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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 (4.48 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 Transitional 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 Transitional 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

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Mean Transitional 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		
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
	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%).

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

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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		
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
	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.

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

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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	
	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

Pharmacoeconomic Variables

Pharmacoeconomic data included the number of patients hospitalized, the number of days spent in ICU, the number of days patients were able to do a majority of their usual daily activities, the number of days patients had unscheduled visits to a Physician, the number of days patients had unscheduled visits to an "other" healthcare provider, and the number of patients who changed their employment status by each visit. The study report does not describe the data, other than to state that it was "generally favorable for tiotropium" [U99-3169.pdf/p146]. The data are presented in tabular format in Appendix 15.9.2, using what is termed the "observed data set" [U99-3169a.pdf/p572-95]. These data were reviewed. In general, the two treatment groups were comparable on these endpoints. The percent of patients unable to perform normal daily activity on at least one day, by test day, was generally lower in the tiotropium group, particularly during the latter half of the treatment period. It is difficult to interpret this data because it is not clear how the "observed" data set was defined.

Pharmacokinetic Data

The pharmacokinetic (PK) data from this study will be reviewed in-depth, along with PK data from the remainder of the clinical program in a separate document by the Office of Clinical Pharmacology and Biopharmaceutics Reviewer. The following is a brief discussion of the PK data from this study. The pharmacokinetic report from this study is located in an appendix to the study report [U99-3169g.pdf/p617].

In a subset of patients, tiotropium concentrations were determined 5 minutes pre-dose, 5 minutes post-dose, and 2 hours post-dose, at Visits 5 (Day 50) and 7 (Day 92). Tiotropium excretion in urine was measured at Visits 4 (Day 29) and 6 (Day 71) in fractions 0-2hours pre-dosing, and 0-2hours post-dosing. Additionally, complete 24-hour urine fractions were measured at Visits 5, 7, and 9 (Day 175). Tiotropium was analyzed in the plasma and urine by a validated HPLC-MS/MS assay with limits of quantification of 2.46 and pg/ml tiotropium cation in plasma and 10.25 pg/mL in urine [U99-3169g.pdf/p622]. **Reviewer's Comment: Due to the timing of the samples, the PK results from this study primarily help to investigate the "steady state" period.**

Urinary excretion and/or plasma concentration data were available from 118 patients (75 male and 43 female) from ten clinical centers. The patients had a mean age of 63.8 years, a mean weight of 77.4kg, a mean FEV_1 of 1.17mL, and a mean predicted creatinine clearance of 78.5mL/min [U99-3169g.pdf/p631].

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Plasma tiotropium concentrations at Visit 5 (Day 50) were 5.61 pg/mL pre-dose, 17.3 pg/mL five minutes post-dose, and 8.72 pg/mL two hours post-dose [U99-3169g.pdf/p634]. At Visit 7 (Day 92), the plasma tiotropium concentrations were similar (6.36 pg/mL pre-dose, and 19.1 and 8.12 pg/mL five minutes and two hours after dosing, respectively). It should be noted that a high percentage of the pre-dose plasma samples had values below the limits of quantification (BLQ) (49% on Day 50 and 42% on Day 92). (The values listed above were calculated by omitting the BLQ values. The Applicant also calculated the plasma concentrations by replacing BLQ values 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 statistically 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 relatively small, but may be clinically meaningful, considering that it is a comparison at the end of the dosing interval. Three-hour serial spirometry performed on six test days throughout the 49-week trial 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.

Bronchodilator efficacy was supported by statistically significant improvements in 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 appeared to demonstrate that the effect size was maintained from Day 8, through the 49 week trial. Statistical superiority 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 appeared to provide 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 Clinical Briefing Document. 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 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].

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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)

Appendix:
Study 205.115/205.128

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

Appendix:
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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

Appendix:
Study 205.115/205.128

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

Appendix:
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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."

Appendix:
Study 205.115/205.128

Another symptomatic assessment was the Mahler Baseline and Transitional 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 Transitional Dyspnea Index Scores (Study 205.115/205.128, ITT data set) [U99-3170-01.pdf/p108]

Component	Test Day	Tiotropium		Placebo		Difference	P-value
		N	Mean	N	Mean		
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

Appendix:
Study 205.115/205.128

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 w*eek 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)

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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

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

Analysis of "Rebound"

Following the end of the treatment period, patients were followed for an additional 3 weeks. During this period patients recorded 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: The post-treatment pattern of decline in morning and evening PEFR, and increase in supplemental albuterol use did not suggest a "rebound" effect. In addition, analysis of the SGRQ, SF-36, COPD Symptoms, Physician's Global Evaluation, and the Energy Fatigue Questionnaire scores did not suggest a rebound effect [U99-3170-01.pdf/p.119-26].**

Pharmacoeconomic Variables

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

Pharmacokinetic Data

This study did not include pharmacokinetic assessments.

Reviewer's Comments on Efficacy

This study compared the effects of tiotropium bromide inhalation powder (18mcg, once daily) and placebo in 451 patients with COPD. Using a 2:1 randomization scheme, a total of 271 patients were assigned to active drug and 180 patients were assigned to placebo. Although the total treatment period was 49 weeks, the primary efficacy determination was made at 13 weeks. The study population was almost exclusively white (97%), with a mean smoking history of 59.3 pack-years, and a mean age of 65 years. The baseline FEV_1 was approximately 1 liter, or 45% of the predicted normal value.

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

(defined as the mean of two pre-dose values) increased from baseline by 0.13 liters in the tiotropium group and decreased by 0.01 liter in the placebo group (p=0.0001). This effect size is considered meaningful, particularly for an end-of-dosing-interval comparison. Three-hour serial spirometry performed on six test days throughout the 49-weeks of active treatment also demonstrated that tiotropium was statistically superior to placebo in terms of the trough, average, and peak FEV_1 responses. The Day 1 mean post-dose FEV_1 in the tiotropium group increased by ≤ 200ml (depending on how the baseline was defined). Customarily a change of ≥12% and ≥200ml is considered to be a clinically significant bronchodilator effect. Of note, the mean peak FEV_1 change from baseline exceeded 200ml on all test days. Study 205.114/205.117 revealed similar findings, suggesting that the time to peak response may differ among patients. A second observation, which was also seen in Study 205.114/205.117, is that the treatment effect was lower on Day 1 than on other test days, suggesting that multiple dosing is required to achieve optimum effect.

