ 1 unit was statistically greater in the tiotropium group than the placebo group at Week 8 (44% vs. 31%) and Week 16 (42% vs. 30%) ($P < 0.05$) [U01-1231-1.pdf/p102]. On this endpoint, salmeterol was numerically, although not statistically, superior to tiotropium (47% vs. 44% at Week 8, and 47% vs. 42% at Week 16). Salmeterol was statistically superior to placebo on all both test days ($p < 0.01$).

The Applicant also analyzed the mean TDI focal score at Weeks 8, 16, and 24. On this analysis, tiotropium was statistically superior to placebo on each test day. The mean difference between groups exceeded 1 unit on all three test days (1.14 - 1.21) [U01-1231-1.pdf/p108]. The differences between tiotropium and salmeterol were not statistically significant. Salmeterol was statistically superior to placebo on all three test days, with differences between groups ranging from 1.26 to 1.66.

In regard to the individual components of the TDI, tiotropium was statistically superior to placebo for all three components on all test days [U01-1231-1.pdf/p108].

The SGRQ consists of 50 questions comprising three domains (Activities, Impacts, and Symptoms). A lower score indicates lesser impairment. In the existing medical literature, a change of 4 units in the SGRQ has been generally considered to be the minimally clinically meaningful difference. The SGRQ was administered at baseline, and after 8, 16, and 24 weeks of treatment. At baseline, the total SGRQ score and the scores for the individual domains were comparable among the treatment groups [U01-1231-1.pdf/p137]. The total SGRQ scores in the tiotropium group were statistically superior to placebo at Weeks 16 and 24 ($p = 0.0444$ and $p = 0.0388$, respectively), but not at Week 8. However, the numerical differences between groups (1.07 at Week 8, 2.54 at Week 16, and 2.82 at Week 24) did not reach the threshold of a clinically meaningful difference (4 units) on any test day. The comparisons between tiotropium and salmeterol and between salmeterol and placebo were not statistically different on any test day [U01-1231-1.pdf/p142].

The Applicant also performed a "responder analysis" on the SGRQ total score data, defining response as a change of more than 4 units. *However, this analysis was not pre-specified in either the protocol or the protocol amendment.* The number of responders was numerically greater in the tiotropium group compared to the placebo group on all three test days. This difference reached statistical significance at Weeks 8 (42% versus 29%, Odds ratio = 1.879, $p < 0.01$) and 16 (51% vs. 40%, Odds ratio = 1.642, $p < 0.05$), but not at Week 24 [U01-1231-1.pdf/p144].

In regard to the individual SGRQ domains, tiotropium was statistically superior to placebo for Activities score at Week 24 only ($p = 0.0469$). No statistical difference was seen for either the Impacts score or the Symptoms score on any test day [U01-1231-1.pdf/p142].

CLINICAL REVIEW

Clinical Review Section

Study 205.137

At each visit during the treatment and post-treatment period, *the investigator* completed the COPD symptom score evaluation. The scores were based on the *investigator's* assessment of the patient's condition during the week just prior to the visit and were completed prior to pulmonary function testing [U01-1236-1.pdf/p307; 416]. The specific symptoms rated were wheezing, shortness of breath, coughing, and tightness of chest. The scoring ranged from 0 – 3, corresponding to “not present”, “mild”, “moderate”, and “severe,” respectively. The baseline scores were comparable among the three treatment groups (Wheezing 0.76 – 0.80; Shortness of breath 1.47 – 1.58; Coughing 0.95 – 1.00; and Tightness of Chest 0.67 – 0.77) [U01-1231-1.pdf/p151]. Tiotropium was statistically superior to placebo ($p < 0.05$) for *shortness of breath* on test days 15, 29, 57, 85, and 141 (but not on test days 113, or 169). Salmeterol was statistically superior to placebo for shortness of breath on test days 15, 29, 57, and 141. Tiotropium was statistically superior to placebo ($p < 0.05$) for *coughing* on test days 57, 85, and 113 (but not on test days 15, 29, 141, or 169). Salmeterol was statistically superior to placebo for coughing on test days 113 only. Tiotropium was statistically superior to placebo for *wheezing* and *tightness of chest* on test day 15 only. Salmeterol was statistically superior to placebo for wheezing on test day 15 only, and was not statistically superior to placebo for tightness of chest on any test day. The effect sizes for tiotropium were 0.17 for Wheezing, 0.17 – 0.24 for Shortness of Breath, and 0.16 – 0.19 for coughing, and 0.14 for Tightness of Chest [U01-1231-1.pdf/p156-8]. The only statistically significant comparison between tiotropium and salmeterol was the Day 15 coughing score, which favored tiotropium.

