

CLINICAL REVIEW

Clinical Review Section Study 205.137

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 584 subjects were randomized and received at least one dose of study medication (tiotropium = 193, salmeterol = 192, and placebo = 199). Of these, 124 subjects withdrew from the study prior to completion (tiotropium = 37, salmeterol = 40, and placebo = 47). The table below summarizes the duration of exposure, by treatment group.

Extent of Exposure, Study 205.137		[U01-1231-1.pdf/p173]		
	Tiotropium N (%)	Salmeterol N (%)	Placebo N (%)	
Total Treated	193 (100)	192 (100)	199 (100)	
1	1 (0.5)	0 (0.0)	0 (0.0)	
2-7	4 (2.1)	1 (0.5)	4 (2.0)	
8-60	15 (7.8)	19 (9.9)	24 (12.1)	
61-100	8 (4.1)	9 (4.7)	8 (4.0)	
101-168	42 (21.8)	47 (24.5)	42 (21.1)	
169-200	123 (63.7)	116 (60.4)	121 (60.8)	
Mean (days)	150.7	149.9	144.6	
Median (days)	169	169	169	
Range (days)	1-198	4-190	2-193	

Adverse events were reported by 71.1% of the subjects. The incidence of adverse events was similar among the treatment groups (tiotropium = 66.8%, salmeterol = 74.0%, and placebo = 72.4% [U01-1231-1.pdf/p174]). As seen in Study 205.130, the most frequent adverse events were categorized as lower respiratory system disorders. These were less common in the tiotropium group (39.4%) than in the salmeterol group (48.4%), and placebo group (47.2%). Upper respiratory system disorders were slightly more common in the tiotropium group (18.7%) than in the salmeterol group (15.1%) and the placebo group (16.1%). As seen in Study 205.130, the most frequent specific AE was COPD exacerbation, which occurred slightly less commonly in the tiotropium group (30.1%), as compared to the salmeterol group (34.9%) and placebo group (35.7%). Common (incidence \geq 3%) adverse events occurring more frequently in the tiotropium group as compared to the placebo group were: upper respiratory tract infection (18.7% vs. 16.1%), mouth dry (6.2% vs. 1.0%), back pain (4.7% vs. 2.5%), coughing (4.7% vs. 3.5%),

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headache (4.1% vs. 3.5%), pharyngitis (3.6% vs. 1.5%), chest pain (3.6% vs. 3.5%), influenza-like symptoms (3.6% vs. 3.5%), accident household (1.6% vs. 1.0%), [U01-1231-1.pdf/p176].

The percentage of subjects experiencing serious adverse events (SAEs) was lower in the tiotropium group (8.3%) than in the salmeterol and placebo groups (12% and 13.6%, respectively) [U01-1231-1.pdf/p174].

Fewer subjects in the tiotropium group discontinued the study due to adverse events (8.8%) compared with the salmeterol group (16.1%) and the placebo group (14.1%) [U01-1231-1.pdf/p174].

There were 5 deaths in the study, 1 in the tiotropium group, 3 in the salmeterol group, and 1 in the placebo group [U01-1231-1.pdf/p179]. None of the deaths were considered by the investigator to be related to treatment. The death in the tiotropium group was due to rupture of an abdominal aortic aneurysm.

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C. One-Year, Active-Controlled Studies

1. Study 205.122A/205.126A: "A multiple dose comparison of 18mcg of Tiotropium Inhalation Capsules and Atrovent Metered Dose Inhaler (2 puffs of 20mcg) in an one-year, double-blind, double-dummy, efficacy and safety study in adults with chronic obstructive pulmonary disease (COPD)"

a. Study Description

This study was performed at multiple centers, from October 4, 1996 to June 10, 1998. The protocol, dated September 20, 1996 [U00-3113.pdf/p199], was amended once on September 20, 1996 [U00-3113.pdf/p295]. The study report is dated February 18, 2000, with a subsequent amendment dated July 11, 2001 [U00-3113.pdf/p10]

Study Design

This was a randomized, double-blind, double-dummy, active-controlled, parallel group study. Randomization was performed in a 2:1 manner, such that 2/3 of the subjects were randomized to tiotropium.

Duration

The duration of treatment was 1 year. The treatment period was preceded by a two-week baseline period and followed by a three-week washout period.

Study Centers

This study was performed at 14 study centers, all in the Netherlands [U00-3113.pdf/p34].

Study Population

Male and female subjects aged ≥ 40 years, with COPD.

Materials

Tiotropium Inhalation Capsules via Handihaler device ¹	18mcg QD ²	Batch #9603001
Atrovent Metered Dose Inhaler	2 puffs of 20mcg QID ³	Batch #602529

¹subjects used a single Handihaler device throughout the study period [U00-3113.pdf/p216]

²between 8AM and 10AM

³8:00-10:00 AM, and at lunch, dinner, and bedtime

Objectives

The primary objective of this study was to compare the long-term (one-year) bronchodilator efficacy and safety of once daily dosing of tiotropium inhalation capsules (18mcg) and Atrovent MDI (2 puffs of ipratropium bromide 20mcg QID) in patients with COPD [U00-3113.pdf/p209]. The secondary objective was to compare the impact of tiotropium and Atrovent on the patients' "Quality of Life" and on resource use.

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Efficacy Variables

The primary efficacy variable was the trough FEV₁ response, defined as the mean change from baseline at the end of the dosing interval. Both the baseline FEV₁ and the trough FEV₁ were calculated as the mean of the two pre-treatment FEV₁ readings measured in the morning prior to administration of study medication. **Reviewer's Note: Thus the primary efficacy measure was performed at a time when the active control medication would, based on its known pharmacodynamic properties, no longer be expected to be effective.**

Secondary efficacy endpoints were:

- FEV₁ for the first 6 hours post dosing on each test day for the first 13 weeks, and for the first 3 hours post dosing on each test day for the remaining 9 months.
- FVC measured at the same time intervals as the FEV₁.
- Individual FEV₁ and FVC measurements at each timepoint.
- PEF_R measured by the patient at home twice daily. Measurements were made upon arising in the morning, and before bedtime (*at least 5 hours after the third daily dose, and prior to the fourth daily dose of the MDI*). **Reviewer's Note: Thus each PEF_R measurement was taken at the end of the dosing interval for the ipratropium.**
- Rescue albuterol MDI use during the treatment period.
- Number and length of exacerbations of COPD and of hospitalizations for respiratory disease during the treatment period.
- Patient reported outcomes: Mahler dyspnea scale, SGRQ, subject assessment of energy and fatigue state, and the SF-36. These assessments were made during the first hour in the clinic, between the two pre-dose pulmonary function tests [U00-3113.pdf/p221].
- Pharmacoeconomic variables such as the number of exacerbations and their treatment, hospitalizations, extra physician and other health care provider visits, concomitant medication use, disability days (defined as those days that the subject is unable to perform his/her usual daily activities), and employment status.

Safety Variables

- Adverse events
- Pulse rate and blood pressure, recorded at the same time intervals as the pulmonary function testing.
- Clinical laboratory testing, assessed at screening and at 3-month intervals, and at the conclusion of subject participation in the study.
- Electrocardiograms, performed at screening and at 3-month intervals. The interpretation of the ECGs was performed by the investigator or designee.
- Physical examination, performed at screening, at 13 weeks, and at the end of the study.

Inclusion Criteria

Notable inclusion criteria were:

- FEV₁ ≤ 65% of predicted and FEV₁ ≤ 70% of FVC
- Age ≥ 40 years
- Smoking history > 10 pack-years

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Exclusion Criteria

Notable exclusion criteria were:

- Significant disease other than COPD
- Clinically significant abnormal baseline laboratory studies
- SGOT or SGPT 2 times normal; bilirubin > 150% normal; creatinine > 125% normal
- Recent (<1 year) myocardial infarction, or recent (<3 years) history of heart failure
- Any cardiac arrhythmia requiring drug therapy
- Regular use of daytime oxygen therapy
- Upper respiratory tract infection within 6 weeks prior to screening or during the baseline period
- Symptomatic prostatic hypertrophy or bladder neck obstruction
- Narrow angle glaucoma
- History of asthma, allergic rhinitis, or atopy or a blood total eosinophil count ≥ 400 per microliter (males) or ≥ 320 per microliter (females)

Conduct

Following an initial screening visit, subjects entered a 2-week baseline period. Subjects who successfully completed the baseline period were randomized into the one-year, double-blind portion of the study in which they received either tiotropium QD or ipratropium bromide MDI QID, along with the appropriate dummy medication. Randomization was performed in a 2:1 manner, such that 2/3 of the subjects were randomized to tiotropium. Pulmonary function testing (spirometry) was performed at one hour prior and just prior to the start of therapy at Visit 2 (the randomization visit, following the 2-week baseline period), and at 30, 60, 120, 180, 240, 300, and 360 minutes post dosing. Pulmonary function testing was repeated at the same time intervals at the end of the first week, and after 7 and 13 weeks of treatment. Subsequently, pulmonary function testing was performed after 26, 39, and 52 weeks of treatment at one hour prior to and just prior to test drug administration, and 30, 60, 120, and 180 minutes post dosing. To ensure adherence to the washout requirements, theophylline levels were measured prior to pulmonary function testing in those subjects taking theophylline. Subjects were followed for an additional 3 weeks after the final dose of study medication. The tables below summarize the study procedures. During the treatment period between 13 and 52 weeks, clinic visits were scheduled every 6 to 7 weeks. During this period, subjects were contacted by telephone mid-way between clinic visits. The procedures for the telephone contacts were not described in the protocol [U00-3113.pdf/p224-9], but presumably adverse events were elicited.