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

The results of various patient- and physician-reported outcome variables generally provided supportive evidence of efficacy. The table below divides the various non-spirometric variables into those for which statistical significance was demonstrated and those for which it was not. *Note that for many of these endpoints, the clinical significance of the effect size is not clear.*

Non-Spirometric Secondary Efficacy Variables (Study 205.115/205.128)	
Statistically Significant Benefit Demonstrated	Statistically Significant Benefit NOT Demonstrated
▪ Physician's Global Evaluation (all test days) ▪ Mahler TDI Focal Score (all test days)[a] ▪ COPD symptom[b]: Shortness of Breath (15/17 test days) ▪ COPD symptom[b]: Wheeze (9/17 test days) ▪ Total SGRQ score (all test days)[c] ▪ SGRQ "Impacts" domain score (all test days)	▪ Energy Fatigue Questionnaire ▪ COPD symptom[b]: Cough ▪ COPD symptom[b]: Tightness in Chest ▪ COPD Exacerbations (all analyses) ▪ Nocturnal Awakenings
[a]Effect size surpassed the Applicant's proposed threshold for minimal clinically important change at 9 and 12 months only. [b]Assessed by the Investigator [c]Effect size did surpassed the accepted threshold for minimal clinically important change at 6 and 12 months only.	

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

d. Safety Review

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

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

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

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

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

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

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

Appendix:
Study 205.130

8.

Six-Month Placebo- and Active-Controlled Studies

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

a. Study Description

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

Study Design

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

Duration

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

Study Centers

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

Study Population

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

Materials

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

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

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The commercially approved product (Serevent® Inhalation Aerosol) was used for the salmeterol clinical supplies [Submission date4/12/02, p9-11]. For blinding purposes, the commercially available product (canister + acutator) was fitted into a blinding device housing. The same housing device was used for all clinical supplies in the study. The Applicant states that, at the time of development, the blinding devices were evaluated to determine if they had any impact on the delivered dose, aerodynamic fine particle dose, weight loss, and valve delivery. The Applicant claims that these tests indicated that the housing device had no effect on these performance characteristics. Such testing was not performed on the actual clinical supplies for this study. The placebo MDIs were manufactured at Boehringer Ingelheim Pharma KG, Germany.

Objectives

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

Inclusion Criteria

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

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

Exclusion Criteria

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

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

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- Current or recent (6 weeks) participation in pulmonary rehabilitation program
- Known symptomatic prostatic hypertrophy or bladder neck obstruction
- Known narrow angle glaucoma
- Current use of cromolyn sodium, nedocromil sodium, or H_1 receptor antagonists
- Current use of oral corticosteroids at unstable doses (< 6 weeks on a stable dose) or at doses in excess of the equivalent of 10mg of prednisolone per day or 20mg of every other day
- History of asthma

Conduct

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

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

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

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

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

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

The table below summarizes the study procedures.

Study Procedures, Study 205.130 [U01-1236-1.pdf/p283]

Visit #:	1	2	3	4	5	6	7	8	9	10
Weeks:		0	2	4	8	12	16	20	24	+3
Day:	-14	1	15	29	57	85	113	141	169	+21
Physical Examination	X								X	
Vital Signs (seated)	X	X	X		X		X		X	
Laboratory Tests (fasting)	X								X	
12-lead ECG	X								X	
Theophylline level[1]	X	X	X		X		X		X	
Issue Diary Cards	X	X	X	X	X	X	X	X	X	
Collect Diary Cards		X	X	X	X	X	X	X	X	X
Dispense Drugs		X		X	X	X	X	X		
PFTs (FEV_1 and FVC)[2]	X	X	X		X		X		X	
Shuttle walking test		X			X		X		X	X
Quality of Life		X			X		X		X	X
Mahler Dyspnea Index (BDI or TDI, as appropriate)		X			X		X		X	X
Patient Preference Questionnaire		X							X	
Health Resource Utilization		X	X	X	X	X	X	X	X	X
Review of PEFR Records		X	X	X	X	X	X	X	X	X
COPD Symptom Scores		X	X	X	X	X	X	X	X	X
Global Evaluations		X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Concomitant Therapy		X	X	X	X	X	X	X	X	X

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

Concomitant Medications

Albuterol inhalation aerosol was provided for as-needed use.

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

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

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

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

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

Data Analysis

Efficacy Endpoints

The final protocol dated 9/14/98 indicated that the primary efficacy endpoint would be the trough FEV_1 response at the end of the six month study [U01-1236-1.pdf/p291]. Trough response was defined as the mean change from baseline at the end of the dosing interval (24 hours post dosing for tiotropium and 12 hours post dosing for salmeterol). Baseline was defined as the mean of two pre-treatment measurements at Visit 2, which was the day of the first dose of study medication.

The protocol amendment changed the primary efficacy endpoints to the trough FEV_1 response, AND the focal score from the Mahler Transitional Dyspnea Index (TDI) at the end of the six-month study (co-primary endpoints) [U01-1236-1.pdf/p380]. The focal score is the sum of the three components of the transitional dyspnea index, functional impairment, magnitude of task, and magnitude of effort. The superiority of tiotropium over placebo for trough FEV_1 response was to be established first, then the TDI scores would be compared.

Secondary efficacy variables were:

- Mahler Transitional Dyspnea (TDI) (focal score) on other test days
- Average and peak FEV_1 response on each test day
- Trough, average and peak FVC measured at the same times as FEV_1 on each test day
- Individual FEV_1 and FVC measurements at each time point

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

Statistical Model

The statistical model for the FEV_1 comparison was an analysis of covariance, with terms for treatment and center and baseline FEV_1 [U01-1236-1.pdf/p381]. The statistical model for the TDI comparison was logistic regression with terms for treatment, center, and BDI focal score. Both analyses were to include all three treatment groups. Centers with less than 12 evaluable patients were pooled.

The statistical model was changed in the protocol amendment [U01-1236-1.pdf/p381]. The hypotheses were tested in a stepwise manner. First, the superiority of tiotropium over placebo in trough FEV_1 was to be established. The null hypothesis is that there is no difference in the mean trough FEV_1 response between tiotropium and placebo. The alternative hypothesis is that the mean trough FEV_1 response is greater than placebo (two-tailed test at 0.05 level of significance).

