Mean FEV_1 Peak Response (Liters) (Combined 1-year, placebo-controlled studies)				[ise.pdf/p488]
Test Day	Gender	Tiotropium	Placebo	Difference
344	Male	0.28	0.05	0.23
	Female	0.22	0.03	0.18

A gender interaction was also noted in regard to the TDI focal score data. Because the six-month studies were submitted as the primary evidence of efficacy in regard to dyspnea, these studies will be discussed first. In the six-month studies, the mean TDI focal score was notably higher (better) among men, as compared to women, as shown in the table below. In fact, in these analyses, among women, there was no difference in mean TDI focal score between tiotropium and placebo (p=0.846 – 0.996) [ise.pdf/p497].

Mean TDI Focal Score, by Gender (Combined 6-month studies)				[ise.pdf/p497]
Test Day	Gender	Tiotropium	Placebo	Difference
57	Male	0.42	-1.19	1.61
	Female	0.24	0.13	0.11
113	Male	0.40	-0.85	1.25
	Female	0.38	0.38	0.00
169	Male	0.52	-0.84	1.36
	Female	0.74	0.62	0.12

In the one-year, placebo-controlled studies, the differences between men and women were not as marked, and on most days the response seen in women was numerically slightly greater than the response seen in men [ise.pdf/495]. Thus, although a clear gender effect was seen in the six-month studies, one was not seen in the one-year, placebo-controlled studies.

Finally, gender does not effect drug plasma concentrations or urinary excretion of tiotropium in patients with COPD [biosum.pdf/p22 and U99-3169.pdf/p149].

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The applicant analyzed the adverse event data for potential age interactions [iss.pdf/p176]. For that purpose, the patients were divided into three age groups: ≤60 years, 61-70 years, and ≥71 years. In those analyses, age interactions for the adverse events dry mouth, constipation, and urinary tract infection were identified. This is discussed further in the section of this document entitled Integrated Review of Safety.

The efficacy data was also analyzed for age interaction, using the same three age categories [ise.pdf/p385]. The tabular data displaying these data, by subgroup were reviewed [ise.pdf/p466-76]. In the one-year placebo-controlled studies the mean average and mean peak responses were notably higher in the youngest age group, whereas the mean trough FEV_1 was slightly higher in the oldest age group [ise.pdf/p466-8]. In the one-year, active-controlled studies, there was also evidence of an age interaction, with the younger patients showing a greater response in terms of

mean average and peak FEV_1 [ise.pdf/p470-1]. This trend was not evident in the 6-month studies [ise.pdf/p473-4].

In regard to age effects on pharmacokinetic parameters, renal clearance of tiotropium is significantly lower in elderly patients (163 mL/min; mean age 74) compared with younger patients (326 mL/min; mean age 53) [biosum.pdf/p22]. This decreased clearance is associated with increased systemic exposure, as indicated by an increase in the $AUC_{0\text{-}4\ hours}$ from 18.2 pg.h/mL to 26.1 pg.h/mL.

The Applicant analyzed the adverse event data and the efficacy data for potential race interactions. Although there was no apparent race interaction, the numbers of non-Caucasian patients were too few to draw conclusions [iss.pdf/p178, 202, 388].

B. Evaluation of Pediatric Program

This drug was developed for COPD. Because COPD is a disease of older adults, pediatric studies were not performed.

C. Comments on Data Available or Needed in Other Populations

As discussed in Section I.C., of the Executive Summary, the Phase 3 program did not provide sufficient data on patients with active cardiac disease, and on non-Caucasian patients. These populations should be studied.

X. Conclusions and Recommendations

A. Conclusions

The data submitted in this Application are adequate, from the clinical perspective, to support approval. The six, large, Phase 3, placebo- and/or active-controlled studies establish the efficacy of tiotropium bromide inhalation powder (18mcg QD) as a bronchodilator in patients with COPD. This was established by the demonstration of clinically meaningful improvements in the FEV_1, measured at the end of the dosing interval, following chronic administration. In addition, improvements in various secondary endpoints, such as peak and average post-dose FEV_1 and FVC, home peak flow rate measurements, and rescue albuterol use further support the bronchodilator efficacy of the drug. The studies did not establish a clinically meaningful degree of benefit in regard to the symptom of dyspnea in these patients. The extent of patient exposure to the drug during the development program was adequate, and the safety profile demonstrated is acceptable, given the established efficacy.

B. Recommendations

The Clinical recommendation for this Application is Approval.

XI. Appendix

A. One-Year, Placebo-Controlled Studies

1. Study 205.114/205.117: "A multiple dose comparison of 18mcg of tiotropium inhalation capsules and placebo in a one-year, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease (COPD)"

a. Study Description

Design

This was a multi-center, randomized, double-blind, placebo-controlled, parallel group study. Randomization was performed using a 3:2 (active:placebo) ratio [U99-3169.pdf/p40].

Duration

The duration of active treatment was 49 weeks. The study included both a 13-week safety and efficacy study (205.114) and a nine-month extension (205.117). The study was performed during the period of January 8, 1997, to May 28, 1998. *The supply of tiotropium used in the trial had an expiration date of April 30, 1998. Thus any patient randomized after May 22, 1997 was unable to complete the 49 weeks on study medication as required by the protocol [U99-3169.pdf/p59].* The final study report is dated September 7, 1999. The final report was amended 5 times (1/23/00, 6/26/00, 11/6/00, 12/6/00, and 8/24/01).

Study Centers

The study was conducted at 25 US centers in the following states: AL, AR, CA, CT, FLA, LA, NC, NH, NJ, NY, OH, OK, PA, SC, TX, VA, WA, and WI [U99-3169.pdf/p48-9].

Population

A total of 470 subjects with relatively stable, moderately severe COPD entered the study. A total of 279 subjects were randomized to treatment with tiotropium and 191 subjects were randomized to treatment with placebo.

Materials

The study treatments were:

- Tiotropium inhalation powder capsules 18mcg
- Placebo inhalation powder capsules

Each treatment was administered once daily, in the morning.

Two lots of tiotropium from the same batch were supplied (PD-1732, and PD-1742). The expiration date for both lots was April 30, 1998. Two lots of placebo were supplied (PD-1734, and PD-1743). These also had an expiration date of April 30, 1998.

Appendix

Study 205.114/205.117

Objective

The objective of this study was to compare the long-term bronchodilator efficacy and safety of once-a-day administration on 18mcg of tiotropium inhalation capsules and placebo in patients with COPD. The secondary objective was to assess the impact of tiotropium on the patients' "quality of life" and on health care resources [U99-3169.pdf/p53].

Inclusion Criteria

- Diagnosis of COPD
- $FEV_1 \leq 65\%$ of predicted (based on predicted values by Morris) and $\leq 70\%$ of FVC
- Male or female
- Age ≥ 40
- Smoking history of > 10 pack-years
- Ability to perform spirometry, maintain records, and inhale medication from the HandiHaler

Exclusion Criteria

Notable exclusion criteria were:

- Significant disease other than COPD
- Recent myocardial infarction (≤ 1 year)
- Recent history of heart failure (≤ 3 years)
- Cardiac arrhythmia requiring drug therapy
- Use of daytime oxygen therapy
- History of life-threatening COPD, or history of cystic fibrosis or bronchiectasis
- History of thoracotomy with pulmonary resection
- Respiratory tract infection within 6 weeks prior to screening
- Known symptomatic prostatic hypertrophy or bladder neck obstruction. **Reviewer's Comment: This exclusion may be important to note in the product label.**
- Known narrow-angle glaucoma **Reviewer's Comment: This exclusion may be important to note in the product label.**
- Current use of cromolyn sodium, nedocromil sodum, or anti-histamines
- Oral corticosteroid use at unstable doses (less than 6 weeks on a stable dose), or at a dose in excess of the equivalent of 10mg of prednisone per day or 20mg every other day
- History of asthma, allergic rhinitis, or atopy
- Total blood eosinophil count $\geq 600/mm^3$

Conduct

Following an initial screening period, patients entered a 2-week baseline period. Patients who successfully completed the baseline period were randomized into the 49-week, double-blind treatment portion of the study, in which they received either tiotropium or placebo once-daily in the morning (between 8AM and 10AM). On-treatment visits were scheduled at the end of the first week, then every 3 weeks during the first 13 weeks, then every 6 weeks for the next 36 weeks. Patients were contacted by phone midway between visits during the final 36-week period. Patients completed a Daily Patient Record indicating each dose of investigational drug

taken and number of doses of rescue albuterol inhalation aerosol taken [U99-3169.pdf/p304]. The treatment portion was followed by a 3-week, post-treatment observation period [U99-3169.pdf/p55]. Compliance with study medication, based on the subject's daily record card, was assessed at each study visit.

Pulmonary function testing was performed at baseline, and after 1, 7, 13, 25, 37, and 49 weeks of treatment. Testing was performed at one hour prior to dosing, immediately prior to dosing, and at 30, 60, 120, and 180 minutes post-dosing. Testing was performed in the morning, between 7AM and noon, following at least a 24-hour washout of theophylline preparations and at least a 12-hour washout of short-acting bronchodilators and inhaled steroids. To ensure theophylline washout compliance, serum theophylline levels were obtained on all patients at screening and on those patients taking theophylline at Visits 2, 3, 5, 7, 9, 11, and 13. *Bronchodilator reversibility testing was not performed.*

Other efficacy assessments included [U99-3169.pdf/p63]:

- Morning and evening PEFR: performed by the subject twice daily during the study period. The AirWatch™ Monitoring System was used to record the measurements electronically. Morning measurements were performed immediately upon arising after the subject had "cleared out" mucus. Evening measurements were performed at bedtime. (Note: The original protocol indicated that "peak flow *and* FEV_1 measurements will be recorded *three times daily* by the patient throughout the 54-week evaluation period including the two-week baseline period and one-year treatment period." [U99-3169.pdf/p306]. This was subsequently changed in Amendment 1 to two times daily. The reference to FEV_1 was not removed [U99-3169.pdf/p353]. In response to a request for information, the Applicant stated that, although the FEV_1 data was captured using the AirWatch Monitor, a decision was made prior to the initiation of the trial to not analyze the home FEV_1 data because of concerns regarding its reliability [Submission 7/16/02, page 4]).
- COPD symptoms (wheezing, shortness of breath, coughing, and tightness of chest): These scores are based upon *the Investigator's assessment* of the patient's condition *during the week just prior* to the contact [U99-3169.pdf/p306]. They were recorded on case report forms (CRFs) at the end of baseline period, at the end of the first week of therapy, and every 3 weeks for the next 12 weeks. During the remaining 36 weeks of treatment the COPD symptom evaluations were made at 3-week intervals, either during clinic visits or during telephone contacts midway between visits.
- Physician (or designee) global evaluation: at the end of the baseline period, at the end of the first week of therapy, and every 3 weeks for the next 12 weeks. During the remaining 36 weeks of treatment the physician global evaluations were made at 6-week intervals. The evaluations were made prior to pulmonary function testing, and reflected the physician's opinion of the overall clinical condition. The evaluation was to be 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. The scores could range from 1 (poor) to 8 (excellent).
- Rescue albuterol use recorded daily by the patient.
- St. George's Hospital Respiratory Questionnaire (SGRQ), SF-36, and the Mahler BDI/TDI: administered at the end of the baseline period, after 7, 13, 25, 37, and 49 weeks of treatment.