Study Procedures, First 13 Weeks: 205.122/205.126							
[U00-3113.pdf/p201]							
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	X						X
12-lead ECG	X						X
Theophylline level ¹	X	X	X		X		X
Dispense Study Drug	X ²	X			X		X

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Study Procedures, First 13 Weeks: 205.122/205.126								[U00-3113.pdf/p201]
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	
Administration of Study Drug in Hospital		X	X		X		X	
PFTs (FEV ₁ and FVC)	X	X ³	X ³		X ³		X ³	
Quality of Life		X	X		X		X	
Pharmacoeconomic Data		X	X	X	X	X	X	
Review of PEFR Records		X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	
Concomitant Therapy	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

²pm albuterol MDI

³7-hour pulmonary function testing: 1 hour and just prior to dosing, and at 30, 60, 120, 180, 240, 300, and 360 minutes post drug administration

Study Procedures, Weeks 13-52: 205.122/205.126													[U00-3113.pdf/p202]
Trial Period:	Treatment Period (Week 13 through Week 52)												**
Visit #:		8		9		10		11		12		13	14
Telephone Calls	T1		T2		T3		T4		T5		T6		
Weeks on Therapy:	16	19	23	26	29	32	36	39	42	45	49	52	+3
Physical Examination												X	
Vital Signs (seated)				X				X				X	
Laboratory Tests				X				X				X	
12-lead ECG				X				X				X	
Theophylline level ¹				X				X				X	
Dispense Study Drug		X		X		X		X		X			
Administration of Study Drug in Hospital				X				X				X	
PFTs (FEV ₁ and FVC)				X ²				X ²				X ²	
Quality of Life				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
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

¹Theophylline levels only on patients taking theophylline

²4-hour pulmonary function testing: 1-hour and just prior to dosing, and 30, 60, 120, and 180 minutes post drug administration

**3-week post-treatment period

Concomitant Medications

All subjects were provided with albuterol MDI for "rescue use" during the study period.

Acute COPD exacerbations could be treated with: up to two 7-day increases in the dose, or addition of, oral corticosteroids during the first 13 weeks of the treatment period; up to two increases in the dose of theophylline preparations during the first 13 weeks of the treatment period; and antibiotics as necessary. During the period between the end of the first 13 weeks and the end of the 1-year treatment period subjects were allowed to use any medications, including theophylline and oral steroids as necessary to treat COPD exacerbations. If additions or increases in medications occurred prior to pulmonary function testing days the testing was postponed for at least 2, but not more than 7 days after the last increased or additional dose was given [U00-3113.pdf/p217].

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The following medications were allowed if stabilized for at least 6 weeks prior to and throughout the study period: oral corticosteroids (doses \leq the equivalent of 10 mg of prednisone QD or 20 mg of prednisone QOD); inhaled corticosteroids; theophylline preparations; mucolytic agents not containing bronchodilators; concomitant prescription or over-the-counter medications for treatment of other conditions unless specifically disallowed.

The following medications were not allowed for at least 1 month prior to the beginning of the study and throughout the study period: Beta-blockers, cromolyn sodium, nedocromil sodium, oral beta-adrenergic agents, long-acting beta-adrenergic agents, and anticholinergic agents.

Data Analysis

The statistical model used in this study was analysis of covariance with terms for treatment, center, and treatment-by-center interaction. The baseline was used as a covariate [U00-3113.pdf/p232]. The null hypothesis was that there is no difference among the treatment groups. The alternative hypothesis was that tiotropium is more effective than ipratropium. The primary analysis was the trough FEV₁ response at "subsequent visits" [U00-3113.pdf/p232].

Reviewer's Note: The protocol does not state which visit will be the basis of the primary comparison.

The secondary analyses described in the protocol were: Average FEV₁ (AUC₀₋₆) response for the six hours post-dose; FVC response at trough and Average FVC (AUC₀₋₆) response; change from baseline in mean weekly PEFR; PRN albuterol use; number and length of COPD exacerbations and of hospitalizations for respiratory disease; "quality of life" measures (TDI, SGRQ, and the physical dimensions score from the SF-36 (other dimensions and the overall score from the SF-36 were described in the protocol as exploratory [U00-3113.pdf/p232]).

The following interim analyses were planned. When all patients completed the first 13 weeks of treatment the database was locked and the treatment code was broken to Boehringer in-house personnel. A separate study report for this 13-week period was completed. An interim analysis for the one-year data was performed when 50% of the subjects completed the one-year study. Despite these interim analyses, the investigators, subjects, and field monitors remained blinded to the treatment codes. All decision processes and conventions made at the time of the blinded report planning meeting for the 13-week report remained in place for the one-year study report.

The efficacy analyses were to be based on all randomized subjects with baseline and data at the end of the first week of treatment. The protocol stated that if a subject discontinued the study early due to lack of efficacy or safety concerns, the missing efficacy data would be estimated by the least favorable data. If a patient missed a visit because of reasons not related to efficacy or safety concerns, the missing data would be estimated by the last observed data. Missing spirometry data would be estimated using other values recorded for that subject on that test day (linear interpolation for random, middle missing values, last available values for data missing for reasons unrelated to efficacy, and minimum observed FEV₁ for that day when values are missing because of rescue medication use) [U00-3113.pdf/p234].

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The sample size was based on previous studies indicating that the standard deviation of the primary variable should be assumed to be 0.17 liters. Based on that assumption, a sample of 240 subjects (160 in the tiotropium group and 80 in the ipratropium group) was expected to detect a difference in mean trough FEV₁ response of 0.075 liters at 5% significance level with approximately 90% power using a two-tailed t-test.

b. Patient Disposition

A total of 362 subjects were screened for entry. Of these, 288 were randomized into the trial: 191 to tiotropium and 97 to ipratropium [U00-3113.pdf/p58]. Because the tiotropium used in this study had an expiration date of April 30, 1998, any subject randomized after May 1, 1997 was unable to complete the 52 weeks on study medication as required by the protocol. Enrollment continued until June 30, 1997. Subjects who were unable to complete all visits due to drug expiration were required to discontinue study drug at nine months, but were considered complete patients.

Slightly more subjects in the tiotropium group completed all visits (84.8% vs. 80.4%). The percentages of subjects who withdrew due to adverse events or lack of efficacy were similar in both groups. The table below summarizes the subject disposition and reasons for withdrawal.

Subject Disposition and Reasons for Withdrawal, Study 205.122A/126A			[U00-3113.pdf/p59]
	Tiotropium	Ipratropium	
Randomized	191	97	
Completed the Trial	162 (84.8%)	78 (80.4%)	
Adverse Event Total	22 (11.5%)	12 (12.4%)	
Worsening of Disease Under Study	7 (3.7%)	6 (6.2%)	
Worsening of Other Pre-existing Disease	1 (0.5%)	1 (1.0%)	
Other Adverse Event	14 (7.3%)	5 (5.2%)	
Lack of Efficacy	3 (1.6%)	1 (1.0%)	
Administrative	2 (1.0%)	3 (3.1%)	
Non-compliant with Protocol	1 (0.5%)	1 (1.0%)	
Lost to Follow-up	1 (0.5%)	0 (0.0%)	
Consent Withdrawn	0 (0.0%)	2 (2.1%)	
Other	2 (1.0%)	3 (3.1%)	

The baseline and demographic features of the study subjects were similar among treatment groups. Eighty-four percent of the study subjects were men, and all subjects but one were caucasian. The mean age of the group was 64.5 years, and the mean FEV₁ was 1.22 liters (41.5% of predicted) at the screening visit [U00-3113.pdf/p60]. The table below summarizes the baseline and demographic features of the study subjects.