If the superiority of tiotropium over placebo in trough FEV_1 response is established, the two treatment groups will be compared in TDI focal score. The null hypothesis is that there is no difference in proportion of patients with TDI focal score greater than or equal to 1 unit between tiotropium and placebo. The alternative hypothesis is that the proportion of patients with TDI focal score greater than or equal to 1 unit is different in those treated with tiotropium compared to those treated with placebo (two-tailed test at 0.05 level of significance).

The protocol amendment also stipulated a secondary comparison for non-inferiority of tiotropium versus salmeterol in trough FEV_1. The null hypothesis for this comparison is that the mean trough FEV_1 response for tiotropium is inferior to the mean trough FEV_1 response for salmeterol by at least 50 ml after 24 weeks of treatment. The alternative hypothesis is that the mean trough FEV_1 response for tiotropium is not 50 ml less than the mean trough FEV_1 response for salmeterol.

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If non-inferiority of tiotropium in comparison with salmeterol is established, the following superiority test of tiotropium will be performed with no penalty for multiple comparison. The null hypothesis for this comparison is that the trough FEV_1 response for tiotropium is less than or equal to the mean trough FEV_1 response for salmeterol. The alternative hypothesis is that the mean trough FEV_1 response for tiotropium is greater than the mean trough FEV_1 response for salmeterol (one-tailed test at 0.025 level of significance).

Reviewer's Comment: Emphasis on a direct comparison between tiotropium and salmeterol on trough FEV_1 would be inappropriate in comparing the overall efficacy of these two drugs. Superiority on this endpoint would primarily reflect differences in pharmacodynamics.

Missing Data

All randomized patients with at least baseline (pre-treatment at Visit 2) and trough FEV_1 after 2 weeks of randomized treatment were used for the efficacy analysis. If a patient discontinued the study early due to unexpected worsening of the disease under study, the missing data were estimated by the least favorable data observed prior to discontinuation. The missing data for patients who miss a visit due to other reasons were estimated by their last observed data. Linear interpolation between the two adjacent measurements was used to estimate random, middle, missing spirometry measurements. For values at the end of the serial spirometry that are missing because rescue medication was taken, the minimum observed FEV_1 value on that test day (even if it is pre-dose) was used as the estimate. The last available value was used as the estimate for data that were missing for reasons unrelated to the patient's response to treatment.

Sample Size

The final protocol indicated that a sample of 450 patients (150 per treatment group) would detect a 0.065 liters difference in mean trough FEV_1 response between tiotropium and salmeterol at 5% level of significance with at least 80% power using a two-tailed t-test. This calculation was based on the assumption of a standard deviation for trough FEV_1 of 0.20 liters. **Reviewer's Note: The original power calculations focused on the comparison of tiotropium to salmeterol. The protocol was subsequently amended to establish the primary comparison as that of tiotropium versus placebo and to add the co-primary TDI comparison.** The protocol amendment indicated that, while still blinded, approximately 170 patients per group were actually randomized [U01-1236-1.pdf/p384]. As discussed above, the amendment specified a (co-) primary analysis of the TDI. A sample size of 170 per group was determined to have a 80% power to detect the same magnitude of difference between tiotropium and placebo that was seen in the prior studies (50% increase over placebo, combined data), at a 5% level of significance [U01-1236-1.pdf/p70 and 384].

b. Patient Disposition

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

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

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

The mean age of the patients in this study was 64.9 years [U01-1236-1.pdf/p77]. The majority (74.6%) were men, and 99.5% were caucasian. The mean FEV_1 was 1.08 L (mean 38% of predicted). As shown in the table below, the baseline features were comparable across treatment groups.

Demographics and Baseline Characteristics, Study 205.130				[U01-1236-1.pdf/p78-9]
	Tiotropium N (%)	Salmeterol N (%)	Placebo N (%)	Total N (%)
Total Treated	209	213	201	623
Sex				
Male (%)	154 (73.7)	160 (75.1)	151 (75.1)	465 (74.6)
Race				
White	209 (100)	213 (100)	198 (98.5)	620 (99.5)
Black	0 (0.0)	0 (0.0)	2 (1)	2 (0.3)
Asian	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)
Age				
Mean	64.5	64.6	65.6	64.9
Range	45 – 84	43 – 82	41 – 83	41 - 84
Smoking History (pack years)				
Mean	46. 89	48.29	45.54	46.93
Range	10 - 170	10 – 160	10 – 132	10 - 170
Duration of COPD (years)				
Mean	9.2	10.4	9.7	9.8
Range	0 – 53	0 – 49	0 – 44	0 - 53
Screening FEV_1 (L)				
Mean	1.11	1.07	1.06	1.08
Range	0.33 – 2.05	0.26 – 2.23	0.44 – 2.14	0.26 – 2.23
FEV_1/FVC x 100				
Mean	43.64	42.02	41.32	42.34
Range	22.0 – 69.3	22.4 – 68.4	22.6 – 64.1	22.0 – 69.3

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

c. Efficacy Review

Data Sets Analyzed

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

For the analysis of spirometry data, all randomized patients with baseline (pre-treatment on test day 1 [Visit 2]) and trough FEV_1on test-day 15 (Visit 3) after 2 weeks of randomized treatment were included in the ITT data set. Additionally, the Applicant states that the protocol amendment specified that analysis of the "per-protocol" population for the co-primary endpoint of trough FEV_1 response on Day 169 would exclude subjects who deviated from the protocol in such a manner as to potentially obscure the trough FEV_1 response to treatment [U01-1236-1.pdf/p75]. Note: this Reviewer could not locate this plan in the protocol amendment. The "per-protocol" analyses will not be discussed in this Clinical Briefing Document.

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

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

Number of subjects in various data sets (Study 205.130) [U01-1236-1.pdf/p77]

Data Set	Tiotropium	Salmeterol	Placebo	Total
Safety	209	213	201	623
TDI ITT	184	179	148*	511
PFT ITT	202	203	179	584

Primary Endpoints

The two co-primary endpoints were the trough FEV_1 response and the TDI focal score, both evaluated on test-day 169 (Week 24) of randomized treatment. These were analyzed in a step-wise fashion. The primary comparison was tiotropium versus placebo. The numbers of patients included in the analyses of these two endpoints are provided in the table above.