Appendix

Study 205.114/205.117

- Patient's scoring of their energy and fatigue, and the severity of their respiratory condition.
- COPD exacerbations, hospitalizations, concomitant medications, non-scheduled contacts with physicians and other health care providers, disability days, and employment data were also collected in order to estimate the direct and indirect cost of treatment with tiotropium.

Pharmacokinetic sampling was performed in a subset of the centers. At 10 of the 25 centers blood and urine samples were collected at Visits 5, 7, and 9 for the measurement of tiotropium levels [U99-3169.pdf/p64]. In five of these 10 centers additional urine samples were collected at Visits 4 and 6. The following samples were obtained:

- Visits 5 and 7:
  - 5 and 10 minutes pre-dose, 5 minutes post-dose, and immediately following the 2-hour post-dose pulmonary function testing.
  - 24-hour urine collection (for the 24-hours prior to the visit)
- Visit 9:
  - 24-hour urine collection (for the 24-hours prior to the visit)
- Visits 4 and 6:
  - Two, 2-hour urine samples (2 hours prior to dosing and 2 hours post dosing)

Safety parameters were: adverse events; pulse and blood pressure performed in conjunction with spirometry; and, laboratory tests/ECGs performed at baseline and every three months throughout the treatment period and at the conclusion of patient participation in the trial. The timing of the ECGs in relation to drug administration was not stated in the protocol or captured on the case report forms [Submission 7/16/02, page 5]. Therefore, these ECGs may have been obtained pre-dose. Pre-dose ECGs may be less informative than ECGs obtained at Cmax. Physical examinations were performed at baseline, Visit 7 and Visit 14, or at the conclusion of patient participation in the trial [U99-3169.pdf/p54]. Worsening COPD symptoms were recorded as an adverse event only if it met the requirements for a serious event, the study drug was discontinued, the event caused termination from the trial, or the patient showed a clear deterioration from baseline [U99-3169.pdf/p66].

The protocol and protocol amendment was approved by the appropriate IRBs. The Applicant states that the study was conducted according to FDA regulations and guidelines and that written informed consent was obtained from each patient prior to participation in the study [U99-3169.pdf/p56].

Appendix
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The following tables outline the study procedures.

Study Procedures, First 13 Weeks: 205.114/205.117 [U99-3169.pdf/p68-9]

Trial Period:	Screen	Treatment Period (First 13 Weeks)					
Visit #:	1	2	3	4	5	6	7
Weeks on Therapy:		0	1	4	7	10	13
Day:	-14	1	8	29	50	71	92
Physical Examination	X						X
Vital Signs (seated)	X	X	X		X		X
Laboratory Tests (fasting)	X						X
12-lead ECG	X						X
Theophylline level[1]							
Dispense Drugs		X	X	X	X	X	X
Investigational Drugs		X	X		X		X
PFTs (FEV_1 and FVC)	X	X[2]	X[2]		X[2]		X[2]
Quality of Life		X			X		X
Energy/Fatigue Questionnaire		X	X	X	X	X	X
Pharmacoeconomic Data		X	X	X	X	X	X
Review of PEFR Records		X	X	X	X	X	X
Global Evaluations		X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X
PK samples[3]				X	X	X	X

[1]Theophylline levels on all patients at Visit 1 and only on patients taking theophylline at subsequent test day visits
[2]Two baseline tests and tests at 30, 60, 120, and 180 minutes post drug administration
[3]Ten sites were designated to perform PK sampling

Study Procedures, Weeks 13-52: 205.114/205.117 [U99-3169.pdf/p68-9]

Trial Period:	Treatment Period (Week 13 through Week 52)												**
Visit #:		8		9		10		11		12		13	14
Telephone Calls	7.1		8.1		9.1		10.1		11.1		12.1		
Weeks on Therapy:	16	19	22	25	28	31	34	37	40	43	46	49	+3
Physical Examination													X
Vital Signs (seated)				X				X				X	
Laboratory Tests (fasting)				X				X				X	
12-lead ECG				X				X				X	
Theophylline level[1]				X				X				X	
Dispense Drugs		X		X		X		X		X			
Investigational Drugs				X				X				X	
PFTs (FEV_1 and FVC)				X[2]				X[2]				X[2]	
Quality of Life				X				X				X	X
Energy/Fatigue Questionnaire		X		X		X		X		X		X	X
Pharmacoeconomic Data	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of PEFR Records		X		X		X		X		X		X	X
Global Evaluations		X		X		X		X		X		X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X

[1]Theophylline levels on all patients at Visit 1 and only on patients taking theophylline at subsequent test day visits
[2]Two baseline tests and tests at 30, 60, 120, and 180 minutes post drug administration
**Post-treatment period

Appendix

Study 205.114/205.117

Concomitant Therapy

The protocol included the following restrictions regarding medications during the course of the study:

- Anticholinergic drugs including Atrovent Inhalation Aerosol and Atrovent Nasal Spray were allowed during the baseline period but not during the treatment period
- Theophylline preparations, excluding 24-hour preparations, orally inhaled steroids, and minimal doses of oral corticosteroids (equivalent to 10mg or less of prednisone daily or 20mg or less every other day) were allowed if stabilized for at least six weeks prior to the screening visit and throughout the study period.
- PRN albuterol was allowed throughout the study period.
- Any medication, including antibiotics, could be used to control acute COPD exacerbations. However, patients were allowed only two, seven-day increases in the dose or the addition of oral steroids or theophylline. If the increases or additions occurred prior to pulmonary function testing days, the testing was postponed for at least two, but not more than seven days after the last increased or additional dose was given.
- All other investigational drugs, all beta-blockers, cromolyn sodium/nedocromil sodium, oral β-adrenergics or long-acting β-adrenergics were not allowed for one month prior to the baseline period.

Data Analysis

A sample size was primarily based on safety consideratins ("i.e. to expose an adequate number of patients to tiotropium"). A sample size of 400 patients (240 in the tiotropium group and 160 in the placebo group) was expected to provide a power of 90% to detect a difference in mean FEV_1 response of 0.056 liters between tiotropium and placebo, using a 5% level of significance and a two tailed t-test [U99-3169.pdf/p59-60]. **Reviewer's Note: Although a total of 400 patients were expected to provide 90% power, a total of 470 patients were randomized. This will not be an issue provided that the effect size demonstrated is felt to be clinically significant.** The Applicant utilized a 3:2 randomization scheme in order to achieve the desired number of subjects for long-term exposure.

The statistical model was analysis of covariance with terms for treatment, center, and baseline as covariates. The statistical model described in the protocol also included a treatment-by-center interaction term as a covariate. The study report indicates that the interaction term was subsequently excluded from the model, based on ICH guidelines [U99-3169.pdf/p75]. The report included analyses both with and without the interaction covariate for the primary endpoint. **Reviewer's Note: This issue was discussed with the DPADP Biometrics Reviewer (Dr. J. Gebert), who felt this was reasonable.** The intention-to-treat principle was used in all efficacy analyses.

An interim analysis was planned and performed on the data from the first 13 weeks of the trial. No treatment codes were communicated to either patients or study personnel in contact with patients [U99-3169.pdf/p76]. The Applicant states that, because all decisions with regard to inclusion/exclusion of data and the analysis plan were made prior to un-blinding, and no changes

were planned or made based on the outcome of the analysis, no adjustment to the p-value was necessary [U99-3169.pdf/p80-1]. This is reasonable.

The final rules for handling missing data were determined at a blinded report planning meeting held prior to un-blinding of the treatment codes for the interim analysis. Linear interpolation between two adjacent measurements was used to estimate random, middle and missing spirometry measurements. For values at the end of the serial spirometry that were missing because rescue medication was taken, the minimum observed FEV_1 value on that test day (even if it was the pre-dose value) was used as the estimate. The last available value was used as the estimate for data that were missing for reasons unrelated to the subject's response to treatment.

For missing visit data due to lack of efficacy, the last observation carried forward approach was used. In the case of missing data due to worsening of COPD, the least favorable data approach was used. The last observation carried forward approach was also used for analyses of the "quality of life" data, to be consistent with the methods used in validation of these questionnaires.

The Applicant states that, based on FDA comments after the end-of-phase-2 meeting, daily record card efficacy data and PEFR data during steroid and theophylline bursts for COPD exacerbation was excluded prior to analysis, and weekly summary data from the daily record card were considered incomplete if the summary was based on less than four observations in a week and were imputed based on current and neighboring weeks [U00-3169.pdf/p77].

The primary efficacy variable was the "trough FEV_1 response," which was defined as the change from baseline in the mean of the two FEV_1 values at the end of the dosing interval (approximately 23 and 24 hours post drug administration) [U99-3169.pdf/p315]. The baseline FEV_1 was calculated as the mean of the two FEV_1 values measured in the morning of the randomization visit, prior to administration of study medication. The primary efficacy endpoint was the trough FEV_1 response at the end of the first 13 weeks of treatment [U99-3169.pdf/p53]. *Note: The original protocol defined the primary efficacy variable, but not the specific endpoint [U99-3169.pdf/315]. The primary efficacy endpoint (i.e. Week 13) was declared in a protocol amendment [U99-3169.pdf/p55 and p352].*

Secondary efficacy endpoints were [U99-3169.pdf/p54 and 78]:

- Average and peak FEV_1 response for the first 3 hours post-treatment on each test day.
- Trough, average, and peak FVC response on each test day.
- Individual FEV_1 and FVC measurements at each time point.
- Weekly mean of PEFR measured by the patient at home twice daily
- Physician's global evaluation
- COPD symptom scores (wheezing, shortness of breath, coughing, and tightness of chest).
- Amount of albuterol therapy used during the treatment period
- Number of nocturnal awakenings during the first 13 weeks
- Number and length of COPD exacerbations and of hospitalizations for respiratory disease during the treatment period.