Demographics and Baseline Characteristics, Study 205.122A/126A				[U00-3113.pdf/p61-2]
	Tiotropium N (%)	Ipratropium N (%)	All N (%)	
Total Treated	191	97	288	
Sex				
Male (%)	156 (81.7)	85 (87.6)	241 (83.7)	

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Demographics and Baseline Characteristics, Study 205.122A/126A		[U00-3113.pdf/p61-2]		
		Tiotropium N (%)	Ipratropium N (%)	All N (%)
Race	White	190 (99.05)	97 (100)	287 (99.7)
	Black	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	1 (0.5)	0 (0.0)	1 (0.3)
Age	Mean	64.21	65.05	64.50
	Range	41 - 82	47 - 81	41 - 82
Smoking History (pack years)	Mean	32.77	34.56	33.38
	Range	10 - 112	10 - 117	10 - 117
Duration of COPD (years)	Mean	10.71	12.32	11.25
	Range	0.3 - 42.2	0.1 - 39.2	0.1 - 42.2
Screening FEV ₁ (L)	Mean	1.24	1.19	1.22
	Range	0.40 - 2.50	0.60 - 2.30	0.40 - 2.50
FEV ₁ /FVC x 100	Mean	44.22	45.59	44.68
	Range	18.45 - 76.88	27.35 - 81.60	18.45 - 81.60

The use of concomitant medication during the two-week baseline period was similar between groups. Of the entire study population, 76.0% used inhaled beta-adrenergic agents, 14.9% used oral theophylline, 78.1% used inhaled corticosteroids, and 8.3% used oral corticosteroids [U00-3113.pdf/p63].

c. Efficacy Review

Data Sets Analyzed

Efficacy analyses used the Intention-to-Treat principle. The ITT populations included all subjects who had baseline data and "adequate" post-treatment data. 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 [U00-3113.pdf/p64]. The ITT populations were determined separately for each endpoint. Therefore, the number of subjects in the ITT data set varies by endpoint.

The following approaches represent "modifications to what was stated in the protocol":

- For spirometry data, SGRQ data, SF-36 data, TDI data, and energy fatigue questionnaire data subjects 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 of study drug.
- For spirometry data, subjects with documented inadequate washout at baseline (theophylline level >6.1mcg/ml) and no data following at least 7 weeks of treatment were excluded from the ITT data set.
- For analysis of daily record data all randomized subjects with baseline data as well as data for two weeks on treatment with at least 4 observations each week were included in the ITT data set.

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Primary Endpoint

The primary efficacy variable was the trough FEV₁ response, defined as the mean change from baseline at the end of the dosing interval for tiotropium (i.e. approximately 23 to 25 hours post tiotropium administration [U00-3113.pdf/p232]. As discussed elsewhere, ipratropium, based on its known pharmacodynamics, would not be expected to be effective at this timepoint. Baseline FEV₁ (Visit 2) and trough FEV₁ (subsequent visits) were calculated as the mean of two pre-treatment FEV₁ readings measured in the morning, prior to administration of study medication. *The protocol did not state which specific treatment visit would serve as the primary efficacy endpoint.*

Tiotropium was superior to ipratropium for the trough FEV₁ response after 13 weeks of treatment (Day 92) ($p=0.0001$) [U00-3113.pdf/p71]. The difference in mean response between the two groups was 0.13 liters. Tiotropium was also statistically superior to ipratropium on this endpoint at all other test days (8, 50, 182, 273, and 364), with treatment differences ranging from 0.13 liters to 0.17 liters.

Secondary Endpoints

Pulmonary Function Endpoints

Six-hour serial spirometry (at -60, -5, 30, 60, 120, 180, 240, 300, and 360 minutes) was performed on the first treatment day and after one, seven, and thirteen weeks of treatment (Days 1, 8, 50, and 92). Subsequently, after 26, 39, and 52 weeks of treatment, 3-hour serial spirometry (at -60, -5, 30, 60, 120, and 180 minutes) was performed.

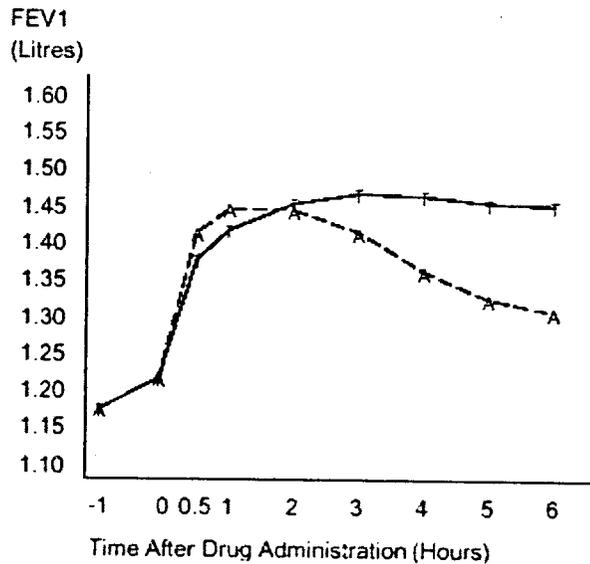
Following the first dose of study medication the mean FEV₁ in the *ipratropium* group was statistically superior to tiotropium at 30 minutes ($p=0.0351$, difference 0.04 liters). Subsequently, at 3, 4, 5, and 6 hours following the first dose of study medication, tiotropium was statistically superior to ipratropium for mean FEV₁, with treatment differences increasing from 0.05 liters at 3 hours to 0.15 liters at 6 hours ($p\leq 0.0126$) [U00-3113.pdf/p68]. The figure below illustrates the serial FEV₁ data following the first dose.

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Test Day 1



[T= tiotropium A=ipratropium Source: U00-3113.pdf/p66]

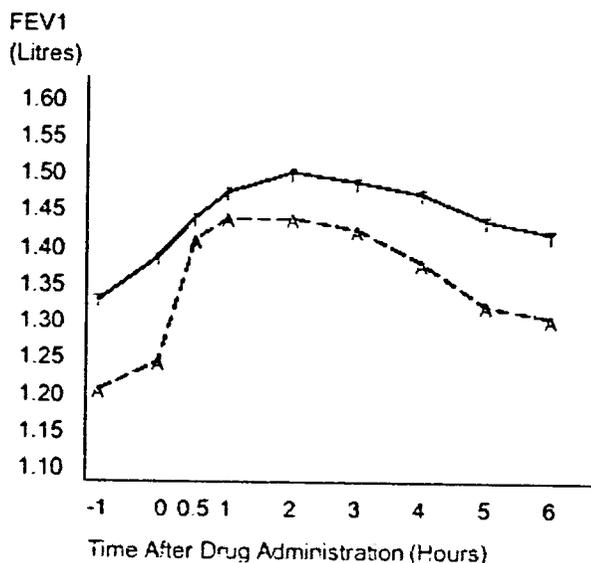
From Day 8 onward, the two pre-dose mean FEV₁ (- 60 minutes and -5 minutes) values were statistically superior in the tiotropium group ($P < 0.0001$), with effect sizes of 0.12 to 0.19 liters [U00-3113.pdf/p68-9]. On all test days, with the exception of test day 182, the mean FEV₁ was not statistically different between groups at the 30 minute and 1 hour timepoints. Tiotropium was, in general, statistically superior to ipratropium on FEV₁ measures beyond one hour. The figures below illustrate the serial FEV₁ values on test day 92 (Week 13), and test day 364 (Week 52).

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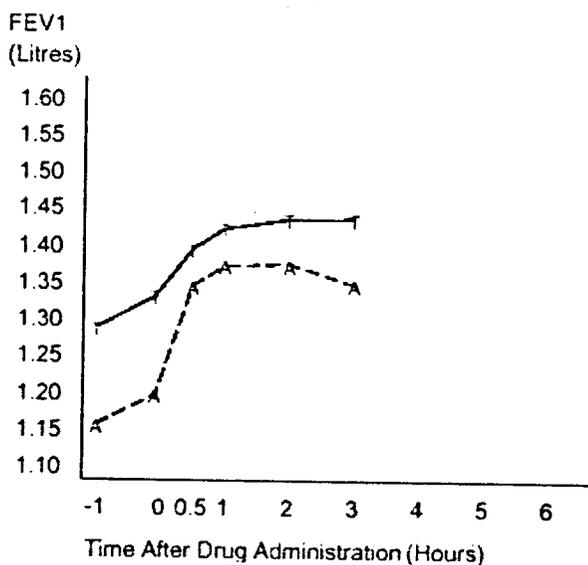
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Test Day 92



[T= tiotropium A=ipratropium Source: U00-3113.pdf/p66]

Test Day 364



[T= tiotropium A= ipratropium Source: U00-3113.pdf/p67]

Tiotropium was statistically superior to ipratropium for the average (0-3hour) FEV₁ response on all treatment days ($p \leq 0.0354$) except Day 1 [U00-3113.pdf/p71]. Tiotropium was statistically superior to ipratropium for the peak (0-3 hour) FEV₁ response on days 8, 50, 182, and 273, but not on days 1, 92, or 364.

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The serial FVC data show a similar pattern, although statistically significant differences were somewhat less frequent [U00-3113.pdf/p76-7]. From Day 8 onward the two pre-dose mean FVC values were statistically greater in the tiotropium group. Statistical separation between the two drugs was not demonstrated until at least hour 3 on any test day, and on the last two test days (Days 273 and 364), for which serial spirometry was performed for only 3 hours, the two groups were not statistically different on FVC at any timepoint. Tiotropium was not statistically superior to ipratropium for either the Average (0-3 hour) FVC Response or the Peak (0-3 hour) FVC Response on any test day [U00-3113.pdf/p79].

The mean morning PEFR during the baseline period was higher for the tiotropium group (254.05 vs. 246.68 liters/min) [U00-3113.pdf/p81]. The PEFR data is expressed as the mean values of weekly means for each week of treatment [U00-3113.pdf/p83-4]. Tiotropium was statistically superior to ipratropium on this variable for all except 6 weeks of the 52-week treatment period. However, the treatment differences, which ranged from 11.8 liters/min to 16.83 liter/min, were not large, given the baseline difference between the groups for this variable (7.31 liters/min).