Appendix:
Study 205.130

Reviewer's Note: In regard to the composition of the ITT data sets, the protocol stated that all randomized patients with at least baseline and trough FEV_1 after two weeks of treatment would be used for the efficacy analysis [U01-1236-1.pdf/p322]. (This was not altered in the protocol amendment). The study report states that the determination of the ITT populations (i.e. the definitions of "adequate" post-treatment data and "other exclusions from the ITT data set") were made at a blinded report planning meeting, which occurred after the completion of the study and prior to "opening of the treatment codes" [U01-1236-1.pdf/p76]. As shown in the table above, considerable numbers of randomized subjects were excluded from the ITT data sets. For example, the ITT data set used to analyze the TDI co-primary endpoint included only 511 of the 623 randomized subjects. The placebo group for this comparison included only 148 of the 201 randomized subjects. This issue was discussed with the Biometrics Reviewer (Dr. Gebert). The decreased size of the ITT population was due to subjects who dropped out prior to Day 57 (the first day the TDI was administered) or for whom there was insufficient data to calculate the BDI or TDI focal scores. Thus, further analyses using the ITT as defined in the protocol would not be possible.

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

Tiotropium was statistically superior to placebo for the trough FEV_1 on test-day 169 ($p<0.001$) [U01-1236-1.pdf/p92]. The magnitude of the effect size (0.14 liters) is considered clinically significant.

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

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

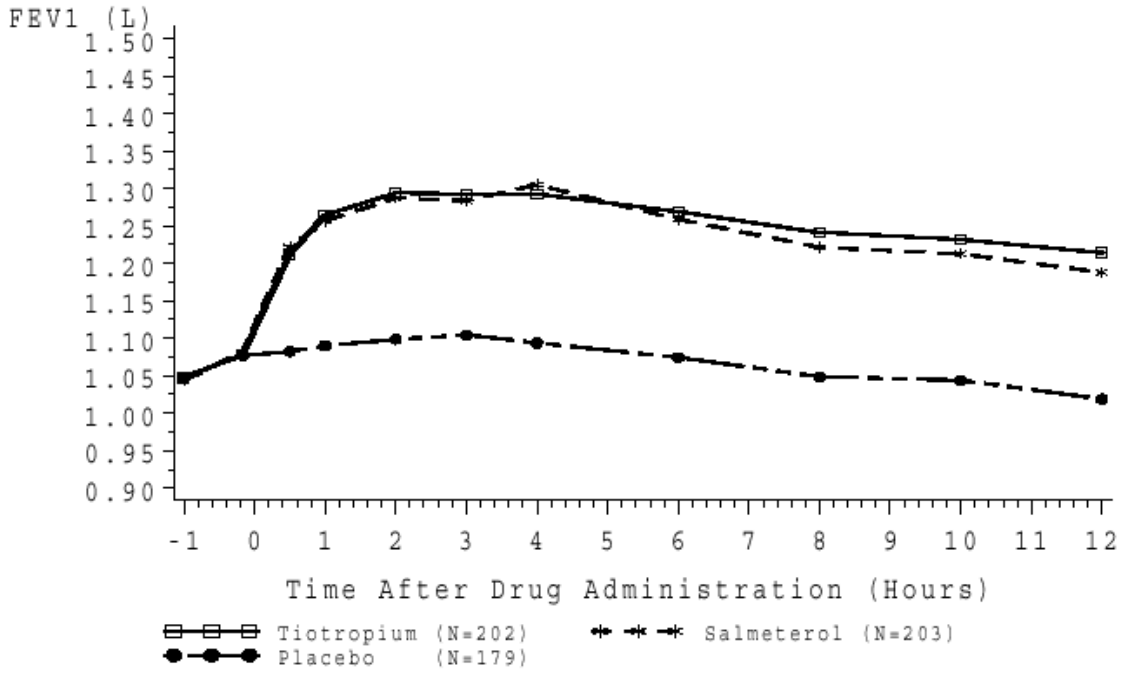
group. The adequacy of the justifications of both the definition of clinical response (i.e. ≥1 unit) and the significance of the observed effect size are be discussed in the Integrated Review of Efficacy section of this Clinical Briefing Document.

Secondary Endpoints

Pulmonary Function Endpoints

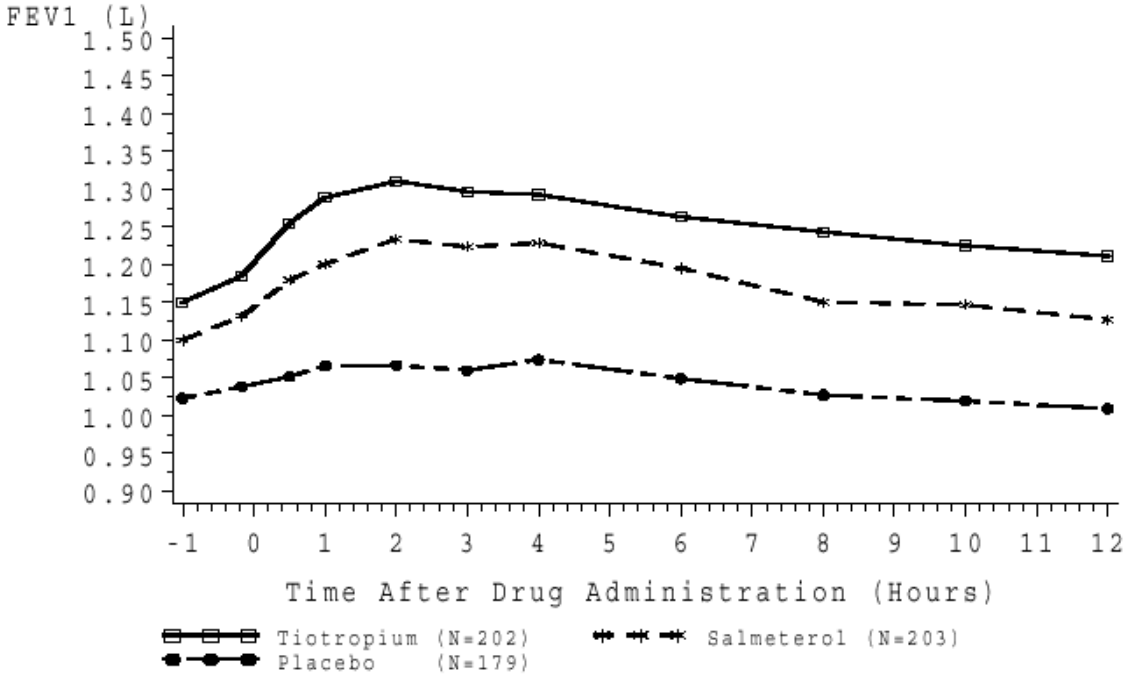
Serial spirometry was performed on the first day of dosing, and after 2, 8, 16, and 24 weeks of treatment. Measures were made 60 minutes and 10 minutes prior to dosing, and 30 minutes, 60 minutes, and 2, 3, 4, 6, 8, 10, and 12 hours after dosing. *The mean FEV_1 was statistically superior to placebo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