- "Quality of life" measures. The protocol stated that "to assess the quality of life, the transition dyspnea index will be considered as primary endpoint" [U99-3169.pdf/p316]. In regard to the SGRQ, the original protocol referred to the overall SGRQ score, and did not discuss the individual domains that make up the SGRQ [U99-3169.pdf/p316]. The first protocol amendment indicated that the total SGRQ would be the primary endpoint, with a change of 4 units being considered clinically significant. The Impact score was designated as a secondary endpoint [U99-3169.pdf/p352]. The Applicant subsequently altered the planned analysis to focus on the Impact domain at the blinded report planning meeting. The Applicant states that the developer of the SGRQ suggested that this domain may be more sensitive to change from a therapeutic intervention. In regard to the SF-36, the original protocol stated that physical dimensions scores would be used to support efficacy, and that the other dimensions and the overall score from the SF-36 would be used as exploratory measures [U99-3169.pdf/p316].
- Pharmacoeconomic vairables such as number of exacerbations and their treatment, hospitalizations, extra physician and other health care provider visits, concomitant medication use, disability days (days patient is unable to do usual daily activities), and employment status.

Note: The original protocol did not describe the planned statistical analyses of the secondary endpoints [U99-3169.pdf/p315]. In addition, analysis of the number of nocturnal awakenings was not included in the list of secondary analyses in the original protocol.

Reviewer's Note: The Applicant states that the protocol called for between group comparisons of the change from baseline. However, the study report provides comparisons of the absolute values. The Applicant states that since the statistical model includes baseline as a covariate the inferences are not altered. This issue was discussed with the DPDADP Biometrics Reviewer (Dr. J. Gebert), who felt that, as long as baseline was in the original model as a covariate, comparing the absolute values is acceptable.

b. Patient Disposition

A total of 655 patients were screened for entry. Of these, 470 were randomized: 279 to tiotropium and 191 to placebo [U99-3169.pdf/p.82]. *Note: The supply of tiotropium used in this trial had an expiration date of April 30, 1998. Therefore, any patient randomized after May 22, 1997 was unable to complete the 49 weeks on study medication. Randomization continued until June 30, 1997. Patients who were unable to complete all visits due to drug expiration were required to discontinue stud drug at nine months but were considered complete patients.* The disposition of randomized patients is outlined in the table below. A greater percentage of tiotropium patients completed all visits, compared with placebo patients. Fewer patients in the tiotropium group failed to complete the study due to adverse events (8.2%) and lack of efficacy (2.5%), compared with placebo patients (13.6% and 6.8%, respectively).

Appendix

Study 205.114/205.117

Patient Disposition and Reasons for Withdrawal, Study 205.114/205117 [U99-3169.pdf/p83]

	Tiotropium N (%)	Placebo N (%)
Entered/Randomized	279	191
Completed the Trial	235 (84.2)	139 (72.8)
Discontinued For:		
Adverse Event Total	23 (8.2)	26 (13.6)
Unexpected Worsening of Disease Under Study	12 (4.3)	12 (6.3)
Unexpected Worsening of Other Pre-existing Disease	1 (0.4)	2 (1.0)
Other Adverse Event	10 (3.6)	12 (6.3)
Lack of Efficacy	7 (2.5)	13 (6.8)
Administrative	14 (5.0)	12 (6.3)
Non-compliant with Protocol	0 (0)	0 (0)
Lost to Follow-up	3 (1.1)	4 (2.1)
Consent Withdrawn	11 (3.9)	1 (0.5)
Other	0 (0)	1 (0.5)

The Application summarizes the protocol violations by treatment group [U99-3169.pdf/p83-4]. These included: failure to meet all entrance criteria (7.5% of tiotropium group, and 10.9% of placebo group), and elevated theophylline level (10% of tiotropium group, and 10.9% of placebo group). In addition, one site randomized patients out of order in a manner that would not bias treatment selection. These violations are unlikely to influence the conclusions of the study.

The table below summarizes the demographics and baseline characteristics of the study population. The majority of subjects were white (92%). The baseline features were similar between groups.

Demographics and Baseline Characteristics, Study 205.114/205.117 [U99-3169.pdf/p85-6]

	Tiotropium	Placebo	Total
Total Treated	279	191	470
Sex			
Male	186 (66.7)	121 (63.4)	307 (65.3)
Race			
Caucasian	264 (94.6)	168 (88.0)	432 (91.9)
Negroid	15 (5.4)	21 (11.0)	36 (7.7)
Mongoloid	0 (0.0)	2 (1.0)	2 (0.4)
Australoid	0 (0.0)	0 (0.0)	0 (0.0)
Age			
Mean	64.95	65.51	65.18
Range	40 – 85	39 – 81	39 - 85
Smoking History (pack years)			
Mean	64.54	60.51	62.90
Range	11 – 240	10 – 160	10 - 240
Duration of COPD (years)			
Mean	9.28	8.57	8.99
Range	0.1 – 50	0.3 – 40	0.1 - 50
Screening FEV_1 (L)			
Mean	1.04	1.00	1.02
Range	0.37 – 3.03	0.30 – 2.63	0.30 – 3.03
FEV_1/FVC x 100			
Mean	46.2	46.18	46.19

Appendix

Study 205.114/205.117

Demographics and Baseline Characteristics, Study 205.114/205.117		[U99-3169.pdf/p85-6]	
	Tiotropium	Placebo	Total
Range	20 – 95.37	21.41–69.62	20 – 95.37

Concomitant pulmonary medications used during the baseline period were similar between groups [U99-3169.pdf/p86-7]. During the baseline period, inhaled anticholinergics were used by 54.7% of patients, inhaled corticosteroids were used by 38.9% of patients, oral corticosteroids were used by 6.8% of patients, theophylline was used by 23.6% of patients, and supplemental oxygen was used by 6.4% of patients.

c. Efficacy Review

Efficacy analyses used the ITT population, including all randomized patients except in cases of missing data. Rules to address cases of missing data were established at a blinded "report-planning" meeting conducted prior to opening treatment codes [U99-3169.pdf/p88]. For spirometry data, Energy-Fatigue Questionnaire data, COPD symptom data, and Physician Global evaluation data patients were excluded from the ITT data set if they had missing baseline data or if they did not have data from at least two visits following multiple administration. For St. George's Hospital Respiratory Questionnaire data, SF-36 Questionnaire data, and TDI data patients were excluded if they had missing baseline data or they did not have any data after multiple administration. For the analysis of spirometry data all randomized patients with baseline and adequate data following multiple administrations were included in the ITT data set, however, those patients with documented inadequate washout (theophylline level >6.1) at Visit 2 (baseline) and no data following at least seven weeks of multiple administration were excluded from the ITT data set. For the analysis of data from daily record cards all randomized patients with baseline data as well as data for at least two weeks on treatment were included in the ITT data set.

Of the 470 patients randomized, 6 patients (1.3%) were excluded from all efficacy analyses because of inadequate data following multiple administration. This included 3 out of 279 (1.1%) tiotropium patients and 3 out of 191 (1.6%) placebo patients.

Primary Endpoint

The primary efficacy endpoint was the trough FEV_1 response at the end of the first 13 weeks of treatment. The trough FEV_1 response was defined as the change from baseline in the mean of the two FEV_1 values at the end of the dosing interval (approximately 23 and 24 hours post drug administration) [U99-3169.pdf/p315]. The baseline FEV_1 was calculated as the mean of the two FEV_1 values measured in the morning of the randomization visit, prior to administration of study medication.

Tiotropium was statistically superior to placebo on the primary endpoint (p=0.0001) [U99-3169.pdf/p96]. The mean trough FEV_1 response at Week 13 (test day 92) was 0.11 liters in the tiotropium group (N=268), and –0.03 liters in the placebo group (N=174).

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Secondary Endpoints

Spirometry Endpoints

Serial spirometry was performed after the first dose and after 1, 7, 13, 25, 37, and 49 weeks of treatment. At each of these visits, spirometry was performed at 1-hour pre-dose, immediately pre-dose, and at 30, 60, 120, and 180 minutes post-dose. The pre-specified secondary spirometry endpoints were the average and peak FEV_1 response for the first 3 hours post-treatment, the trough, average, and peak FVC response, and the individual FEV_1 and FVC measurements at each time point, on each test day.

In regard to FEV_1, tiotropium was statistically significantly superior to placebo for the trough, average, and peak FEV_1 responses on all test days. The FEV_1 data, provided in the table below, raise an interesting observation regarding the pharmacodynamic time course of tiotropium. Unlike other orally inhaled bronchodilators, the treatment effect (defined here as the difference between the mean responses for active and placebo groups) was lower on Day 1 than on subsequent test days, suggesting that multiple dosing is required to achieve "steady state". For instance, both the average and peak responses were lower on Day 1 than on other test days. The "average" and "peak" responses decreased subsequent to Day 8 in both the tiotropium and the placebo groups. Thus the effect size (active minus placebo) remained relatively constant from Day 8, onward.

Mean FEV_1 Trough, Average, and Peak Responses (Liters) (Study 205.114/205.117, ITT data set) [U99-3169.pdf/p96]

Response	Test Day	Tiotropium (N=268)	Placebo (N=174)	Difference	P-value
Trough	Baseline	1.01	1.01		
	8	0.12	-0.00	0.12	0.0001
	50	0.11	-0.00	0.11	0.0001
	92	0.11	-0.03	0.14	0.0001
	176	0.11	-0.04	0.15	0.0001
	260	0.11	-0.04	0.15	0.0001
	344	0.11	-0.05	0.16	0.0001
Average	1	0.16	0.02	0.14	0.0001
	8	0.22	0.02	0.20	0.0001
	50	0.20	0.01	0.19	0.0001
	92	0.20	-0.02	0.22	0.0001
	176	0.19	-0.02	0.21	0.0001
	260	0.19	-0.01	0.20	0.0001
	344	0.19	-0.03	0.21	0.0001
Peak	1	0.24	0.08	0.15	0.0001
	8	0.28	0.08	0.21	0.0001
	50	0.27	0.08	0.19	0.0001
	92	0.26	0.05	0.21	0.0001
	176	0.26	0.04	0.22	0.0001
	260	0.25	0.06	0.20	0.0001
	344	0.26	0.04	0.22	0.0001

In addition, each individual FEV_1 measurement on each test day (excluding the pre-dose measurements on test day 1) was statistically superior to placebo.

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Reviewer's Comment: Pharmacodynamic features of bronchodilators are customarily described in the label. The onset of action of bronchodilators is often defined as the time point after the first dose at which the mean FEV_1 reaches a clinically significant threshold. In the product labels for two related products (Atrovent Inhalation Aerosol, and Combivent Inhalation Aerosol), this threshold is defined as an improvement of 15%. More recently, in keeping with American Thoracic Society standards, the threshold has been defined as 12% and at least 200ml. This newer threshold was used in the label for Serevent DISKUS for the COPD indication, which was approved in March, 2002. The table below would suggest that, despite the mean peak response reported in the table above, the mean FEV_1 did not reach this newer threshold at any time point on test Day 1 (using either of two definitions of Baseline: the –5 minute value, or the mean of the –1 hour and –5 minutes values).