The mean evening PEFR during the baseline period was higher for the tiotropium group (264.91 vs. 255.33 liters/min) [U00-3113.pdf/p85]. The evening PEFR data is expressed as the mean values of weekly means for each week of treatment [U00-3113.pdf/p87-8]. Tiotropium was statistically superior to ipratropium on this variable for 30 weeks of the 52-week treatment period. However, the treatment differences, which ranged from 8.42 liters/min to 16.18 liter/min, were not large, given the baseline difference between the groups for this variable (9.58 liters/min).

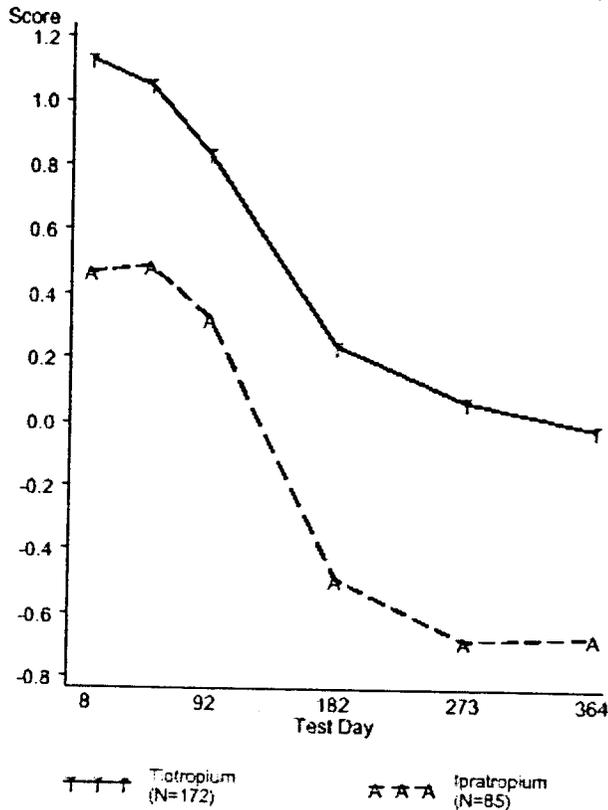
Patient Reported Outcomes

The Mahler Baseline Dyspnea Index and Transition Dyspnea Index (BDI/TDI) include three components (Functional Impairment, Magnitude of Task, and Magnitude of Effort) which are summed to arrive at the Focal Score. Each component of the BDI is scored from 0 to 4. Each component of the TDI is scored from -3 (major deterioration) to +3 (major improvement). The BDI was administered at baseline, and the TDI was administered at days 8, 50, 92, 182, 273, and 364. The BDI scores were similar between the two groups [U00-3113.pdf/p102]. The results of the TDI indicate that in both groups there was initial improvement followed by decline beginning at test day 92. The decline was numerically greater in the ipratropium group, such that the ipratropium subjects were below baseline (i.e. TDI focal score less than 0) from test day 182 onward, while the tiotropium group declined only to the baseline level (i.e. focal score of approximately 0). The TDI focal score was statistically superior in the tiotropium group at days 8, 182, 273, and 364. However, the absolute difference between groups was ≤ 0.75 units, a relatively minor difference. The figure below illustrates the pattern of the TDI focal score findings.

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Mean TDI Focal Score, Study 205.122A/205.126A (ITT Data Set)
[U00-3113.pdf/p105]



The St. George's Hospital Respiratory Questionnaire (SGRQ) is a disease-specific quality of life instrument that consists of 50 questions and comprises 3 domains (activities, impacts, and symptoms) and a total score. A lower score indicates lesser impairment. In the medical literature, a change in the SGRQ total score of 4 units is generally considered to represent a clinically meaningful change. The SGRQ was administered at baseline and at test days 50, 92, 182, 273, and 364. The baseline scores were similar between groups [U00-3113.pdf/p94-6]. With the exception of the total score on test day 50, the two groups were not statistically different in regard to the total score or any of the individual domain scores. On test day 50, tiotropium was statistically superior to ipratropium ($p=0.0435$), but the magnitude of the difference (2.32 units) did not reach the accepted threshold for a clinically meaningful difference.

The Medical Outcomes Study SF-36 Questionnaire is a general quality of life instrument that consists of 36 items, grouped into 8 domains, with each score ranging from 0 to 100, and higher scores indicating lesser impairment. The eight domains are combined into two summary scores. The baseline scores were similar between groups [U00-3113.pdf/p97-9]. The SF-36 was

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administered at baseline and at test days 50, 92, 182, 273, and 364. The SF-36 did not demonstrate statistically significant differences between groups.

The Energy Fatigue Questionnaire consisted of three questions regarding the subjects' perception of their energy and fatigue levels, and the severity of their respiratory condition. The fatigue scale ranged from 1 (very severe) to 6 (no fatigue). The energy scale ranged from 1 (very good) to 5 (very poor). The Severity of Respiratory Condition scale ranged from 1 (very severe) to 6 (no problems at all). The questionnaire was administered at baseline and at test days 8, 50, 92, 182, 273, and 364. The baseline scores were similar between the two groups [U00-3113.pdf/p100-1]. Although tiotropium was statistically superior to ipratropium for severity of condition on several test days, the magnitude of the differences was small, and overall, no consistent significant differences were demonstrated between groups on the Energy Fatigue Questionnaire.

COPD Exacerbations and Hospitalizations

There were no significant differences between treatment groups with regard to the number of subjects with COPD exacerbations, the time to first COPD exacerbation, the number of COPD exacerbations, the number of COPD exacerbation days, the number of patients with hospitalization due to COPD exacerbation, or the number of hospitalization days due to COPD exacerbation [U00-3113.pdf/p113]. Interestingly, there were fewer hospitalizations (all cause) (20 vs. 34 events per 100 subject-years) and fewer subjects with at least one hospitalization (all cause) (12% vs. 25%) in the tiotropium group ($p < 0.01$) [U00-3113.pdf/p113]. Other "pharmacoeconomic data," such as the ICU days, unscheduled medical visits, employment status changes, and inability to perform the majority of daily activities, did not show differences between groups [U00-3113.pdf/p114].

Other Secondary Endpoints

During the baseline period, subjects in the tiotropium group used more rescue albuterol (2.68 puffs/day vs. 2.18 puffs/day) [U00-3113.pdf/p90]. Despite this baseline difference, subjects in the tiotropium group used numerically less rescue albuterol during each week of the study. Statistically significant differences on this variable were demonstrated during 36 of the 52 weeks [U00-3113.pdf/p92-3]. It should be noted that 14 of the 16 weeks during which the use of rescue albuterol was not significantly different between groups occurred during the second half of the study.

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, SGRQ, SF-36, Energy Fatigue Questionnaire) were performed [U00-3113.pdf/p107-14]. These analyses include only those subjects who completed the study and had at least some post-treatment data. The mean weekly AM and PM PEFR in both groups decreased gradually during the washout period (with the exception of the third week of washout in the ipratropium group, in which there was a slight improvement in both) [U00-3113.pdf/p107-8]. Likewise, the improvements in the SGRQ slowly decreased during the washout period. In both groups, the use of supplemental albuterol was greater in the post-treatment period, as compared with the baseline period. This might be

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interpreted as evidence of a post-treatment “rebound” phenomenon, present in both treatment groups. However, this was not substantiated by the other data during the washout period. The table below provides the data for the supplemental albuterol use.

Mean of Weekly Baseline and Change from Baseline Number of Puffs per Day of Supplemental Albuterol (ITT data set, only subjects with post-treatment data) (Study 205.122A/205.126A) [U00-3113.pdf/p108]								
		Tiotropium			Ipratropium			
		N	Mean	(SE)	N	Mean	(SE)	
Baseline	Pre-Treatment Week	153	2.54	(0.24)	77	2.08	(0.31)	
Change from Baseline	Last Treatment Week	153	-1.08	(0.22)	77	-0.40	(0.34)	
Change from Baseline	Post Treatment Weeks	Week 1	153	0.95	(0.27)	76	2.03	(0.44)
		Week 2	152	1.11	(0.28)	74	2.02	(0.46)
		Week 3	137	1.06	(0.29)	70	1.78	(0.50)

Pharmacokinetic Data

Pharmacokinetic data were not collected in this study.

Reviewer’s Comments on Efficacy

In this active-controlled study, the primary efficacy variable (trough FEV₁ response) was determined at a timepoint at which the active comparator, based on its known pharmacodynamic properties, would not be expected to be effective. The active comparator, ipratropium bromide, is indicated for use four times daily. Given the relatively long interval between the evening and the subsequent morning doses of ipratropium, little if any bronchodilator effect is likely to be detected on morning pre-dose spirometry. Nonetheless, the comparison between drugs at this timepoint may be clinically relevant, given that the ipratropium was dosed as labeled and used. However, for the purposes of NDA approval, the primary regulatory requirement is that the proposed drug be demonstrated to be superior to placebo. Therefore, for regulatory purposes the ipratropium arm may be considered analogous to placebo. In that case, superiority of tiotropium over ipratropium could be interpreted as evidence that tiotropium would be superior to placebo.