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



Appendix:
Study 205.130

Mean FEV_1, Week 24 (ITT data set, Study 205.130) [U01-1236-1.pdf/p86]



The trough FEV_1 response in the tiotropium group was statistically superior to placebo on all test days ($p<0.001$; absolute difference = 0.14 – 0.15L) and was statistically superior to salmeterol ($p<0.05$; absolute difference 0.03 – 0.05L) on all test days except Week 2 [U01-1236-1.pdf/p93]. Note that the absolute difference between tiotropium and salmeterol, while statistically significant, is quite small.

The average FEV_1 response over the 12-hour post-dosing period in the tiotropium group was also statistically superior to placebo at each test day. The difference between tiotropium and placebo was 0.19L on the first treatment day, and ranged from 0.21 – 0.23L during the remainder of the treatment period [U01-1236-1.pdf/p98]. Tiotropium was not superior to salmeterol on this endpoint on the first treatment day. On subsequent days, although tiotropium was statistically superior to salmeterol on this endpoint ($p<0.001$), the magnitude of the difference was small (0.06 – 0.08L) [U01-1236-1.pdf/p98].

The peak FEV_1 response over the 12-hour post-dosing period in the tiotropium group was statistically superior to placebo on all test days. The mean peak FEV_1 response in the tiotropium group on test day 1 was 0.31 liters. The difference between tiotropium and placebo was 0.19L

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

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

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

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

Patient Reported Outcomes

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

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

Appendix:
Study 205.130

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

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

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

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

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

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

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

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

COPD Exacerbations and Hospitalizations

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

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

Other Secondary Endpoints

Appendix:
Study 205.130

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

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

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

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

Appendix:
Study 205.130

Analysis of Washout Period

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

Pharmacokinetic Data

This study did not include pharmacokinetic assessments.

Reviewer's Comments on Efficacy

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

The amended protocol established two co-primary endpoints, the trough FEV_1 response and the TDI focal score, both evaluated on test day 169 (Week 24). Tiotropium was statistically and clinically superior to placebo on the trough FEV_1 endpoint ($p<0.001$; effect size 0.14 liters). The trough FEV_1 endpoint helps to establish the duration of action of tiotropium. However, the threshold for a "clinically relevant" effect at the trough timepoint is not as well established as for the peak timepoint. At peak, one might consider a change of 12% (and at least 200ml) to be clinically relevant. The effect size seen in this study in regard to the trough FEV_1 is less than that, but is still considered to be clinically relevant. One further point regarding the trough FEV_1 endpoint is that comparisons to other drugs based on this endpoint would not be wholly appropriate. Differences on this endpoint may reflect differences in pharmacodynamic profiles, and miss other, perhaps more relevant performance characteristics.

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

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

The secondary endpoints generally support the efficacy of tiotropium as a bronchodilator. Secondary endpoints for which tiotropium was statistically superior to placebo included: individual FEV_1 and FVC measurements on all test days; morning and evening PEFR; TDI "responder analyses" at Weeks 8 and 16; physician's assessment of COPD symptoms of wheezing, shortness of breath, and tightness of chest (but not coughing); physician's global evaluation; COPD exacerbations (number of events and number of event days, but not number of subjects with at least one exacerbation); and rescue medication. It must be noted that the clinical significance of the observed effects on some of these endpoints is not clear. Secondary endpoints that did not establish superiority of tiotropium over placebo include the SGRQ (for which the differences between tiotropium and placebo did not reach the minimal threshold representing a clinically meaningful change); patient satisfaction questionnaire; shuttle walk test/ Borg Dyspnea scale; and hospitalizations for COPD exacerbation.

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

d. Safety Review

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

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

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

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

Appendix:
Study 205.130

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

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

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

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

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

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

a. Study Description

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

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

b. Patient Disposition

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

Patient Disposition and Reasons for Withdrawal, Study 205.137 [U01-1231-1.pdf/p75]

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

Appendix:
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Patient Disposition and Reasons for Withdrawal, Study 205.137				[U01-1231-1.pdf/p75]
	Tiotropium	Salmeterol	Placebo	Total
Administrative	15 (7.8%)	8 (4.2%)	13 (6.5%)	36 (6.2%)
Non-compliant with Protocol	10 (5.2%)	2 (1.0%)	3 (1.5%)	15 (2.6%)
Lost to Follow-up	0 (0.0%)	1 (0.5%)	2 (1.0%)	3 (0.5%)
Consent Withdrawn	5 (2.6%)	5 (2.6%)	8 (4.0)%	18 (3.1%)
Other	4 (2.1%)	1 (0.5%)	6 (3.0%)	11 (1.9%)

The mean age of the patients in this study was 63.4 years [U01-1231-1.pdf/p78]. The majority (77.9%) were men, and 99.5% were caucasian. The mean FEV_1 was 1.11 L (mean 39% of predicted). As shown in the table below, the baseline features were comparable across treatment groups.