Subjects also completed Patient Satisfaction and Patient Preference Questionnaires on the first day of treatment and at the end of the treatment period [U01-1231-1.pdf/p204-206]. The Patient Satisfaction questionnaire included ratings for satisfaction with: current medication, side effects, “how COPD medication makes you feel,” “how quickly medication starts to work,” “COPD medication on your sleep,” control of COPD symptoms, and current dosing schedule (first treatment visit only). These were rated on a 1-7 scale. Statistical analyses were not performed on these data. There were no notable differences between the tiotropium and the placebo groups on these questions at the end of treatment. Specifically, the difference in mean scores between treatment groups did not reach 1 for any question. The Patient Preference questionnaire addressed the following: which treatment preferred, “how often do you prefer to take an inhaler?”, “how important is the number of times/day you take inhalers?”, and “does treatment frequency affect compliance?” Interestingly, the median responses indicated that dosing frequency had “no impact” on compliance in the two active treatment groups whereas the placebo group indicated that more times per day makes compliance easier.

COPD Exacerbations and Hospitalizations

There were no significant differences between treatment groups in number of patients with at least one COPD exacerbation, number of COPD exacerbations, and number of exacerbation days [U01-1231-1.pdf/p167-8]. There was also no difference between the treatment groups in the time to first COPD exacerbation. The percentage of patients with at least one COPD exacerbation was 31 in the tiotropium group, 33 in the salmeterol group, and 35 in the placebo group (tiotropium vs. placebo, $p = 0.4254$). The number of COPD exacerbations per 100 patient-years was 111 in the tiotropium group, 110 in the salmeterol group, and 135 in the placebo group (tiotropium vs. placebo, $p = 0.3549$). The number of “event days” per 100 patient-years was 1677

CLINICAL REVIEW

Clinical Review Section Study 205.137

in the tiotropium group, 2015 in the salmeterol group, and 2076 in the placebo group (tiotropium vs. placebo, $p=0.3115$).

Hospitalizations for COPD exacerbation were infrequent. There were no notable differences between treatment groups regarding the number of patients with at least one hospitalization for COPD exacerbation (4%, 5%, and 4%), number of hospitalizations for COPD exacerbation (13 per 100 patient-years in the tiotropium group compared with 14 and 13 in the salmeterol and placebo groups, respectively), or number of hospitalization days for COPD exacerbation (112 event-days per 100 patient years in the tiotropium group compared with 118 and 117 in the salmeterol and placebo groups, respectively) [U01-1231-1.pdf/p168]. The number of hospitalizations (all cause) per 100 patient-years was also similar among the treatment groups (20 - 32).