Mean FEV_1 (Liters) On Test Day 1, Tiotropium Treatment Group (Study 205.114/205.117, ITT data set, N=268)
[derived from data found at: U99-3169.pdf/p93]

Time Point	Mean FEV_1	Change from Baseline (Liters) (Baseline defined as the –5 minute value)	Change from Baseline (Liters) (Baseline defined as the mean of –1hour and –5minute values)
-1 hour	1.00		
-5 minutes	1.02		
30 minutes	1.14	0.12	0.13
1 hour	1.17	0.15	0.16
2 hours	1.19	0.17	0.18
3 hours	1.20	0.18	0.19

This apparent discrepancy between the mean peak FEV_1 and the mean FEV_1 might indicate that the time to peak FEV_1 may differ among individual patients, such that the mean for the entire group never reached 200ml at any single post-dose time point. To investigate this issue further, the Applicant was asked to provide data regarding the percentage of patients who reached their peak FEV_1 at each time point. On test day 1, the percentage of patients who reached their peak FEV_1 gradually increased at each timepoint, with the greatest percentage at 3 hours [Submission date 7/16/02, page 8]. Data for the remaining test days indicated that at all of the four timepoints, <30% of the patients exhibited their peak FEV_1. Thus, there is no single timepoint at which the majority of patients reached their peak FEV_1. The description of the pharmacodynamic features in the product label should capture this.

Percentage of Patients Who Reached Their Peak FEV_1 at Each Timepoint (Test Day 1; Study 205.114/205.117)
[Submission dated 7/16/02; page 8]

Timepoint	Tiotropium (N=279)	Placebo (N=191)
30 minutes	14.7%	26.2%
1 hour	20.4%	25.1%
2 hours	29.7%	26.7%
3 hours	35.1%	22.0%

Given that the maximum treatment response is not seen until after multiple dosing, the use of the first dose to describe the onset of action may not be optimal.

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In regard to FVC, tiotropium was also statistically significantly superior to placebo for the trough, average, and peak FVC responses on all test days. The FVC data shown in the table below suggest that bronchodilator efficacy increased between Day 1 and Day 8. The "average" and "peak" responses decreased subsequent to Day 8 in both the tiotropium and the placebo groups. Thus the effect size (active minus placebo) remained relatively constant from Day 8, onward.

Mean FVC Trough, Average, and Peak Responses (Liters) (Study 205.114/205.117, ITT data set) [U99-3169.pdf/p103]

Response	Test Day	Tiotropium (N=268)	Placebo (N=174)	Difference	P-value
Trough	Baseline	2.21	2.21		
	8	0.27	0.00	0.27	0.0001
	50	0.27	0.01	0.26	0.0001
	92	0.24	-0.04	0.28	0.0001
	176	0.27	-0.04	0.31	0.0001
	260	0.26	-0.04	0.30	0.0001
	344	0.25	-0.03	0.29	0.0001
Average	1	0.39	0.07	0.31	0.0001
	8	0.50	0.10	0.40	0.0001
	50	0.47	0.05	0.42	0.0001
	92	0.42	0.02	0.40	0.0001
	176	0.45	0.02	0.42	0.0001
	260	0.43	0.04	0.39	0.0001
	344	0.41	0.01	0.40	0.0001
Peak	1	0.56	0.21	0.35	0.0001
	8	0.67	0.25	0.42	0.0001
	50	0.64	0.20	0.45	0.0001
	92	0.59	0.18	0.40	0.0001
	176	0.61	0.16	0.45	0.0001
	260	0.57	0.18	0.39	0.0001
	344	0.57	0.15	0.42	0.0001

In addition, each individual FEV_1 measurement on each test day (excluding the pre-dose measurements on test day 1) was statistically superior to placebo.

Peak Expiratory Flow Rate (PEFR) Endpoints

Morning (AM) and evening (PM) peak flow measurements were performed and recorded by the patients. Baseline AM and PM PEFRs were very similar between groups [U99-3169.pdf/p104].

The mean difference in AM PEFR between treatment groups ranged from 8 liters/minute to 24 liters/minute. Tiotropium was statistically superior to placebo for AM PEFR during 24 of the 49 weeks of treatment [U99-3169.pdf/p106-7]. The weeks during which tiotropium was superior occurred throughout the treatment period, without a particular pattern.

The mean difference in PM PEFR between treatment groups ranged from 13 liters/minute to 24 liters/minute. Tiotropium was statistically superior to placebo for PM PEFR during 41 of the 49 weeks of treatment [U99-3169.pdf/p110-11].

Physicians Global Evaluation

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The Physician's Global Evaluation was scored on a scale of 1-8, as follows: 1-2 (poor), 3-4 (fair), 5-6 (good), and 7-8 (excellent). These assessments were made at baseline, and after 8, 29, 50, 71, 92, 134, 155, 197, 218, 260, 302, and 344 days of treatment. The mean scores at baseline were comparable between groups (4.48 for Tiotropium and 4.57 for Placebo) [U99-3169.pdf/p133]. At all test days, the improvement in the tiotropium group was statistically superior to that of the placebo group ($p<0.01$). The difference in mean scores ranged from 0.35 to 0.59 [U99-3169.pdf/p135].

COPD Symptom Scores

Patients were asked three questions regarding their perception of their energy level (scored 1 to 5, ranging from very good to very poor) and fatigue level (scored 1 to 6, ranging from very severe to no fatigue) and the severity of their respiratory condition (scored 1 to 6, ranging from very severe to no problems at all). This questionnaire was termed the Energy Fatigue Questionnaire. Baseline scores for each of these questions were similar in the two treatment groups [U99-3169.pdf/p123]. No consistent significant differences were noted between tiotropium and placebo on these questions.

Another symptomatic assessment was the Mahler Baseline and Transition Dyspnea Index (BDI/TDI) scores, assessed at baseline (BDI) and after 7, 13, 25, 37, and 49 weeks of treatment (Days 50, 92, 176, 270, and 344, respectively). These scores include three components: Functional Impairment, Magnitude of Task, and Magnitude of Effort. The Focal Score is the sum of the three components. At baseline, the two treatment groups were comparable for each component and for the focal score [U99-3169.pdf/p125]. Tiotropium was statistically superior to placebo for all three components and for the focal score, except for Day 260 for Functional Impairment. The effect size that would represent a clinically meaningful benefit has not been firmly established in the literature. The Applicant states that the developer of the instrument has expressed the opinion that a value of 1 in the focal score would be clinically meaningful. *The difference in focal score between tiotropium and placebo was >1 on the final test day only.* Note that this was related to a marked decline in focal score among the placebo patients on Day 344. It is not clear why one might expect such a notable decline in the TDI in the placebo group between Days 260 and 344. The table below provides the TDI data.

Mean Transition Dyspnea Index Scores (Study 205.114/205.117, ITT data set) [U99-3169.pdf/p128]

Component	Test Day	Tiotropium		Placebo		Difference	P-value
		N	Mean	N	Mean		
Functional Impairment	50	262	0.30	171	0.04	0.26	0.0007
	92	262	0.37	171	0.05	0.32	0.0001
	176	262	0.28	171	0.08	0.19	0.0285
	260	262	0.20	171	0.04	0.16	0.0875
	344	262	0.28	171	-0.05	0.33	0.0004
Magnitude of Task	50	262	0.35	174	0.06	0.30	0.0001
	92	262	0.31	174	0.08	0.23	0.0039
	176	262	0.25	174	-0.03	0.29	0.0003
	260	262	0.18	174	0.01	0.17	0.0443
	344	262	0.29	174	-0.06	0.36	0.0001
Magnitude of Effort	50	265	0.30	174	0.04	0.25	0.0020
	92	265	0.40	174	0.04	0.36	0.0001
	176	265	0.25	174	-0.01	0.25	0.0081

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Mean Transition Dyspnea Index Scores (Study 205.114/205.117, ITT data set) [U99-3169.pdf/p128]

Component	Test Day	Tiotropium		Placebo		Difference	P-value
		N	Mean	N	Mean		
	260	265	0.22	174	-0.03	0.25	0.0085
	344	265	0.29	174	-0.17	0.45	0.0001
Focal Score	50	258	0.95	171	0.14	0.81	0.0002
	92	258	1.09	171	0.16	0.93	0.0001
	176	258	0.78	171	0.05	0.74	0.0028
	260	258	0.59	171	0.01	0.58	0.0268
	344	258	0.86	171	-0.29	1.15	0.0001

COPD symptoms were recorded on a 0 to 3 scale, ranging from none to severe: wheezing, shortness of breath, coughing, and tightness of chest. These assessments were made *by the investigator [U99-3169.pdf/;306]* at baseline, and after 8, 29, 50, 71, 92, 113, 134, 155, 176, 197, 218, 239, 260, 281, 302, 323, and 344 days of treatment. At baseline, the scores were similar in the two treatment groups [U99-3169.pdf/p129]. Tiotropium was statistically superior to placebo for shortness of breath on all test days and for wheezing on all except three test days. There was no statistically significant difference between groups for cough or tightness in chest scores [U99-3169.pdf/p131-2]. A minimal clinically meaningful difference in these scores has not been established.

Supplemental Albuterol Use

The use of supplemental albuterol, as recorded in daily record cards, was similar in the two treatment groups during the baseline period [U99-3169.pdf/p113]. During each week of treatment, tiotropium was statistically superior to placebo in regard to the mean number of doses of albuterol per day, averaged weekly ($p<0.01$). On average, patients in the tiotropium group took approximately 6 fewer doses of albuterol per week compared to patients in the placebo group [U99-3169.pdf/p113].

Nocturnal Awakenings

The number of awakenings due to COPD symptoms were collected on daily record cards at baseline and for the first 13 weeks of treatment. *Note: The protocol did not include analysis of nocturnal awakenings in the list of secondary efficacy endpoints.* During the baseline period, the number of awakenings per night was similar between groups (0.49 for tiotropium and 0.58 for placebo). The number of awakenings per night was numerically lower in the tiotropium group for each of the 13 weeks, but the difference was statistically significant for only 7 of the 13 weeks. Of note, the weeks for which statistical significance was observed included the last five of the thirteen weeks. However, the absolute differences between groups were small. Over the 13 individual weeks of treatment, the differences between groups ranged from 0.08 to 0.16 awakenings per night.