Demographics and Baseline Characteristics, Study 205.137				[U01-1231-1.pdf/p79-80]
	Tiotropium N (%)	Salmeterol N (%)	Placebo N (%)	Total N (%)
Total Treated	193	192	199	584
Sex				
Male (%)	157 (81.3)	144 (75.0)	154 (77.4)	455 (77.9)
Race				
White	191 (99.0)	192 (100)	198 (99.5)	581 (99.5)
Black	2 (1.0)	0 (0.0)	0 (0.0)	2 (0.3)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Age				
Mean	63.0	63.5	63.7	63.4
Range	41 – 80	42 – 81	39 – 87	39 - 87
Smoking History (pack years)				
Mean	41.09	40.82	39.16	40.34
Range	10 - 144	10 – 147	10 – 126	10 - 147
Duration of COPD (years)				
Mean	8.9	9.4	9.9	9.4
Range	0 - 36	0 - 40	0 - 45	0 - 45
Screening FEV_1 (L)				
Mean	1.14	1.06	1.13	1.11
Range	0.37 – 2.51	0.35 – 2.06	0.37 – 2.30	0.35 – 2.51
FEV_1/FVC x 100				
Mean	43.67	42.30	43.19	43.05
Range	13.7 – 67.3	21.9 – 67.5	21.1 – 67.5	13.7 – 67.5

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

c. Efficacy Review

Data Sets Analyzed

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

decisions regarding the adequacy of the post-treatment data "as well as other exclusions from the ITT data set" were determined at a blinded "report planning meeting" prior to opening of the treatment codes. For the analysis of the spirometry data, all randomized subjects with baseline (pre-treatment on test day 1) and trough FEV_1 on test-day 15 after 2 weeks of randomized treatment were included in the ITT data set. An additional "per-protocol" data set was also analyzed. The per-protocol analyses will not be discussed in this document.

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

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

Primary Endpoint

The two co-primary endpoints were the trough FEV_1 response and the TDI focal score, both evaluated on test-day 169 (Week 24) of randomized treatment. These were analyzed in a step-wise fashion. The primary comparison was tiotropium versus placebo. The numbers of patients included in the analyses of these two endpoints are provided in the table above.

> **Reviewer's Note: In regard to the composition of the ITT data sets, the protocol stated that all randomized patients with at least baseline and trough FEV_1 after two weeks of treatment would be used for the efficacy analysis [U01-1231-1.pdf/p307]. (This was not altered in the protocol amendment). The study report states that the determination of the ITT populations (i.e. the definitions of "adequate" post-treatment data and "other exclusions from the ITT data set") were made at a blinded report planning meeting, which occurred after the completion of the study and prior to "opening of the treatment codes" [U01-1231-1.pdf/p77]. As shown in the table above, considerable numbers of randomized subjects were excluded from the TDI ITT data set. This issue was discussed with the Biometrics Reviewer (Dr. Gebert). The decreased size of the ITT population was due to subjects who dropped out prior to Day 57 (the first day the TDI was administered) or for whom there was insufficient data to calculate the BDI or TDI focal scores. Thus, further analyses using the ITT as defined in the protocol would not be possible.**

Tiotropium was statistically superior to placebo for the trough FEV_1 on test-day 169 ($p<0.001$) [U01-1231-1.pdf/p92]. The magnitude of the effect size (0.11 liters) is considered clinically significant.

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

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

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

Secondary Endpoints

Pulmonary Function Endpoints

Serial spirometry was performed on the first day of dosing, and after 2, 8, 16, and 24 weeks of treatment. Measures were made 60 minutes and 10 minutes prior to dosing, and 30 minutes, 1, 2, and 3 hours after dosing. *The mean FEV_1 was statistically superior to placebo at all individual timepoints on all test days ($p<0.001$) [U01-1231-1.pdf/p83].* The mean FEV_1 for tiotropium and salmeterol were not statistically different at any timepoint on any test day except Day 169 (and 1-hour post dose on test day 15). On test day 169, the mean FEV_1 in the tiotropium group was statistically superior to that of the salmeterol group at 1, 2, and 3 hours ($p<0.05$), but the absolute difference was only 0.04 to 0.06 liters [U01-1231-1.pdf/p91]. The figures below illustrate the mean FEV_1 at Day 1 and Week 24.