Other Secondary Endpoints

A “shuttle walk test” (SWT) was performed after the first dose of study medication and on Days 57, 113, and 169. The SWT is a standardized test in which subjects walk at a steady pace on a 10-meter course until they are unable to maintain the required speed “without becoming unduly breathless” [U01-1236-1.pdf/p338-41]. The Modified Borg Dyspnea Scale was administered before and after each SWT. The Modified Borg scale ranges from 0 (“nothing at all”) to 10 (“maximal”). Of note, a score of 5 indicates “severe” dyspnea, with higher scores indicating “very severe” and “very, very severe” dyspnea. After the first dose of study medication there were no differences between groups in regard to the pre- or post-exercise Borg Dyspnea scores [U01-1231-1.pdf/p145]. Likewise, at Weeks 8, 16, and 25, there was no difference in pre- and post-exercise Borg scores between the tiotropium and placebo groups [U01-1231-1.pdf/p146]. There was also no difference in these scores between the salmeterol and placebo groups. There was no difference between groups in regard to the walking distance, and the walking distance did not increase during the study in any group. On each test day the mean walking distance was numerically superior in the placebo group, as compared to the tiotropium group [U01-1231-1.pdf/p147].

At each visit during the treatment and post-treatment periods, the investigator completed the Physician’s Global Evaluation. This evaluation was made prior to pulmonary function testing, (when applicable) and was scored on a scale of 1-8 [ranging from poor to excellent], based on the need for concomitant medication, number and severity of exacerbations since the last visit, severity of cough, ability to exercise, amount of wheezing, “etc.” Investigators reviewed their previous score before completing each new evaluation [U01-1236-1.pdf/p308]. The baseline scores were comparable among the groups (mean score 4.41 – 4.58) [U01-1231-1.pdf/p148]. The tiotropium group had statistically greater improvement than placebo on all test days except test day 169 (Week 24) ($p<0.01$) [U01-1231-1.pdf/p150]. The absolute difference between the tiotropium group and the placebo group in mean score ranged from 0.11 to 0.37.

During the treatment period all subjects were provided with albuterol for use as a rescue medication as needed. Subjects recorded the number of puffs of albuterol used in their daily diaries. Weekly means were computed for total number of puffs taken per day for each subject.

CLINICAL REVIEW

Clinical Review Section Study 205.137

During the baseline period the use of albuterol was slightly lower in the placebo group as compared with the two active treatment groups (tiotropium = 3.20 puffs/day; salmeterol = 3.11 puffs/day; placebo = 2.74 puffs/day) [U01-1231-1.pdf/p133]. Tiotropium was statistically superior to placebo during the first treatment week only. Salmeterol was statistically superior to placebo during the first two treatment weeks only. During the last week of treatment (Week 24), subjects the tiotropium group used 3.33 puffs per day, subjects in the salmeterol group used 2.85 puffs per day, and subjects in the placebo group used 3.35 puffs per day [U01-1231-1.pdf/p135-6].

The protocol also specified that “pharmacoeconomic data” would be analyzed as a secondary endpoint. This was to include the number of subjects hospitalized, the number of days spent in the ICU, the number of days the subjects were unable to perform the majority of their daily activities, the number of days subjects had unscheduled visits to a physician, the number of days subjects had an unscheduled visit to an other healthcare provider, and the number of subjects who changed their employment status at each visit. The Applicant states that these data were comparable across the treatment groups [U01-1231-1.pdf/p167].

Analysis of Washout Period

Following the active treatment period, subjects were followed for 3 additional weeks. Analyses of various data from the washout period (PEFRs, rescue medication use, patient reported outcomes, shuttle walk test, physicians global evaluation, and COPD symptoms) were performed. These analyses include only those subjects who completed the study and had a least some post-treatment data. During the washout period, the TDI focal score decreased in all treatment groups (by 1.72 in the tiotropium group, 1.10 in the salmeterol group, and 0.15 in the placebo group) [U01-1231-1.pdf/p158]. *At the end of the washout period, the mean TDI focal score was -0.55, indicating a status that is worse than baseline.* The mean TDI focal score at the end of the washout period was -0.13 in the placebo group. The mean weekly AM PEFR in the tiotropium group decreased only slightly from 28.66 L/min above baseline at the end of the treatment period to 26.46 L/min above baseline during the third week of the washout period [U01-1231-1.pdf/p160]. The mean weekly AM PEFR in the placebo group actually improved slightly during the washout period (from 9.16 L/min above baseline at the end of the treatment period to 14.66 L/min greater than baseline during the last week of the washout period) [U01-1231-1.pdf/p160]. PM PEFR values followed a similar pattern during the washout period. Apart from the focal TDI score at the end of the washout period, these data, and the remainder of the washout period data do not suggest a “rebound” effect related to discontinuation of tiotropium [U01-1231-1.pdf/p159-66]. The failure of the PEFR to return to baseline values in the tiotropium group may indicate continued effect of the drug.