The primary efficacy variable was the trough FEV₁ response, defined as the mean change from baseline at the end of the dosing interval for tiotropium. It is important to note that the protocol did not state which specific treatment visit would serve as the primary efficacy endpoint. Nonetheless, tiotropium was demonstrated to be superior to ipratropium on this variable on all test days, with effect sizes of 0.13 to 0.17 liters.

Serial, post-dose spirometry was the basis for several secondary efficacy endpoints. It should be noted that, because the first post-dose spirometry was performed at 30 minutes, earlier bronchodilation due to ipratropium may have been missed. The product label for Atrovent (ipratropium bromide) Inhalation Aerosol indicates that in clinical studies significant improvements in FEV₁ (increases of 15% or more) occurred within 15 minutes.

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Following the first dose of study medication, *ipratropium* was statistically superior to tiotropium for FEV₁ at 30 minutes. On most test days the two groups were not statistically different at 30 minutes or 1 hour post dose. However, tiotropium was superior to ipratropium for FEV₁ beyond 1 hour on most test days, and tiotropium was superior on the FEV₁ AUC_{0-3hours} on all treatment days except Day 1. Bronchodilator efficacy was also supported by morning PEFR data, although the effect size was slight. For evening PEFR, tiotropium was statistically superior to ipratropium for only 30 of the 52 weeks, perhaps reflecting the fact that the time interval between prior dosing with ipratropium and measurements of PEFR was greater for the AM measurements. Finally, the tiotropium group used statistically fewer puffs of rescue medication during 36 of the 52 weeks of the study. The superiority in this regard was most evident during the first half of the study.

Patient reported outcome assessments did not suggest a benefit of tiotropium over ipratropium. While the mean TDI focal score in the tiotropium group was statistically superior to ipratropium on 4 of the 6 test days, the effect size was slight and was not likely clinically significant. Likewise, the SGRQ, the MOS SF-36, and the Energy Fatigue Questionnaire instruments did not suggest a benefit of tiotropium over ipratropium. There were also no significant differences between groups in regard to COPD exacerbations (the number of subjects with COPD exacerbation, the time to first COPD exacerbation, the number of COPD exacerbations, the number of COPD exacerbation days, the number of patients with hospitalization due to COPD exacerbation, or the number of hospitalization days due to COPD exacerbation). However, there were fewer hospitalizations (all cause) and fewer subjects with at least one hospitalization (all cause) in the tiotropium group.

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 205.122B/205.126B, 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 288 subjects were randomized and received at least one dose of study medication (tiotropium = 191, ipratropium = 97). Of these, 27 subjects discontinued study medication at 39 weeks because of expiry of the study drug (tiotropium = 16, ipratropium = 11) [U00-3113.pdf/p117]. The table below summarizes the duration of exposure, by treatment group.

Extent of Exposure, Study 205.122A/205.126A		[U00-3113.pdf/p117]	
	Tiotropium N (%)	Ipratropium N (%)	All N (%)
Total Treated	191 (100)	97 (100)	288 (100)
1	2 (1.0)	1 (1.0)	3 (1.0)
2-7	5 (2.6)	2 (2.1)	7 (2.4)

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Extent of Exposure, Study 205.122A/205.126A		[U00-3113.pdf/p117]	
	Tiotropium N (%)	Ipratropium N (%)	All N (%)
8-60	9 (4.7)	5 (5.2)	14 (4.9)
61-100	2 (1.0)	3 (3.1)	5 (1.7)
101-200	2 (1.0)	4 (4.1)	6 (2.1)
201-330	22 (11.5)	14 (14.4)	36 (12.5)
> 330	149 (78.0)	68 (70.1)	217 (75.3)
Mean (days)	317.9	305.4	313.7
Range (days)	1-382	1-386	1-386

Adverse events were reported by 91.7% of the subjects. The incidence of adverse events was similar in both treatment groups (tiotropium = 91.1%, ipratropium 92.8%) [U00-3113.pdf/p118]. Adverse events classified as Gastrointestinal Disorders were more frequent in the tiotropium group, due to a higher incidence of dry mouth in the tiotropium group (17.8% vs. 11.3%). The incidence of upper Respiratory System Disorders was also higher in the tiotropium group, due to a greater incidence of upper respiratory tract infection (49.2% vs. 37.1%). However, lower Respiratory Tract Disorders were less common in the tiotropium group, due to fewer COPD exacerbations (35.6% vs. 45.4%). Also, influenza-like symptoms were less frequent in the tiotropium group (9.9% vs. 16.5%). Common (incidence \geq 3%) adverse events occurring more frequently in the tiotropium group as compared to the placebo group were: upper respiratory tract infection (49.2% vs. 37.1%), mouth dry (17.8% vs. 11.3%), back pain (5.8% vs. 4.1%), pharyngitis (5.8% vs. 0.0%), chest pain (4.7% vs. 0.0%), urinary tract infection (4.2% vs. 3.1%), fatigue (3.1% vs. 1.0%), eczema (3.1% vs. 1.0%), and skin disorder (3.1% vs. 0.0%), [U00-3113.pdf/p120-1].

The percentage of subjects experiencing serious adverse events (SAEs) was lower in the tiotropium group (14.1%) than in the ipratropium group (26.8%) [U00-3113.pdf/p124].

The occurrence of discontinuation from the study due to adverse events was similar in the two groups (11.0% and 11.3%) [U00-3113.pdf/p126].

There were 8 deaths in the study, 5 in the tiotropium group (2.6%) and 3 in the ipratropium group (3.1%) [U00-3113.pdf/p122]. None of the deaths were considered by the investigator to be related to treatment. The deaths in the tiotropium group were due to: myocardial infarction and cerebral hemorrhage, stomach carcinoma, lung carcinoma (2 subjects), and pulmonary embolism. The diagnoses of carcinoma were not known at study entry.

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2. Study 205.122B/205.126B

a. Study Description

This study was performed under a protocol that was identical to the protocol for Study 205.122A/205.126B. The reader is referred to the description of the protocol discussed in the section above. This study was performed between November 26, 1996 and May 27, 1998 [U00-3114.pdf/p6]. The study was conducted at 15 centers, all of which were non-US (Belgium and The Netherlands). A total of 247 patients were entered, 165 assigned to tiotropium and 82 assigned to ipratropium.

The test product (tiotropium inhalation capsules) were from batch number 9603001 (placebo batch #9602001). The reference product (ipratropium) was from batch numbers 602529 (placebo batch #601202).

b. Patient Disposition

A total of 305 subjects were screened for entry. Of these, 247 were randomized into the trial: 165 to tiotropium and 82 to ipratropium [U00-3114.pdf/p53]. Because the tiotropium used in this study had an expiration date of April 30, 1998, any subject randomized after May 1, 1997 was unable to complete the 52 weeks on study medication as required by the protocol. Enrollment continued until June 30, 1997. Subjects who were unable to complete all visits due to drug expiration were required to discontinue study drug at nine months, but were considered complete patients.

More subjects in the tiotropium group completed all visits (84.8% vs. 76.8%). Also, fewer subjects withdrew due to adverse events (8.5%) or lack of efficacy (0%) in the tiotropium group, as compared to the ipratropium group (13.4% and 2.4%, respectively). The table below summarizes the subject disposition and reasons for withdrawal.

Subject Disposition and Reasons for Withdrawal, Study 205.122B/126B			[U00-3114.pdf/p54]
	Tiotropium	Ipratropium	
Randomized	165	82	
Completed the Trial	140 (84.8%)	63 (76.8%)	
Adverse Event Total	14 (8.5%)	11 (13.4%)	
Worsening of Disease Under Study	4 (2.4%)	5 (6.1%)	
Worsening of Other Pre-existing Disease	1 (0.6%)	3 (3.7%)	
Other Adverse Event	9 (5.5%)	3 (3.7%)	
Lack of Efficacy	0 (1.0%)	2 (2.4%)	
Administrative	8 (1.0%)	4 (3.1%)	
Non-compliant with Protocol	2 (1.2%)	2 (2.4%)	
Lost to Follow-up	1 (0.6%)	0 (0.0%)	
Consent Withdrawn	5 (6.0%)	2 (2.4%)	
Other	3 (1.8%)	2 (2.4%)	

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The baseline and demographic features of the study subjects were similar among treatment groups. Eighty-six percent of the study subjects were men, and all subjects were caucasian. The mean age of the group was 63.2 years, and the mean FEV₁ was 1.23 liters (40.5% of predicted) at the screening visit [U00-3114.pdf/p55]. The table below summarizes the baseline and demographic features of the study subjects.