COPD Exacerbations

There was no significant difference between tiotropium and placebo in number of patients with COPD exacerbations, time to COPD exacerbation, number of COPD exacerbation days, number of patients with hospitalization or number of hospitalizations [U99-3169.pdf/p146-7]. Fewer patients in tiotropium group required oral and/or systemic corticosteroid bursts for the control of COPD exacerbations (16.8% vs. 25.7%).

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Health-Related Quality of Life

The St. George's Hospital Respiratory Questionnaire (SGRQ) was administered at baseline and after 7, 13, 25, 37, and 49 weeks of treatment. The SGRQ consists of 50 questions comprising three domains, Activities, Impacts, and Symptoms. A lower score indicates less impairment in "health related quality of life." In the medical literature, a change in the total score of ≥4 is considered to represent a clinically meaningful change. The protocol did not discuss analysis of individual SGRQ domains. However, prior to un-blinding the data, the Applicant amended the protocol to indicate that analysis of the Impacts domain would be a secondary endpoint. This decision was made after consultation with the developer of the SGRQ, Dr. Paul Jones, who suggested that the Impacts domain may better detect changes attributable to drug treatment. However, the use of the Impacts domain alone has been less common in the medical literature and there is no consensus on what constitutes a minimal clinically meaningful change in the Impacts score.

The baseline SGRQ scores by treatment group, are shown in the table below. Interestingly, although the Impacts domain is predicted to be the most sensitive, the mean scores for this domain were notably lower (better) at baseline, compared to the other two domains.

Mean Baseline SGRQ Scores (Study 205.114/205.117, ITT data set) [U99-3169.pdf/p117]

Score	Tiotropium			Placebo		
	N	Mean	(SE)	N	Mean	(SE)
Symptoms	268	59.01	(1.23)	174	60.45	(1.65)
Activities	265	63.84	(1.17)	171	66.43	(1.52)
Impacts	265	34.50	(1.08)	171	36.27	(1.34)
Total	265	47.53	(0.98)	171	49.65	(1.25)

The table below summarizes the SGRQ scores (total and by domain), at each measure. The only statistically significant differences between tiotropium and placebo occurred on or after Week 25 (Day 176). For the total SGRQ score, statistically significant differences between groups were noted at Days 176, 260, and 344 (Weeks 25, 37, and 49). However, at no time did the difference between groups reach the generally accepted threshold indicating a clinically meaningful change (4). Tiotropium was statistically superior to placebo for the Impacts score at Days 260 and 344 (Weeks 37 and 49), for the Symptoms score at Days 176 and 344 (Weeks 25 and 49), and for the Activities score at Days 260 and 344 (Weeks 37 and 49). However the clinical significance of these statistical observations is not known.

Mean SGRQ Scores (Study 205.114/205.117, ITT data set) [U99-3169.pdf/p119]

Score	Test Day	Tiotropium		Placebo		Difference	p-value
		N	Mean	N	Mean		
Symptoms	Baseline[1]	268	59.58	174	59.58		
	50	268	56.32	174	57.58	-1.26	0.4276
	92	268	55.78	174	57.76	-1.99	0.2027
	176	268	54.81	174	59.19	-4.38	0.0043
	260	268	54.96	174	58.04	-3.08	0.0514
	344	268	55.26	174	58.83	-3.57	0.0229
Activities	Baseline[1]	265	64.86	171	64.86		
	50	265	62.58	171	64.15	-1.58	0.1895
	92	265	62.31	171	63.77	-1.46	0.2626

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Mean SGRQ Scores (Study 205.114/205.117, ITT data set) [U99-3169.pdf/p119]

Score	Test Day	Tiotropium		Placebo		Difference	p-value
		N	Mean	N	Mean		
	176	265	61.40	171	63.81	-2.41	0.0898
	260	265	61.34	171	64.08	-2.74	0.0463
	344	265	62.25	171	65.89	-3.64	0.0085
Impacts	Baseline[1]	265	35.19	171	35.19		
	50	265	32.25	171	34.14	-1.89	0.1072
	92	265	32.47	171	33.66	-1.19	0.3187
	176	265	31.91	171	33.55	-1.64	0.1726
	260	265	32.45	171	35.74	-3.29	0.0123
	344	265	32.14	171	35.81	-3.67	0.0063
Total	Baseline[1]	265	48.36	171	48.36		
	50	265	45.64	171	47.13	-1.49	0.1128
	92	265	45.56	171	46.85	-1.28	0.1988
	176	265	44.83	171	46.98	-2.15	0.0394
	260	265	45.08	171	48.02	-2.94	0.0077
	344	265	45.34	171	48.78	-3.44	0.0021

[1]Common baseline mean

The Medical Outcomes Study SF-36 Questionnaire (SF-36), a "quality of life" instrument that is not disease-specific, was administered at baseline and after 7, 13, 25, 37, and 49 weeks of treatment (Days 50, 92, 176, 270, and 344, respectively). The instrument consists of 36 items grouped into 8 domains (Physical Functioning, Role Physical, Bodily Pain, General Physical Health, Vitality, Social Function, Role Emotional, and General Mental Health). The physical and mental domains are then grouped into "summaries" (Physical Health Summary, and Mental Health Summary). Higher scores indicate less impairment. At baseline, the mean scores for each domain were similar between groups [U99-3169.pdf/p120]. All of the physical domains were numerically (although not always statistically) higher in the tiotropium group, and the "Physical Health Summary" scores were statistically higher in the tiotropium group compared to the placebo group on all test days. All of the mental health domains were numerically higher in the tiotropium group. Of these, the Social Function scores were statistically higher for the tiotropium group on the last three test days (Days 176, 260, and 344) [U99-3169.pdf/p121-2]. 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 PEFRs 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: While there not evidence of a rebound effect, it is interesting to note that both the morning and evening PEFRs decreased slowly over the 3 week post-treatment period in the tiotropium group, but increased at post-treatment weeks 2 and 3 in the placebo group.

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Post-Treatment PEFR, Weekly Means (Liters/minute) (Data set: Patients with Post-Treatment Data) (Study 205.114/205.117) [U99-3169.pdf/p139-40]

		Tiotropium		Placebo		Difference
		N	Mean	N	Mean	
Morning PEFR						
Baseline	Pre-Treatment Week	162	201.21	102	208.47	-7.26
Change from Baseline	Last Treatment Week	162	36.32	102	22.17	14.15
Change from Baseline	Post-Treatment Weeks					
	Week 1	161	31.63	99	22.16	9.47
	Week 2	161	23.89	102	28.51	-4.62
	Week 3	156	24.23	96	29.86	-5.63
Evening PEFR						
Baseline	Pre-Treatment Week	133	205.68	88	205.99	-0.31
Change from Baseline	Last Treatment Week	133	29.49	88	12.94	16.54
Change from Baseline	Post-Treatment Weeks					
	Week 1	133	16.58	88	12.59	4.00
	Week 2	132	12.77	88	15.62	-2.85
	Week 3	130	12.02	82	16.99	-4.97

Analysis of the SGRQ, SF-36, COPD Symptoms, Physician's Global Evaluation, and Energy Fatigue Questionnaire scores, and the weekly mean number of doses per day of albuterol in the post-treatment period did not suggest a rebound effect [U99-3169.pdf/p.140-5]. The only possible exception was the data for the COPD symptoms of coughing and tightness of chest. Both of these symptoms were not markedly changed from baseline at the last measurement on treatment in either group. However, in the post-treatment phase these symptoms worsened in the tiotropium group but not in the placebo group. The table below provide these data. For reference, the symptoms were scored on a scale of 0-3, ranging from no symptoms to severe symptoms.

COPD Symptom Scores (Data set: Patients with Post-Treatment Data) (Study 205.114/205.117) [U99-3169.pdf/p145]

		Tiotropium		Placebo		Difference
		N	Mean	N	Mean	
Wheezing	Baseline	226	0.90	133	0.95	-0.05
	Last Measurement on Treatment, Change from Baseline	226	-0.08	133	0.11	-0.18
	Post-Treatment Measurement, Change from Baseline	226	0.10	133	0.07	0.03
Shortness of Breath	Baseline	225	1.49	133	1.4	0.05
	Last Measurement on Treatment, Change from Baseline	225	-0.04	133	0.24	-0.28
	Post-Treatment Measurement, Change from Baseline	225	0.22	133	0.20	0.02
Coughing	Baseline	226	1.09	133	1.14	-0.04
	Last Measurement on Treatment, Change from Baseline	226	-0.03	133	-0.02	0.00
	Post-Treatment Measurement, Change from Baseline	226	0.19	133	-0.05	0.24
Tightness of Chest	Baseline	225	0.68	133	0.66	0.02
	Last Measurement on Treatment, Change from Baseline	225	-0.03	133	0.02	-0.05
	Post-Treatment Measurement, Change from Baseline	225	0.16	133	-0.02	0.19

with either the lower limit value or half of the lower limit value.) Thus, this period represented a steady state condition, with the absence of continued accumulation.

The PK data were analyzed with respect to gender, age, renal function, and lung function. Male and female patients showed no important difference in tiotropium plasma concentration [U99-3169g.pdf/p638]. The greatest difference between males and females was seen at 2 hours post-dose, at which time females had 40% (Visit 5) and 28% (Visit 7) higher tiotropium concentrations than males. The oldest age group (>69 years) exhibited 30-40% higher 2-hour post-dose tiotropium concentrations [U99-3169g.pdf/p639-40]. With increasing age, the 0-2 hour urinary excretion tended to diminish, whereas the 0-24 hour excretion did not change concentration [U99-3169g.pdf/p640].

Approximately 10% of the patients in this study had moderate renal dysfunction (creatinine clearance of 30-50 mL/min). In the clinical study report, the Applicant states that these patients had slightly higher 5-minute post-dose plasma tiotropium concentrations (+10% at Visit 5 and +58% at Visit 7), and more notably higher 2-hour post-dose plasma tiotropium concentrations (+110% for Visit 5, and +76% for Visit 7) [U99-3169.pdf/p150]. *However, the data provided in the pharmacokinetics report submitted as an appendix to the clinical study report, suggest a considerably more significant increase in plasma tiotropium concentration in patients with renal impairment [U99-3169g.pdf/p641]. The table below illustrates this data. It should be noted that the numbers of subjects in the lowest creatinine clearance group, particularly at the 5-minute post-dose time point, are small. Also, although the post-dose values are fairly high in the group with the poorest renal function, the pre-dose values are not.*

Effect of Creatinine Clearance on Tiotropium Plasma Concentrations (Study 205.114) [U99-3169g.pdf/p641]

Creatinine Clearance (mL/min) [mean]	Tiotropium Plasma Concentration (pg/mL) [n]					
	Visit 5 (Day 50)			Visit 7 (Day 92)		
	C_{-5min}	C_{5min}	C_{2h}	C_{-5min}	C_{5min}	C_{2h}
30-50 [41.2]	2.21 [5]	17.0 [7]	16.1 [7]	3.59 [5]	37.1 [4]	10.4 [7]
50-80 [66.4]	2.97 [20]	22.3 [35]	8.34 [47]	3.12 [29]	23.7 [40]	8.75 [45]
>80 [110]	3.64 [21]	10.6 [45]	5.68 [54]	2.83 [15]	12.9 [41]	6.5 [52]
Ratio vs >80:						
30-50mL/min	0.607	1.60	2.83	1.27	2.88	1.60
50-80mL/min	0.816	2.10	1.47	1.10	1.84	1.35
>80mL/min	1.00	1.00	1.00	1.00	1.00	1.00

The Applicant also states that plasma drug concentrations and urinary excretion did not differ between patients with FEV_1<0.8L and patients with FEV_1>1.5L, indicating that pre-dose lung function does not affect the pharmacokinetics of tiotropium delivered as a dry powder by the Handihaler.