Appendix:
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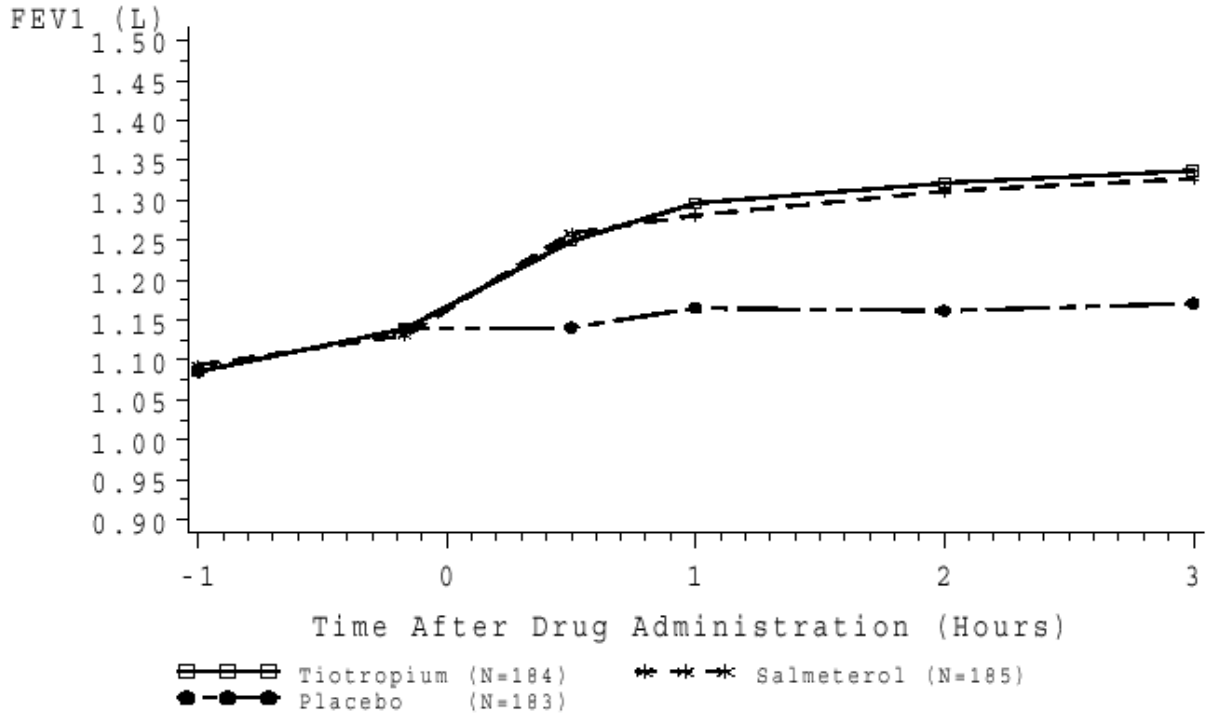
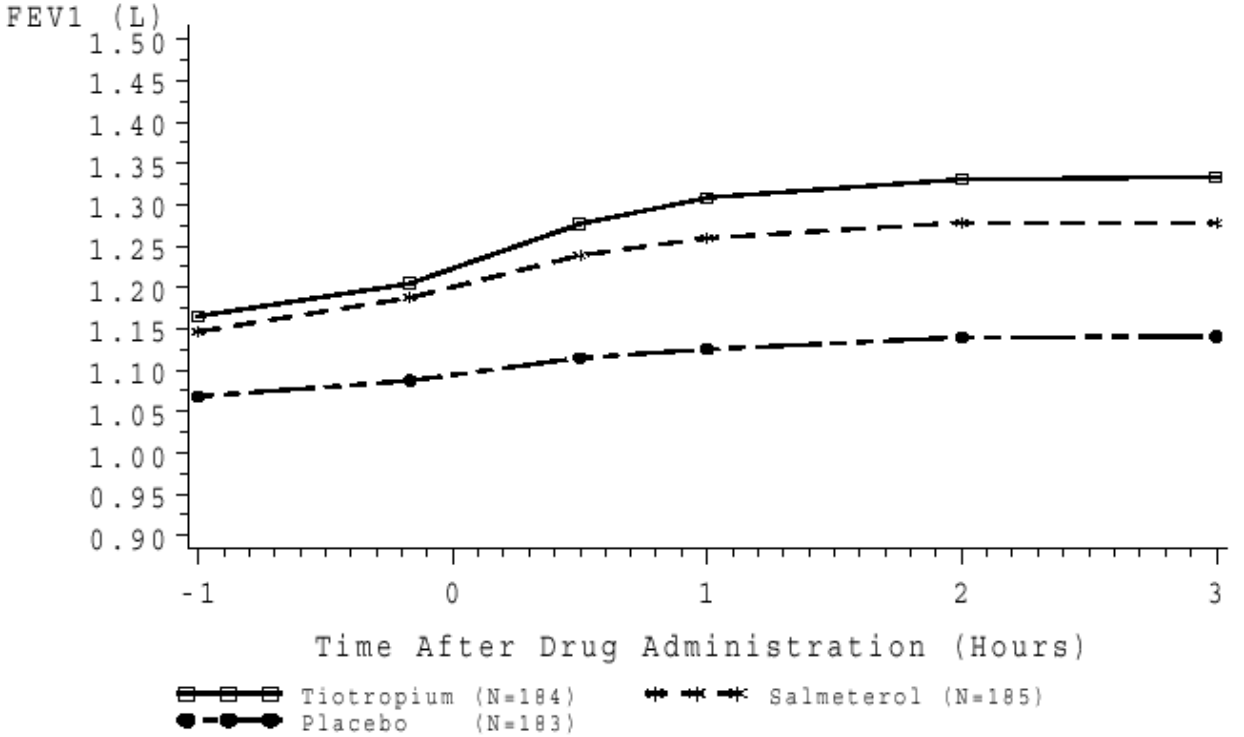
Mean FEV_1, Day 1 (ITT data set, Study 205.137) [U01-1231-1.pdf/p84]



Mean FEV_1, Week 24 (ITT data set, Study 205.137) [U01-1231-1.pdf/p88]



Appendix:
Study 205.137

The trough FEV_1 response in the tiotropium group was statistically superior to placebo on all test days ($p<0.001$; absolute difference = 0.11 – 0.12L). The difference between tiotropium and salmeterol was not significant on any test day [U01-1231-1.pdf/p94].

The average FEV_1 response over the 3-hour post-dosing period in the tiotropium group was also statistically superior to placebo at each test day ($p<0.001$). The difference between tiotropium and placebo was 0.13L on the first treatment day, and ranged from 0.18 – 0.20L during the remainder of the treatment period [U01-1231-1.pdf/p98]. Tiotropium was not statistically superior to salmeterol on any test day except Day 169 ($p=0.0436$, absolute difference 0.05 L) [U01-1231-1.pdf/p98].

The peak FEV_1 response over the 3-hour post-dosing period in the tiotropium group was statistically superior to placebo on all test days ($p<0.001$). The difference between tiotropium and placebo was 0.16L on the first treatment day (0.27L greater than baseline) and ranged from 0.19 to 0.21L during the remainder of the treatment period (0.27 – 0.30 L greater than baseline) [U01-1231-1.pdf/p96]. Tiotropium was statistically superior to salmeterol on this endpoint only on test days 15 and 169 ($p<0.05$, absolute difference 0.05L and 0.07L, respectively) [U01-1231-1.pdf/p96].

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

Subjects measured their PEFR twice daily and recorded the values in their diaries. The mean morning PEFRs during the baseline period were similar among the treatment groups [U01-1231-1.pdf/p123]. The daily morning PEFR (averaged weekly) in the tiotropium group was statistically superior to placebo throughout the treatment period ($p\leq0.01$) [U01-1231-1.pdf/p125-6]. The difference between tiotropium and placebo ranged from 14.9 L/min (during Week 1) and 21 L/min. The difference between tiotropium and salmeterol was not statistically significant at any treatment week.

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

Patient Reported Outcomes

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

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

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

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

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

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

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

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

Appendix:
Study 205.137

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

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

COPD Exacerbations and Hospitalizations

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

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

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

Other Secondary Endpoints

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

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

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

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

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

Analysis of Washout Period

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

Pharmacokinetic Data

This study did not include assessments of pharmacokinetic parameters.

Reviewer's Comments on Efficacy

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

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

The amended protocol established two co-primary endpoints, the trough FEV_1 response and the TDI focal score, both evaluated on test day 169 (Week 24). Tiotropium was statistically and clinically superior to placebo on the trough FEV_1 endpoint ($p<0.001$, effect size 0.11 liters). The trough FEV_1 endpoint helps to establish the duration of action of tiotropium. However, the threshold for a "clinically relevant" effect at the trough timepoint is not as well established as for the peak timepoint. At peak, one might consider a change of 12% (and at least 200ml) to be clinically relevant. The effect size seen in this study in regard to the trough FEV_1 is less than that, but is still considered to be clinically relevant. One further point regarding the trough FEV_1 endpoint is that comparisons to other drugs based on this endpoint would not be wholly appropriate. Differences on this endpoint may reflect differences in pharmacodynamic profiles, and miss other, perhaps more relevant performance characteristics.