Demographics and Baseline Characteristics, Study 205.122B/126B		[U00-3114.pdf/p56-7]		
		Tiotropium N (%)	Ipratropium N (%)	All N (%)
Total Treated		165	82	247
Sex	Male (%)	144 (87.3)	69 (84.1)	213 (86.2)
Race	White	165 (100)	82 (100)	247 (100)
	Black	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	0 (0.0)	0 (0.0)	0 (0.0)
Age	Mean	62.87	63.77	63.17
	Range	41 - 82	42 - 77	41 - 82
Smoking History (pack years)	Mean	35.99	31.67	34.54
	Range	10 - 140	10 - 70	10 - 140
Duration of COPD (years)	Mean	12.27	9.83	11.46
	Range	0.1 - 54.2	0.11 - 53.0	0.1 - 54.2
Screening FEV ₁ (L)	Mean	1.26	1.16	1.23
	Range	0.29 - 2.60	0.47 - 2.45	0.29 - 2.60
FEV ₁ /FVC x 100	Mean	47.49	45.42	46.80
	Range	24.38 - 70.17	25.73 - 63.71	24.38 - 70.17

The use of concomitant medication during the two-week baseline period was similar between groups. Of the entire study population, 76.1% used inhaled beta-adrenergic agents, 17.0% used oral theophylline, 83.4% used inhaled corticosteroids, and 10.5% used oral corticosteroids [U00-3114.pdf/p58].

c. Efficacy Review

Primary Endpoint

The primary efficacy variable was the trough FEV₁ response, defined as the mean change from baseline at the end of the dosing interval for tiotropium (i.e. approximately 23 to 25 hours post tiotropium administration. As discussed elsewhere, ipratropium, based on its known pharmacodynamics, would not be expected to be effective at this timepoint. Baseline FEV₁ (Visit 2) and trough FEV₁ (subsequent visits) were calculated as the mean of two pre-treatment FEV₁ readings measured in the morning, prior to administration of study medication. *The protocol did not state which specific treatment visit would serve as the primary efficacy endpoint.*

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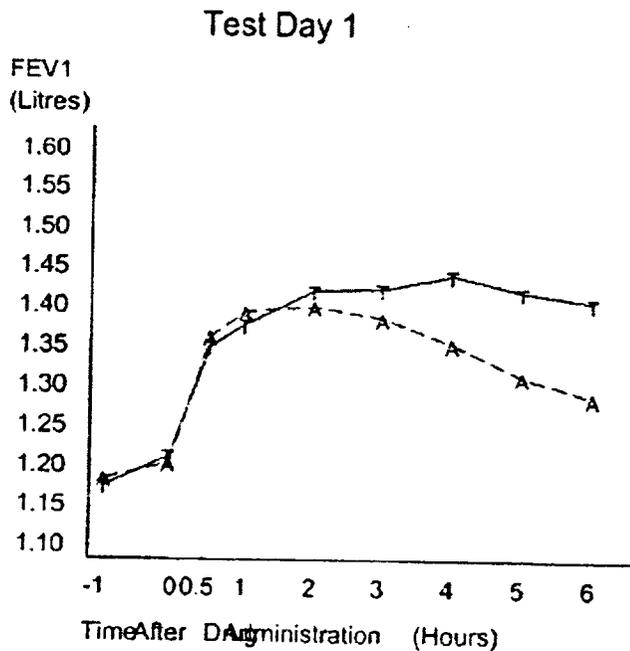
The baseline mean FEV₁ was slightly higher for the tiotropium group (1.22 liters vs. 1.13 liters) [U00-3114.pdf/p60]. Tiotropium was superior to ipratropium for the trough FEV₁ response after 13 weeks of treatment (Day 92) (p=0.0001) [U00-3114.pdf/p67]. The difference in mean response between the two groups was 0.15 liters. Tiotropium was also statistically superior to ipratropium on this endpoint at all other test days (8, 50, 182, 273, and 364), with treatment differences ranging from 0.11 liters to 0.18 liters.

Secondary Endpoints

Pulmonary Function Endpoints

Six-hour serial spirometry (at -60, -5, 30, 60, 120, 180, 240, 300, and 360 minutes) was performed on the first treatment day and after one, seven, and thirteen weeks of treatment (Days 1, 8, 50, and 92). Subsequently, after 26, 39, and 52 weeks of treatment, 3-hour serial spirometry (at -60, -5, 30, 60, 120, and 180 minutes) was performed.

Following the first dose of study medication there was no statistically significant difference between groups for the mean FEV₁ until Hour 4. [U00-3114.pdf/p63] On that day, the mean FEV₁ in the tiotropium group was statistically superior to ipratropium at hours 4, 5, and 6 (p≤ 0.0024; treatment differences 0.09 to 0.12 liters). On Test Days 8 and 50, tiotropium was statistically superior to ipratropium from Hour 2 onward (treatment differences 0.08 to 0.17 liters). On the remaining test days (92, 182, 273, and 364) tiotropium was superior to ipratropium at all post-dose timepoints (treatment difference 0.08 to 0.18 liters). The figure below illustrates the serial FEV₁ data following the first dose.



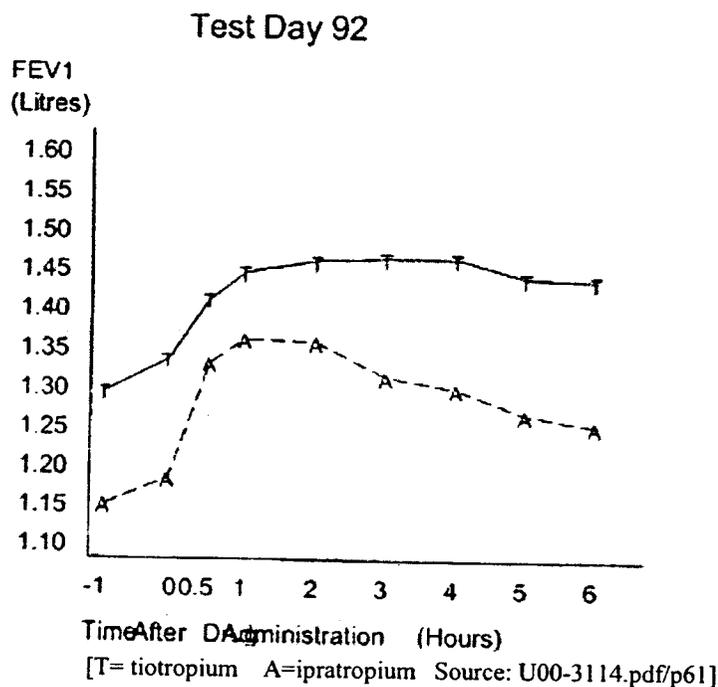
[T= tiotropium A=ipratropium Source: U00-3114.pdf/p61]

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From Day 8 onward, the two pre-dose mean FEV₁ (-60 minutes and -5 minutes) values were statistically superior in the tiotropium group ($P \leq 0.0005$), with effect sizes of 0.09 to 0.20 liters [U00-3114.pdf/p63-4]. The figures below illustrate the serial FEV₁ values on test day 92 (Week 13), and test day 364 (Week 52).

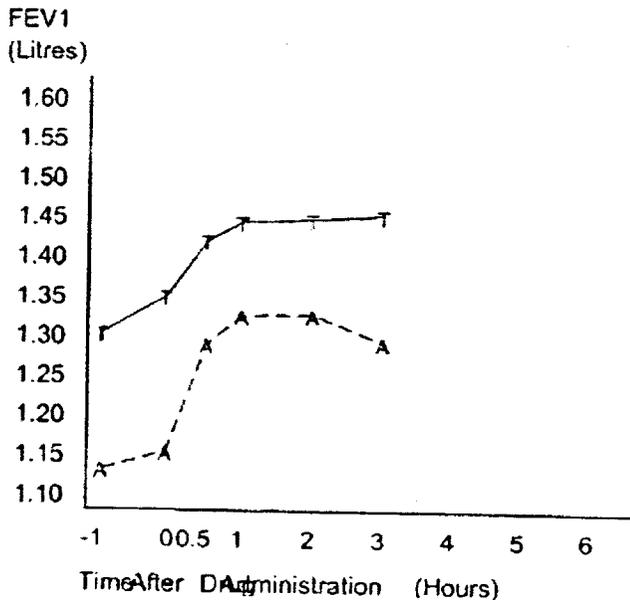


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Test Day 364



[T= tiotropium A= ipratropium Source: U00-3114.pdf/p62]

Tiotropium was statistically superior to ipratropium for the average (0-3hour) FEV₁ response on all treatment days ($p \leq 0.0201$) except Day 1 [U00-3114.pdf/p67]. Tiotropium was statistically superior to ipratropium for the peak (0-3 hour) FEV₁ response on all treatment days ($p \leq 0.0238$) except Day 1.

The serial FVC data show a pattern that is similar to that seen with the FEV₁ data [U00-3114.pdf/p69]. The difference between treatment groups for the mean FVC response was statistically significant starting at the 4 Hour timepoint for the first three visits, and by the 3 Hour timepoint for the remainder of the study. Tiotropium was also statistically superior to ipratropium for the trough FVC response (excluding baseline). Tiotropium was not statistically superior to ipratropium for either the Average (0-3 hour) FVC Response or the Peak (0-3 hour) FVC Response on most test days (with the exception of test days 182 and 273) [U00-3114.pdf/p75].