Reviewer's Comments on Efficacy

This study demonstrated that tiotropium was superior to placebo on the pre-specified primary efficacy endpoint: trough FEV_1 response after 13 weeks of treatment. The 13-week trough FEV_1

(the mean of two pre-dose values) increased from baseline by 0.11 liters in the tiotropium group and decreased by 0.03 in the placebo group. 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-week trial also demonstrated that tiotropium was statistically superior to placebo in terms of the trough, average, and peak FEV_1 responses. Two points should be made regarding the spirometry pharmacodynamics. First, the Day 1 mean post-dose FEV_1 in the tiotropium group did not reach the threshold customarily used to indicate a significant bronchodilator response (≥12% and ≥200ml improvement) at any of the serial spirometry time points. However, the mean peak FEV_1 response (without subtracting placebo) on Day 1 and on all subsequent test days was >200ml. This apparent discrepancy might indicate that the time to peak response following dosing varied among patients. Second, the treatment effect was lower on Day 1 than on other test days, suggesting multiple dosing is required to achieve optimum effect.

Efficacy was supported by statistically significant improvements in numerous secondary spirometry variables, including mean, trough, and peak FEV_1 and FVC during 3-hour serial spirometry assessments on multiple study days. These assessments also demonstrated that the effect size was maintained from Day 8, through the 49 week trial. Statistical benefit was also demonstrated in evening PEFR for most of the weeks of treatment (41 of 49) and for morning PEFR for approximately 50% of the weeks of treatment (24 of 49).

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 205.114/205.117)

Statistically Significant Benefit Demonstrated	Statistically Significant Benefit NOT Demonstrated
▪ Physician's Global Evaluation (all test days) ▪ Mahler TDI Focal Score (all test days)[a] ▪ COPD symptom[b]: Shortness of Breath (all test days) ▪ COPD symptom[b]: Wheeze (most test days) ▪ Nocturnal Awakenings (7 of 13 weeks) ▪ Total SGRQ score (3 of 5 test days)[c]	▪ Energy Fatigue Questionnaire ▪ COPD symptom[b]: Cough ▪ COPD symptom[b]: Tightness in Chest ▪ COPD Exacerbations (all analyses)

[a]Effect size surpassed the Applicant's proposed threshold for minimal clinically important change on the final test day only.
[b]Assessed by the Investigator
[c]Effect size did not reach the accepted threshold for minimal clinically important change.

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 are described below.

All 470 patients who received at least one dose of test drug were included in the safety analysis [U99-3169.pdf/p153]. A total of 248 patients received tiotropium for more than 6 months and

Appendix
Study 205.114/205.117

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

Extent of Exposure, Study 205.114/205.117		[U99-3169.pdf/p153]
	Tiotropium N (%)	Placebo N (%)
Total Treated Maximum Exposure (Days)	279	191
1	0 (0.0)	1 (0.5)
2-7	2 (0.7)	1 (0.5)
8-60	10 (3.6)	17 (8.9)
61-100	8 (2.9)	5 (2.6)
101-200	11 (3.9)	14 (7.3)
201-330	91 (32.6)	58 (30.4)
>330	157 (56.3)	95 (49.7)
Median (days)	339	328
Range (days)	5 –408	1 - 371

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 (92.5% and 95.8%, respectively) [U99-3169.pdf/p155]. Dry mouth was reported more frequently in the tiotropium group (12.5%) than in the placebo group (2.6%). All except one case of dry mouth were mild or moderate in severity. The incidence of AEs classified as GI Disorders, excluding dry mouth was also higher in the tiotropium group (33%) than in the placebo group (25.1%). Other specific GI Disorders that occurred more frequently in the tiotropium group were abdominal pain (5.7% vs. 2.6%), constipation (5.7% vs. 1.6%), diarrhea (7.5% vs. 6.3%), dyspepsia (6.1% vs. 3.1%), nausea (6.1% vs. 5.8%), and vomiting (4.7% vs. 2.6%). Other AEs occurring more commonly in the tiotropium group included: Upper Respiratory Disorders (54.9% vs. 49.7%), and the specific AEs of chest pain (6.5% vs. 3.1%), accidents (12.9% vs. 11.5%), allergic reactions (3.9% vs. 1.0%), dependent edema (4.6% vs. 3.1%), fatigue (5.4% vs. 4.7%), infection (4.3% vs. 3.1%), moniliasis (4.7% vs. 3.7%), pharyngitis (7.9% vs. 5.8%), URI (41.2% vs. 37.2%), rash (5.4% vs. 2.6%), and urinary tract infection (6.4% vs. 5.8%) [U99-3169.pdf/p157-8].

Serious adverse events (SAEs) were reported by 20.4% of patients in the tiotropium group and 22.5% of patients in the placebo group [U99-3169.pdf/p162]. 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 8.2% of the tiotropium treatment group and 13.1% of the placebo group [U99-3169.pdf/p165].

A total of 8 patients died during the course of the study, 3 (1.1%) on tiotropium, and 5 (2.6%) on placebo. None were considered by the investigator to be related to study medication. Deaths in the tiotropium group were attributed to myocardial infarction, cardiac arrhythmia, and coronary artery disease. Deaths in the placebo group were attributed to coronary artery disease, COPD exacerbation, and cancer (3).

2. Study 205.115/205.128 "A multiple dose comparison of 18mcg of tiotropium inhalation capsules and placebo in a one-year, double-blind, safety and efficacy study in adults with chronic obstructive pulmonary disease (COPD)"

a. Study Description

This study was performed under a protocol that was identical to the protocol for Study 205.114/205.117. The only difference between the two protocols is that Study 205.115/205.128 did not include pharmacokinetic assessments. The reader is referred to the description of the protocol discussed in the section above. This study was performed between January 8, 1997 and May 28, 1998. The study centers were all in the US and were located in the following states: AL, AZ, CA, CO, CT, FL, IA, IL, LA, MT, NE, NM, OH, TX, VA, WA, and WI [U99-3170-01.pdf/p20]. A total of 451 patients were included, 271 assigned to tiotropium and 180 assigned to placebo. The test product (tiotropium inhalation capsules) were from batch numbers PD-1732, and PD-1742. The reference product (placebo) were from batch # PD-1734, and PD-1743.

b. Patient Disposition

A total of 632 patients were screened for entry. Of these, 451 were randomized: 271 to tiotropium and 180 to placebo [U99-3170-01.pdf/p.59*]. Note: One additional patient was randomized to placebo (#1630, Center 28), but had been randomized to tiotropium in Study 205.114/205.117 two weeks prior. He never received placebo alone and his data is not included in the analyses. Note: The supply of tiotropium used in this trial had an expiration date of April 30, 1998. Therefore, any patient randomized after May 22, 1997 was unable to complete the 49 weeks on study medication. Randomization continued until June 30, 1997. Patients who were unable to complete all visits due to drug expiration were required to discontinue stud drug at nine months but were considered complete patients.* The disposition of randomized patients is outlined in the table below. A greater percentage of tiotropium patients completed all visits, compared with placebo patients (78.2% vs. 71.7%). Fewer patients in the tiotropium group failed to complete the study due to lack of efficacy (2.2%, compared to 7.2% of patients in the placebo group).

Patient Disposition and Reasons for Withdrawal, Study 205.115/205.128 [U99-3170-01.pdf/p60]

	Tiotropium N (%)	Placebo N (%)
Entered/Randomized	271	180
Completed the Trial	212 (78.2)	129 (71.7)
Discontinued For:		
Adverse Event Total	30 (11.1)	25 (13.9)
Unexpected Worsening of Disease Under Study	12 (4.4)	11 (6.1)
Unexpected Worsening of Other Pre-existing Disease	0 (0.0)	0 (0.0)
Other Adverse Event	18 (6.6)	14 (7.8)
Lack of Efficacy	6 (2.2)	13 (7.2)
Administrative	15 (5.5)	10 (5.6)
Non-compliant with Protocol	0 (0)	0 (0)
Lost to Follow-up	2 (0.7)	1 (0.6)
Consent Withdrawn	13 (4.8)	9 (5.0)
Other	8 (3.0)	3 (1.7)

The Application summarizes the protocol violations by treatment group [U99-3170-01.pdf/p60-1]. These included: failure to meet all entrance criteria (4.1 % of tiotropium group, and 5.0% of placebo group), and elevated theophylline level (8.9% of tiotropium group, and 20.0% of placebo group). In addition, five sites randomized patients out of order in a manner that would not bias treatment selection. These violations are unlikely to influence the conclusions of the study.

The table below summarizes the demographics and baseline characteristics of the study population. The majority of subjects were white (97%). The baseline features were similar between groups.