Pharmacokinetic Data

This study did not include assessments of pharmacokinetic parameters.

Reviewer’s Comments on Efficacy

The efficacy analyses utilized an ITT data set, defined as all randomized patients who had baseline data and “adequate” post-treatment data. Decisions regarding the adequacy of the data as well as other exclusions from the ITT data set were made at a “blinded report planning

CLINICAL REVIEW

Clinical Review Section Study 205.137

meeting.” As seen in Study 205.130, a greater number of subjects were excluded from the TDI ITT data set than from the PFT ITT data set.

The amended protocol established two co-primary endpoints, the trough FEV₁ response and the TDI focal score, both evaluated on test day 169 (Week 24). Tiotropium was statistically and clinically superior to placebo on the trough FEV₁ endpoint ($p < 0.001$, effect size 0.11 liters). The trough FEV₁ endpoint helps to establish the duration of action of tiotropium. However, the threshold for a “clinically relevant” effect at the trough timepoint is not as well established as for the peak timepoint. At peak, one might consider a change of 12% (and at least 200ml) to be clinically relevant. The effect size seen in this study in regard to the trough FEV₁ is less than that, but is still considered to be clinically relevant. One further point regarding the trough FEV₁ endpoint is that comparisons to other drugs based on this endpoint would not be wholly appropriate. Differences on this endpoint may reflect differences in pharmacodynamic profiles, and miss other, perhaps more relevant performance characteristics.

The TDI comparison was specified to be a “responder analysis”, with a pre-defined change of 1 unit being considered to represent a meaningful response. A statistically greater percentage of subjects in the tiotropium group, as compared to the placebo group, demonstrated a response on test day 169 (45% versus 33%). Thus, tiotropium was statistically superior to placebo on each of the two co-primary endpoints. However, the study report does not address two important issues in regard to the TDI analysis. The first issue is whether the observed effect size (i.e. 45% versus 33%) is clinically meaningful. The second issue is whether the pre-specified responder definition (1 unit) is appropriate.

The secondary endpoints generally support the efficacy of tiotropium as a bronchodilator. Secondary endpoints for which tiotropium was statistically superior to placebo included: individual FEV₁ and FVC measurements on all test days; morning and evening PEFr; TDI “responder analyses” at Weeks 8 and 16 and analyses of mean TDI focal scores at Weeks 8, 16, and 24; physician’s assessment of COPD symptoms of shortness of breath (most test days) (but not consistently for coughing, wheezing, and tightness of chest); and physician’s global evaluation (except Week 24). It must be noted that the clinical significance of the observed effects on some of these endpoints is not clear. Secondary endpoints that did not establish superiority of tiotropium over placebo include the SGRQ (for which the differences between tiotropium and placebo, where statistically significant, did not reach the minimal threshold representing a clinically meaningful change); all analyses of COPD exacerbations, patient satisfaction questionnaire; shuttle walk test/ Borg Dyspnea scale; rescue medication; and hospitalizations for COPD exacerbation.

In summary, the analyses of the primary and secondary endpoints of this study establish the efficacy of tiotropium as a bronchodilator in this patient population. It must be noted that the failure to demonstrate superiority on rescue albuterol use beyond the first week of treatment is not supportive of bronchodilator efficacy. However, the active comparator also did not demonstrate superiority on this parameter beyond two weeks. The data may support the effect of tiotropium on the symptom of dyspnea; however, this depends on the determination as to