The mean morning PEFR during the baseline period was higher for the tiotropium group (252.11 vs. 241.40 liters/min) [U00-3114.pdf/p77]. The PEFR data is expressed as the mean values of weekly means for each week of treatment [U00-3114.pdf/p79-80]. Tiotropium was statistically superior to ipratropium on this variable for every week during the treatment period, except Week 1. The treatment differences ranged from 14.64 liters/min to 22.10 liter/min.

The mean evening PEFR during the baseline period was slightly higher for the tiotropium group (259.46 vs. 253.15 liters/min) [U00-3114.pdf/p81]. The evening PEFR data is expressed as the mean values of weekly means for each week of treatment [U00-3114.pdf/p83-4]. Tiotropium

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was statistically superior to ipratropium on this variable for each of the 52 weeks of the treatment period. The treatment differences ranged from 10.33 liters/min to 21.46 liter/min.

Patient Reported Outcomes

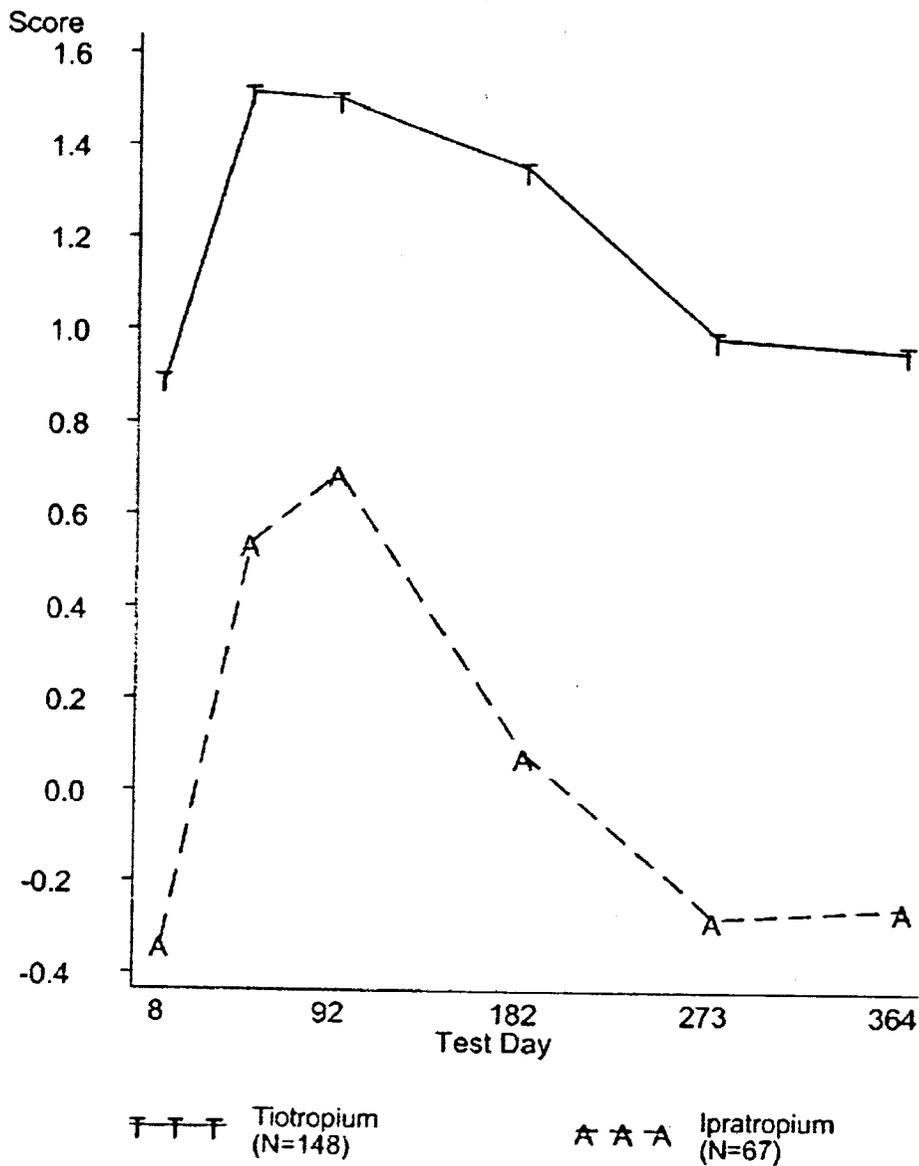
The Mahler Baseline Dyspnea Index and Transition Dyspnea Index (BDI/TDI) include three components (Functional Impairment, Magnitude of Task, and Magnitude of Effort) which are summed to arrive at the Focal Score. Each component of the BDI is scored from 0 to 4. Each component of the TDI is scored from -3 (major deterioration) to +3 (major improvement). The BDI was administered at baseline, and the TDI was administered at days 8, 50, 92, 182, 273, and 364. The BDI scores were similar between the two groups [U00-3114.pdf/p98]. The results of the TDI indicate that in both groups there was initial improvement followed by decline following test day 92. The decline was numerically greater in the ipratropium group, such that the ipratropium subjects were below baseline (i.e. TDI focal score less than 0) on test 273 and 364, while the tiotropium group declined only to a focal score of approximately of approximately 1 [U00-3114.pdf/p101]. The TDI focal score was statistically superior in the tiotropium group at each test day. The treatment differences were 1.23, 0.97, 0.81, 1.27, 1.26, and 1.21 on test days 8, 50, 92, 182, 273, and 364. The figure below illustrates the pattern of the TDI focal score findings.

Mean TDI Focal Score, Study 205.122B/205.126B (ITT Data Set)
[U00-3114.pdf/p101]

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The St. George's Hospital Respiratory Questionnaire (SGRQ) is a disease-specific quality of life instrument that consists of 50 questions and comprises 3 domains (activities, impacts, and symptoms) and a total score. A lower score indicates lesser impairment. In the medical literature, a change in the SGRQ total score of 4 units is generally considered to represent a clinically meaningful change. The SGRQ was administered at baseline and at test days 50, 92, 182, 273, and 364. The baseline total scores were higher in the tiotropium group (45.46 vs. 42.37) [U00-3114.pdf/p90]. The tiotropium group was statistically superior to the ipratropium group on test days 273 and 36, but not on test days 8, 50, 92, or 182 [U00-3114.pdf/p92]. The treatment differences were 3.73 and 4.86 on days 273 and 364, respectively.

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The Medical Outcomes Study SF-36 Questionnaire is a general quality of life instrument that consists of 36 items, grouped into 8 domains, with each score ranging from 0 to 100, and higher scores indicating lesser impairment. The eight domains are combined into two summary scores. The baseline scores were similar between groups with the exception of the General Mental Health and the Mental Health Summary scores, both of which were significantly higher ($P < 0.05$) in the tiotropium group [U00-3114.pdf/p92-3]. The SF-36 was administered at baseline and at test days 50, 92, 182, 273, and 364. The SF-36 generally did not demonstrate statistically significant differences between groups.

The Energy Fatigue Questionnaire consisted of three questions regarding the subjects' perception of their energy and fatigue levels, and the severity of their respiratory condition. The fatigue scale ranged from 1 (very severe) to 6 (no fatigue). The energy scale ranged from 1 (very good) to 5 (very poor). The Severity of Respiratory Condition scale ranged from 1 (very severe) to 6 (no problems at all). The questionnaire was administered at baseline and at test days 8, 50, 92, 182, 273, and 364. At baseline, the mean score for Energy Level was significantly lower (worse) in the tiotropium group ($p < 0.05$; 2.63 vs. 2.83) [U00-3114.pdf/p96]. The Fatigue Level and the Severity of Condition scores were comparable at baseline. During treatment there were no statistically significant differences between treatment groups.

COPD Exacerbations and Hospitalizations

The tiotropium group had significantly fewer subjects with COPD exacerbations (31% vs. 49%), fewer COPD exacerbations (73 vs. 103 events per 100 patient-years), and fewer COPD exacerbation days (1132 vs. 1870 event days per 100 patient years) ($p < 0.01$) [U00-3114.pdf/p109]. In addition, the time to first COPD exacerbation was longer in the tiotropium group ($p < 0.01$). There was no difference in the number of patients with hospitalization due to COPD exacerbation, the number of hospitalization days due to COPD exacerbation, or the hospitalizations due to all causes. Other "pharmacoeconomic data," such as the ICU days, unscheduled medical visits, employment status changes, and inability to perform the majority of daily activities, did not show differences between groups [U00-3114.pdf/p110].

Other Secondary Endpoints

During the baseline period, the use of rescue albuterol was similar between groups [U00-3114.pdf/p86]. Despite this baseline difference, subjects in the tiotropium group used numerically less rescue albuterol during each week of the study. During the treatment period, the use of rescue albuterol was not statistically significantly different in the two groups [U00-3114.pdf/p88-9].

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, SGRQ, SF-36, Energy Fatigue Questionnaire) were performed [U00-3114.pdf/p103]. These analyses include only those subjects who completed the study and had a least some post-treatment data. The mean weekly AM and PM PEFR in the tiotropium group decreased gradually during the washout period [U00-3114.pdf/p103]. Likewise, the improvements in the SGRQ decreased during the washout period. In both groups, the use of supplemental albuterol was greater in the post-treatment period, as

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compared with the baseline period. This might be interpreted as evidence of a post-treatment “rebound” phenomenon, present in both treatment groups. However, this was not substantiated by the other data during the washout period. The table below provides the data for the supplemental albuterol use.