Demographics and Baseline Characteristics, Study 205.115/205.128 [U99-3170-01.pdf/p62-3]

	Tiotropium	Placebo	Total
Total Randomized	271	180	451
Sex			
Male	180 (66.4)	112 (62.2)	292 (64.7)
Race			
Caucasian	260 (95.9)	117 (97.8)	432 (96.7)
Negroid	11 (4.1)	4 (2.2)	15 (3.3)
Age			
Mean	65.21	65.17	65.19
Range	41 – 87	41 – 82	41 - 87
Smoking History (pack years)			
Mean	60.6	57,4	59.3
Range	14 - 165	11 – 160	11 - 160
Duration of COPD (years)			
Mean	7.95	7.67	7.84
Range	0.3 – 43	0.1 – 36	0.1 - 43
Screening FEV_1 (L)			
Mean	1.05	1.01	1.03
Range	0.31 – 2.37	0.29 – 2.62	0.29 – 2.62
FEV_1/FVC x 100			
Mean	45.45	44.67	45.14
Range	20.37 – 93.38	23.22 – 92.31	20.37 – 93.38

Concomitant pulmonary medications used during the baseline period were generally similar between groups [U99-3170-01.pdf/p64]. During the baseline period, inhaled anticholinergics were used by 58.1% of patients, inhaled corticosteroids were used by 45.5% of patients, oral corticosteroids were used by 7.1% of patients, theophylline was used by 23.5% of patients, and supplemental oxygen was used 7.1% of patients. Minor differences were noted in the percentages of patients on oral corticosteroids (5.2% in the tiotropium group vs. 10.0% in the placebo group) and oral theophylline (21.8% in the tiotropium group vs. 26.1% in the placebo group).

c. *Efficacy Review*

A total of 14 patients (3%) of the 451 patients randomized were excluded from all efficacy analyses because they had inadequate data following multiple administration. This included 3

(1.1%) patients in the tiotropium group and 11 (6.1%) patients in the placebo group. Of these 14 patients, 1 patient in the tiotropium group and 5 patients in the placebo group discontinued the trial due to lack of efficacy [U99-3170-01.pdf/p66].

Primary Endpoint

The primary efficacy endpoint was the trough FEV_1 response at the end of the first 13 weeks of treatment. The trough FEV_1 response was defined as the change from baseline in the mean of the two FEV_1 values at the end of the dosing interval (approximately 23 and 24 hours post drug administration). The baseline FEV_1 was calculated as the mean of the two FEV_1 values measured in the morning of the randomization visit, prior to administration of study medication.

Tiotropium was statistically superior to placebo on the primary endpoint (p=0.0001) [U99-3170-01.pdf/p73]. The mean trough FEV_1 response at Week 13 (test day 92) was 0.13 liters in the tiotropium group (N=250), and –0.01 liters in the placebo group (N=154).

Secondary Endpoints

Spirometry Endpoints

Serial spirometry was performed after the first dose and after 1, 7, 13, 25, 37, and 49 weeks of treatment. At each of these visits, spirometry was performed at 1-hour pre-dose, immediately pre-dose, and at 30, 60, 120, and 180 minutes post-dose. The pre-specified secondary spirometry endpoints were the average and peak FEV_1 response for the first 3 hours post-treatment, the trough, average, and peak FVC response, and the individual FEV_1 and FVC measurements at each time point, on each test day.

In regard to FEV_1, tiotropium was statistically significantly superior to placebo for the trough, average, and peak FEV_1 responses on all test days [U99-3170-01.pdf/p73]. The FEV_1 data, provided in the table below, raise an interesting observation regarding the pharmacodynamic time course of tiotropium. Unlike other orally inhaled bronchodilators, the treatment effect (defined here as the difference between the mean responses for active and placebo groups) was lower on Day 1 than on subsequent test days, suggesting that multiple dosing is required to achieve "steady state". For instance, both the average and peak responses were lower on Day 1 than on other test days. The "average" and "peak" responses decreased slightly subsequent to Day 50 in both the tiotropium and the placebo groups. Thus the effect size (active minus placebo) remained relatively constant from Day 8, onward. These same observations were made in regard to Study 205.114/205.117.

Mean FEV_1 Trough, Average, and Peak Responses (Liters) (Study 205.115/205.128, ITT data set) [U99-3170-01.pdf/p73]

Response	Test Day	Tiotropium (N=250)	Placebo (N=154)	Difference	P-value
Trough	Baseline	1.00	1.00		
	8	0.12	0.01	0.12	0.0001
	50	0.15	0.01	0.13	0.0001
	92	0.13	-0.01	0.14	0.0001
	176	0.12	-0.04	0.16	0.0001
	260	0.13	-0.02	0.15	0.0001
	344	0.12	-0.03	0.15	0.0001

Mean FEV_1 Trough, Average, and Peak Responses (Liters) (Study 205.115/205.128, ITT data set) [U99-3170-01.pdf/p73]					
Response	**Test Day**	**Tiotropium (N=250)**	**Placebo (N=154)**	**Difference**	**P-value**
Average	1	0.17	0.02	0.15	0.0001
	8	0.23	0.02	0.21	0.0001
	50	0.24	0.02	0.22	0.0001
	92	0.21	0.01	0.21	0.0001
	176	0.21	-0.02	0.23	0.0001
	260	0.20	-0.00	0.21	0.0001
	344	0.20	-0.01	0.20	0.0001
Peak	1	0.24	0.08	0.15	0.0001
	8	0.31	0.09	0.22	0.0001
	50	0.31	0.08	0.23	0.0001
	92	0.28	0.07	0.21	0.0001
	176	0.28	0.04	0.24	0.0001
	260	0.26	0.06	0.21	0.0001
	344	0.26	0.05	0.21	0.0001

In addition, each individual FEV_1 measurement on each test day (excluding the pre-dose measurements on test day 1) was statistically superior to placebo [U99-3170-01.pdf/p70].

Reviewer's Comment: Pharmacodynamic features of bronchodilators are customarily described in the label. The onset of action of bronchodilators is often defined as the time point after the first dose at which the mean FEV_1 reaches a clinically significant threshold. In the product labels for two related products (Atrovent Inhalation Aerosol, and Combivent Inhalation Aerosol), this threshold is defined as an improvement of 15%. More recently, in keeping with American Thoracic Society standards, the threshold has been defined as 12% and at least 200ml. This newer threshold was used in the label for Serevent DISKUS for the COPD indication, which was approved in March, 2002. While the Applicant did not submit data regarding the time to reach this threshold or the numbers of patients who reached this threshold, the table below would suggest that, despite the mean peak response reported in the table above, the mean FEV_1 barely reached this newer threshold on test Day 1. Using the mean of the –1hour and –5minute values as the "baseline", the mean FEV_1 reached 200ml greater than baseline at 3 hours post-dose. However, using the –5 minute value alone as the baseline, the mean FEV_1 never reached 200ml greater than baseline. It is noted that the FEV_1 response on subsequent test days did surpass the 200ml threshold, when compared to test Day 1.

Mean FEV_1 (Liters) On Test Day 1, Tiotropium Treatment Group (Study 205.115/205.128, ITT data set, N=250) [derived from data found at: U99-3170-01.pdf/p70]			
Time Point	**Mean FEV_1**	**Change from Baseline (Liters) (Baseline defined as the –5 minute value)**	**Change from Baseline (Liters) (Baseline defined as the mean of –1hour and –5minute values)**
-1 hour	0.99		
-5 minutes	1.01		
30 minutes	1.13	0.12	0.13
1 hour	1.16	0.15	0.16
2 hours	1.18	0.17	0.18
3 hours	1.20	0.19	0.20

The apparent discrepancy in the FEV_1 response reported as the mean peak FEV_1 versus the mean FEV_1 (see tables above) might indicate that the time to peak FEV_1 may differ among individual patients. To investigate this issue further, the Applicant was asked to provide data regarding the percentage of patients who reached their peak FEV_1 at each time point. On test day 1, the percentage of patients who reached their peak FEV_1 gradually increased at each timepoint, with the greatest percentage at 3 hours [Submission date 7/16/02, page 8]. Data for the remaining test days indicated that at all of the four timepoints, <32.5% of the patients exhibited their peak FEV_1. Thus, there is no single timepoint at which the majority of patients reached their peak FEV_1. The description of the pharmacodynamic features in the product label should capture this.

Percentage of Patients Who Reached Their Peak FEV_1 at Each Timepoint (Test Day 1; Study 205.115/205.128) [Submission dated 7/16/02; page 8]

Timepoint	Tiotropium (N=271)	Placebo (N=180)
30 minutes	18.8%	30.0%
1 hour	19.2%	25.0%
2 hours	29.2%	19.4%
3 hours	32.8%	25.6%

Given that the maximum treatment response is not seen until after multiple dosing, the use of the first dose to describe the onset of action may not be optimal.

In regard to FVC, tiotropium was also statistically significantly superior to placebo for the trough, average, and peak FVC responses on all test days. The FVC data shown in the table below suggest that bronchodilator efficacy increased between Day 1 and Day 8.

Mean FVC Trough, Average, and Peak Responses (Liters) (Study 205.115/205.128, ITT data set) [U99-3170-01.pdf/p80]

Response	Test Day	Tiotropium (N=250)	Placebo (N=154)	Difference	P-value
Trough	Baseline[1]	2.27	2.27		
	8	0.26	0.01	0.25	0.0001
	50	0.32	0.01	0.31	0.0001
	92	0.28	-0.00	0.28	0.0001
	176	0.26	-0.05	0.32	0.0001
	260	0.28	-0.01	0.29	0.0001
	344	0.26	-0.05	0.30	0.0001
Average	1	0.41	0.09	0.32	0.0001
	8	0.52	0.09	0.43	0.0001
	50	0.53	0.07	0.47	0.0001
	92	0.48	0.03	0.45	0.0001
	176	0.49	0.00	0.49	0.0001
	260	0.44	0.02	0.43	0.0001
	344	0.44	0.01	0.45	0.0001
Peak	1	0.58	0.24	0.34	0.0001
	8	0.67	0.25	0.42	0.0001
	50	0.69	0.21	0.48	0.0001
	92	0.65	0.17	0.48	0.0001
	176	0.66	0.14	0.51	0.0001
	260	0.60	0.14	0.46	0.0001
	344	0.58	0.12	0.46	0.0001

Mean FVC Trough, Average, and Peak Responses (Liters) (Study 205.115/205.128, ITT data set) [U99-3170-01.pdf/p80]

Response	Test Day	Tiotropium (N=250)	Placebo (N=154)	Difference	P-value
[1] common baseline mean					

In addition, each individual FVC measurement on each test day (excluding the pre-dose measurements on test day 1) was statistically superior to placebo (p=0.0001) [U99-3170-01.pdf/p77].

Peak Expiratory Flow Rate (PEFR) Endpoints

Morning (AM) and evening (PM) peak flow measurements were performed and recorded by the patients. Baseline AM and PM PEFRs were very similar between groups [U99-3170-01.pdf/p81, 85].

The mean difference in AM PEFR between treatment groups ranged from 12 liters/minute to 31 liters/minute. Tiotropium was statistically superior to placebo for AM PEFR during 48 of the 49 weeks of treatment [U99-3170-01.pdf/p83-4].

The mean difference in PM PEFR between treatment groups ranged from 19 liters/minute to 40 liters/minute. Tiotropium was statistically superior to placebo for PM PEFR during each of the 49 weeks of treatment [U99-3170-01.pdf/p87-8].

Physicians Global Evaluation

The Physician's Global Evaluation was scored on a scale of 1-8, as follows: 1-2 (poor), 3-4 (fair), 5-6 (good), and 7-8 (excellent). These assessments were made at baseline, and after 8, 29, 50, 71, 92, 134, 155, 197, 218, 260, 302, and 344 days of treatment. The mean scores at baseline were comparable between groups (4.59 for Tiotropium and 4.52 for Placebo) [U99-3170-01.pdf/p113]. At all test days, the improvement in the tiotropium group was statistically superior to that of the placebo group ($p<0.05$). The difference in mean scores ranged from 0.25 to 0.41 [U99-3170-01.pdf/p115].

COPD Symptom Scores

Patients were asked three questions regarding their perception of their energy level (scored 1 to 5, ranging from very good to very poor) and fatigue level (scored 1 to 6, ranging from very severe to no fatigue) and the severity of their respiratory condition (scored 1 to 6, ranging from very severe to no problems at all). This questionnaire was termed the Energy Fatigue Questionnaire. Baseline scores for each of these questions were similar in the two treatment groups [U99-3170-01.pdf/p102]. No consistent significant differences were noted between tiotropium and placebo on these questions. Of note, tiotropium was numerically superior to placebo on all test days for "fatigue" and "severity of condition," but was numerically inferior to placebo on all test days for "energy level."

Another symptomatic assessment was the Mahler Baseline and Transition Dyspnea Index (BDI/TDI) scores, assessed at baseline (BDI) and after 7, 13, 25, 37, and 49 weeks of treatment (Days 50, 92, 176, 270, and 344, respectively). These scores include three components: Functional Impairment, Magnitude of Task, and Magnitude of Effort. The Focal Score is the sum of the three components. At baseline, the two treatment groups were comparable for each component and for the focal score [U99-3170-01.pdf/p104]. Tiotropium was statistically superior to placebo for all three components and for the focal score. The effect size that would represent a clinically meaningful benefit has not been firmly established in the literature. The Applicant states that the developer of the instrument has expressed the opinion that a change of 1 in the focal score would be clinically meaningful. The difference in focal score between tiotropium and placebo was >1 at 9 and 12 months only. Note that this was associated with a marked decline in focal score among the placebo and tiotropium patients from Day 176, onward. It is not clear why one might expect such a notable decline in the TDI in during that period. The table below provides the TDI data.

Mean Transition Dyspnea Index Scores (Study 205.115/205.128, ITT data set) [U99-3170-01.pdf/p108]

Component	Test Day	Tiotropium N	Tiotropium Mean	Placebo N	Placebo Mean	Difference	P-value
Functional Impairment	50	251	0.48	154	0.19	0.29	0.0010
	92	251	0.51	154	0.22	0.29	0.0008
	176	251	0.41	154	0.08	0.34	0.0003
	260	251	0.45	154	0.11	0.34	0.0002
	344	251	0.46	154	0.08	0.38	0.0001
Magnitude of Task	50	250	0.46	154	0.20	0.26	0.0015
	92	250	0.49	154	0.17	0.32	0.0002
	176	250	0.35	154	0.05	0.29	0.0007
	260	250	0.43	154	0.07	0.36	0.0001
	344	250	0.41	154	0.06	0.35	0.0002
Magnitude of Effort	50	252	0.50	154	0.13	0.36	0.0001
	92	252	0.51	154	0.16	0.35	0.0001
	176	252	0.36	154	0.02	0.33	0.0009
	260	252	0.42	154	0.04	0.38	0.0002
	344	252	0.41	154	-0.02	0.43	0.0001
Focal Score	50	249	1.42	154	0.53	0.89	0.0001
	92	249	1.50	154	0.55	0.95	0.0001
	176	249	1.11	154	0.15	0.97	0.0002
	260	249	1.29	154	0.22	1.06	0.0001
	344	249	1.25	154	0.11	1.13	0.0001

COPD symptoms were recorded on a 0 to 3 scale, ranging from none to severe: wheezing, shortness of breath, coughing, and tightness of chest. These assessments were made *by the investigator* at baseline, and after 8, 29, 50, 71, 92, 113, 134, 155, 176, 197, 218, 239, 260, 281, 302, 323, and 344 days of treatment. At baseline, the scores were similar in the two treatment groups [U99-3179-01.pdf/p109]. Tiotropium was statistically superior to placebo for shortness of breath on 15 of the 17 test days and for wheezing on 9 of the 17 test days. There was no statistically significant difference between groups for cough or tightness in chest scores [U99-3170-01.pdf/p111-2]. A minimal clinically meaningful difference in these scores has not been established.

Supplemental Albuterol Use

The use of supplemental albuterol, as recorded in daily record cards, was similar in the two treatment groups during the baseline period (3 to 4 doses per day)[U99-3170-01.pdf/p91]. During each week of treatment, tiotropium was statistically superior to placebo in regard to the mean number of doses of albuterol per day, averaged weekly ($p<0.01$). On average, patients in the tiotropium group took approximately 5 fewer doses of albuterol *per* week compared to patients in the placebo group [U99-3170-01.pdf/p91-4].

Nocturnal Awakenings

The number of awakenings due to COPD symptoms were collected on daily record cards at baseline and for the first 13 weeks of treatment. *Note: The protocol did not include analysis of nocturnal awakenings in the list of secondary efficacy endpoints.* During the baseline period, the number of awakenings per night was similar between groups (0.44 for tiotropium and 0.42 for placebo). The number of awakenings per night was not clinically or statistically different between groups during the 13-week treatment period [U99-3170-01.pdf/p116-7].

COPD Exacerbations

There was no significant difference between tiotropium and placebo in number of patients with COPD exacerbations, time to COPD exacerbation, number of COPD exacerbation days, number of patients with hospitalization or number of hospitalizations [U99-31670-01.pdf/p126-7]. Fewer patients in tiotropium group required oral and/or systemic corticosteroid bursts for the control of COPD exacerbations (15.9% vs. 22%), although this difference was not statistically significant ($p=0.09$) [U99-3170-01.pdf/p91].

Health-Related Quality of Life

The St. George's Hospital Respiratory Questionnaire (SGRQ) was administered at baseline and after 7, 13, 25, 37, and 49 weeks of treatment. The SGRQ consists of 50 questions comprising three domains, Activities, Impacts, and Symptoms. A lower score indicates less impairment in "health related quality of life". In the medical literature, a change in the total score of ≥ 4 is considered to represent a clinically meaningful change. The protocol did not discuss analysis of individual SGRQ domains. However, prior to un-blinding the data, the Applicant amended the protocol to indicate that the analysis of the Impacts domain would be a secondary endpoint. This decision was made after consultation with the developer of the SGRQ, Dr. Paul Jones, who suggested that the Impacts domain may better detect changes attributable to drug treatment. However, the use of the Impacts domain alone has been less common in the medical literature and there is no consensus on what constitutes a minimal clinically meaningful change in the Impacts score.

The baseline SGRQ scores by treatment group, are shown in the table below. Interestingly, although the Impacts domain is predicted to be the most sensitive, the mean scores for this domain were notably lower (better) at baseline, compared to the other two domains.

Mean Baseline SGRQ Scores (Study 205.115/205.128, ITT data set) [U99-3170-01.pdf/p95]

Score	Tiotropium			Placebo		
	N	Mean	(SE)	N	Mean	(SE)
Symptoms	252	58.43	(1.31)	154	57.89	(1.73)
Activities	251	63.45	(1.23)	153	61.35	(1.52)

Mean Baseline SGRQ Scores (Study 205.115/205.128, ITT data set) [U99-3170-01.pdf/p95]

Score	Tiotropium			Placebo		
	N	Mean	(SE)	N	Mean	(SE)
Impacts	251	31.49	(1.10)	153	29.40	(1.35)
Total	251	45.68	(1.01)	153	43.90	(1.20)

The table below summarizes the SGRQ scores (total and by domain), at each measure. For the total SGRQ score, statistically significant differences between groups were noted at all test days. The difference in total SGRQ score between groups was greater than the generally accepted threshold indicating a clinically meaningful change (4) at Days 176 and 344. Tiotropium was statistically superior to placebo for the Impacts score at all test days. Tiotropium was not shown to be statistically superior to placebo for Symptoms score at any measure. Tiotropium was statistically superior to placebo for the Activities score at each test day except Day 260. The clinical significance of these statistical observations is not known.

Mean SGRQ Scores (Study 205.115/205.128, ITT data set) [U99-3170-01.pdf/p98]

Score	Test Day	Tiotropium		Placebo		Difference	p-value
		N	Mean	N	Mean		
Symptoms	Baseline[1]	252	58.23	154	58.23		
	50	252	56.40	154	56.21	0.19	0.9009
	92	252	54.89	154	55.08	-0.19	0.9100
	176	252	52.76	154	55.65	-2.89	0.1072
	260	252	53.67	154	56.65	-2.98	0.1061
	344	252	53.95	154	56.46	-2.51	0.1700
Activities	Baseline[1]	251	62.65	153	62.65		
	50	251	58.69	153	62.47	-3.77	0.0039
	92	251	57.84	153	61.43	-3.59	0.0151
	176	251	58.49	153	62.57	-4.08	0.0087
	260	251	59.01	153	61.86	-2.86	0.0665
	344	251	58.15	153	61.88	-3.73	0.0164
Impacts	Baseline[1]	251	30.70	153	30.70		
	50	251	28.77	153	30.91	-2.14	0.0440
	92	251	28.27	153	30.64	-2.37	0.0497
	176	251	28.23	153	32.70	-4.47	0.0007
	260	251	29.08	153	32.63	-3.54	0.0067
	344	251	28.34	153	32.92	-4.58	0.0004
Total	Baseline[1]	251	45.01	153	45.01		
	50	251	42.41	153	44.74	-2.33	0.0121
	92	251	41.64	153	44.08	-2.43	0.0206
	176	251	41.50	153	45.62	-4.11	0.0004
	260	251	42.20	153	45.54	-3.34	0.0053
	344	251	41.61	153	45.69	-4.08	0.0006

[1]Common baseline mean

The Medical Outcomes Study SF-36 Questionnaire (SF-36), a "quality of life" instrument that is not disease-specific, was administered at baseline and after 7, 13, 25, 37, and 49 weeks of treatment (Days 50, 92, 176, 270, and 344, respectively). The instrument consists of 36 items grouped into 8 domains (Physical Functioning, Role Physical, Bodily Pain, General Physical Health, Vitality, Social Function, Role Emotional, and General Mental Health). The physical and mental domains are then grouped into "summaries" (Physical Health Summary, and Mental Health Summary). Higher scores indicate less impairment. At baseline, the mean scores for each domain were similar between groups [U99-3170-01.pdf/p99]. All of the physical domains