Mean of Weekly Baseline and Change from Baseline Number of Puffs per Day of Supplemental Albuterol (ITT data set, only subjects with post-treatment data) (Study 205.122A/205.126A) [U00-3113.pdf/p108]								
		Tiotropium			Ipratropium			
		N	Mean	(SE)	N	Mean	(SE)	
Baseline	Pre-Treatment Week	133	2.85	(0.27)	59	2.97	(0.40)	
Change from Baseline	Last Treatment Week	133	-0.65	(0.29)	59	-0.49	(0.44)	
Change from Baseline	Post Treatment Weeks	Week 1	133	0.79	(0.33)	58	1.22	(0.53)
		Week 2	131	0.90	(0.34)	59	1.14	(0.54)
		Week 3	125	0.68	(0.37)	58	0.86	(0.53)

Pharmacokinetic Data

Pharmacokinetic data were not collected in this study.

Reviewer’s Comments on Efficacy

In this active-controlled study, the primary efficacy variable (trough FEV₁ response) was determined at a timepoint at which the active comparator, based on its known pharmacodynamic properties, would not be expected to be effective. The active comparator, ipratropium bromide, is indicated for use four times daily. Given the relatively long interval between the evening and the subsequent morning doses of ipratropium, little if any bronchodilator effect is likely to be detected on morning pre-dose spirometry. Nonetheless, the comparison between drugs at this timepoint may be clinically relevant, given that the ipratropium was dosed as labeled and used. However, for the purposes of NDA approval, the primary regulatory requirement is that the proposed drug be demonstrated to be superior to placebo. Therefore, for regulatory purposes the ipratropium arm may be considered analogous to placebo. In that case, superiority of tiotropium over ipratropium could be interpreted as evidence that tiotropium would be superior to placebo.

The primary efficacy variable was the trough FEV₁ response, defined as the mean change from baseline at the end of the dosing interval for tiotropium. It is important to note that the protocol did not state which specific treatment visit would serve as the primary efficacy endpoint. Nonetheless, tiotropium was demonstrated to be superior to ipratropium on this variable on all test days, with effect sizes of 0.11 to 0.18 liters.

Serial, post-dose spirometry was the basis for several secondary efficacy endpoints. It should be noted that, because the first post-dose spirometry was performed at 30 minutes, earlier bronchodilation due to ipratropium may have been missed. The product label for Atrovent (ipratropium bromide) Inhalation Aerosol indicates that in clinical studies significant improvements in FEV₁ (increases of 15% or more) occurred within 15 minutes.

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Following the first dose of study medication, there was no statistically significant difference between groups until Hour 4. At Hours 4, 5, and 6, on the first dosing day the mean FEV₁ in the tiotropium group was statistically superior to ipratropium with treatment differences ranging from 0.09 to 0.12 liters). On the remaining dosing days, tiotropium was statistically superior to ipratropium for mean FEV₁ at all timepoints (excepting 30 minutes and 1 hour on test days 8 and 50). Bronchodilator efficacy was also supported by morning and evening PEFr data throughout the treatment period (except Week 1 for morning PEFr). However, the use of rescue albuterol medication was not statistically different between the two groups.

Patient reported outcome assessments provided varying results. In regard to the symptom of dyspnea, the mean TDI focal score in the tiotropium group was statistically superior to ipratropium on all test days. However, the effect reached the Sponsor's proposed minimally important change value on only four of the six test days. None of the other patient reported outcome instruments (the SGRQ, the MOS SF-36, or the Energy Fatigue Questionnaire) suggested a benefit of tiotropium over ipratropium. Unlike Study 205.122A/205.126A, this study demonstrated significant differences between groups in regard to COPD exacerbations. The number of subjects with COPD exacerbation, the number of COPD exacerbations, and the number of COPD exacerbation days, all favored tiotropium over ipratropium. There were no differences between groups in the indices of hospitalizations due to COPD or the hospitalizations due to any cause.

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 205.122A/205.126A, 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 247 subjects were randomized and received at least one dose of study medication (tiotropium = 165, ipratropium = 82). Of these, 44 subjects discontinued study medication at 39 weeks because of expiry of the study drug (tiotropium = 31, ipratropium = 13) [U00-3114.pdf/p113]. The table below summarizes the duration of exposure, by treatment group.

Extent of Exposure, Study 205.122B/205.126B		[U00-3113.pdf/p117]	
	Tiotropium N (%)	Ipratropium N (%)	All N (%)
Total Treated	165 (100)	82 (100)	247 (100)
1	0 (0.0)	0 (0.0)	0 (0.0)
2-7	4 (2.4)	1 (1.2)	5 (2.0)
8-60	7 (4.2)	9 (11.0)	16 (6.5)
61-100	2 (1.2)	2 (2.4)	4 (1.6)
101-200	7 (4.2)	3 (3.7)	10 (4.0)

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Extent of Exposure, Study 205.122B/205.126B		[U00-3113.pdf/p117]	
	Tiotropium N (%)	Ipratropium N (%)	All N (%)
Total Treated	165 (100)	82 (100)	247 (100)
201-330	34 (20.6)	17 (20.7)	51 (20.6)
> 330	111 (67.3)	68 (70.1)	161 (65.2)
Mean (days)	365.0	364.0	364.0
Range (days)	3-388	5-380	3-388

The overall incidence of adverse events was similar in both treatment groups (tiotropium = 87.3%, ipratropium 87.8%) [U00-3114.pdf/p114]. The incidence of dry mouth was higher in the tiotropium group (5.5% vs. 0.0%), but these incidences were noticeably lower than those seen in Study 205.122A/205.126A (17.8% in the tiotropium group and 11.3% in the ipratropium group). The incidence of lower respiratory System Disorders was lower in the tiotropium group, due to fewer COPD exacerbations (33.9% vs. 50.0%). However the incidence of upper Respiratory System Disorders was higher in the tiotropium group, due to a greater incidence of upper respiratory tract infection (35.8% vs. 31.7%), rhinitis (3.0% vs. 0%), and sinusitis (4.8% vs. 2.4%). There was also a higher incidence of Urinary System Disorders in the tiotropium group, attributed to an increased incidence of urinary tract infection (3.6% vs. 1.2%). Common (incidence \geq 3%) adverse events occurring more frequently in the tiotropium group as compared to the placebo group were: upper respiratory tract infection (35.8% vs. 31.7%), headache (13.9% vs. 13.4%), influenza-like symptoms (12.1% vs. 11.0%), back pain (9.7% vs. 6.1%), pharyngitis (7.3% vs. 6.1%), chest pain (6.7% vs. 4.9%), abdominal pain (6.7% vs. 4.9%), mouth dry (5.5% vs. 0.0%), hypertension (5.5% vs. 3.7%), arthritis (5.5% vs. 3.7%), edema (dependent) (4.8% vs. 3.7%), pain (4.8% vs. 2.4%), sinusitis (4.8% vs. 2.4%), moniliasis (4.2% vs. 1.2%), dysphonia (4.2% vs. 1.2%), nausea (4.2% vs. 3.7%), diarrhea (4.2% vs. 3.7%), myalgia (3.6% vs. 2.4%), urinary tract infection (3.6% vs. 1.2%), and nervousness (3.0% vs. 0.0%) [U00-3114.pdf/p116-7].

The percentage of subjects experiencing serious adverse events (SAEs) was slightly lower in the tiotropium group (18.2%) than in the ipratropium group (24.4%) [U00-3114.pdf/p119].

The occurrence of discontinuation from the study due to adverse events was similar in the two groups (8.5% in the tiotropium group, and 13.4% in the ipratropium group) [U00-3114.pdf/p121].

There were 4 deaths in the study, all of which were in the tiotropium group [U00-3114.pdf/p118]. None of the deaths were considered by the investigator to be related to treatment. The deaths in the tiotropium group were due to: cardiorespiratory failure, meningitis, myocardial infarction, and multiple organ failure. Deaths occurring in patients treated with tiotropium are discussed further in the Integrated Review of Safety section of this Review.

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Clinical Review Section

Study 205.131

D. Supportive Study

1. **Study 205.131: "Effect of tiotropium on exercise tolerance and static and dynamic lung volumes in COPD patients (A randomized, double-blind, placebo-controlled, parallel group study). Oral inhalation once daily for 6 weeks from an inhalation capsule containing 18mcg tiotropium."**

The study report was submitted along with the 120-day Safety Update (April 18, 2002). The study was submitted in support of the proposed "dyspnea" claim. The protocol and study results will be briefly summarized below. The study report is located at [4/18/02; U02-1202.pdf/p1], and the protocol, with amendments, is located at [4/18/02; U02-1202.pdf/p472].

Reviewer's Note: The study report does not contain the results of the central analysis of the ECGs, which is currently underway [4/18/02; U02-1202.pdf/p43].

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