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

The secondary endpoints generally support the efficacy of tiotropium as a bronchodilator. Secondary endpoints for which tiotropium was statistically superior to placebo included: individual FEV_1 and FVC measurements on all test days; morning and evening PEFR; TDI "responder analyses" at Weeks 8 and 16 and analyses of mean TDI focal scores at Weeks 8, 16, and 24; physician's assessment of COPD symptoms of shortness of breath (most test days) (but not consistently for coughing, wheezing, and tightness of chest); and physician's global evaluation (except Week 24). It must be noted that the clinical significance of the observed effects on some of these endpoints is not clear. Secondary endpoints that did not establish superiority of tiotropium over placebo include the SGRQ (for which the differences between tiotropium and placebo, where statistically significant, did not reach the minimal threshold representing a clinically meaningful change); all analyses of COPD exacerbations, patient satisfaction questionnaire; shuttle walk test/ Borg Dyspnea scale; rescue medication; and hospitalizations for COPD exacerbation.

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

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 ≥ 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%),

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.

Appendix:
Study 205.122A/205.126A

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

[1]subjects used a single Handihaler device throughout the study period [U00-3113.pdf/p216]
[2]between 8AM and 10AM
[3]8:00-10:00 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.

Appendix:
Study 205.122A/205.126A

Efficacy Variables

The primary efficacy variable was the trough FEV_1 response, defined as the mean change from baseline at the end of the dosing interval. Both the baseline FEV_1 and the trough FEV_1 were calculated as the mean of the two pre-treatment FEV_1 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:

- FEV_1 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 FEV_1.
- Individual FEV_1 and FVC measurements at each timepoint.
- PEFR 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 PEFR 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 screeing 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:

- $FEV_1 \leq 65\%$ of predicted and $FEV_1 \leq 70\%$ of FVC
- Age $\geq$ 40 years
- Smoking history > 10 pack-years

Appendix:
Study 205.122A/205.126A

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

Appendix:
Study 205.122A/205.126A

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

[1]Theophylline levels on all patients at Visit 1 and only on patients taking theophylline at subsequent test day visits
[2] prn albuterol MDI
[3]7-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

[1]Theophylline levels only on patients taking theophylline
[2]4-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].

Appendix:
Study 205.122A/205.126A

The following medications were allowed if stabilized for at least 6 weeks prior to and throughout the study period: oral corticosteroids (doses ≤ 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 FEV_1 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 FEV_1 (AUC_{0-6}) response for the six hours post-dose; FVC response at trough and Average FVC (AUC_{0-6}) 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 FEV_1 for that day when values are missing because of rescue medication use) [U00-3113.pdf/p234].

Appendix:
Study 205.122A/205.126A

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 FEV_1 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 FEV_1 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)

Appendix:
Study 205.122A/205.126A

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.

Appendix:
Study 205.122A/205.126A

Primary Endpoint

The primary efficacy variable was the trough FEV_1 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 FEV_1 (Visit 2) and trough FEV_1 (subsequent visits) were calculated as the mean of two pre-treatment FEV_1 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 FEV_1 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.

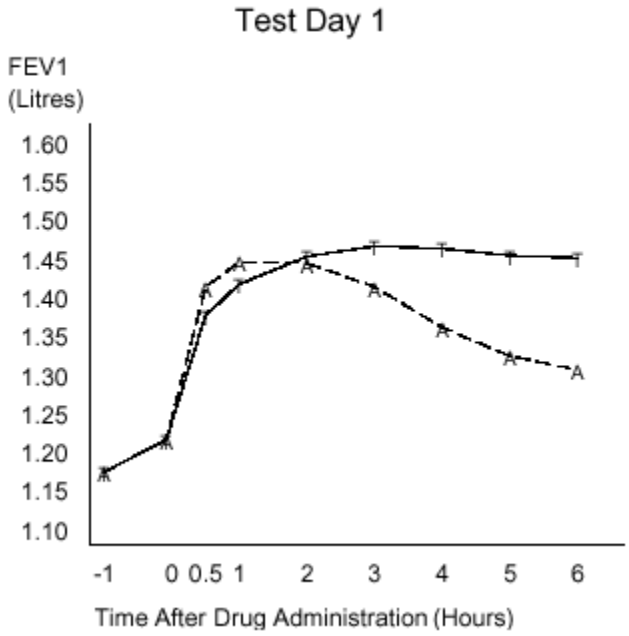
Secondary Endpoints

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 FEV_1 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 FEV_1, 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 FEV_1 data following the first dose.

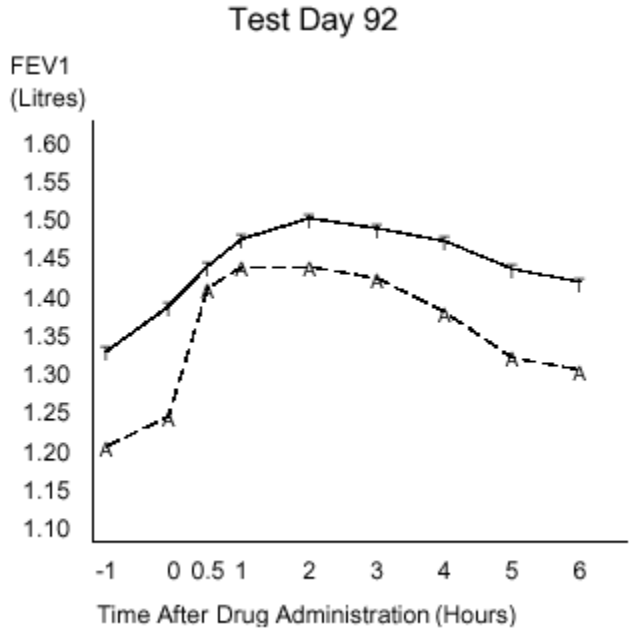
Appendix:
Study 205.122A/205.126A



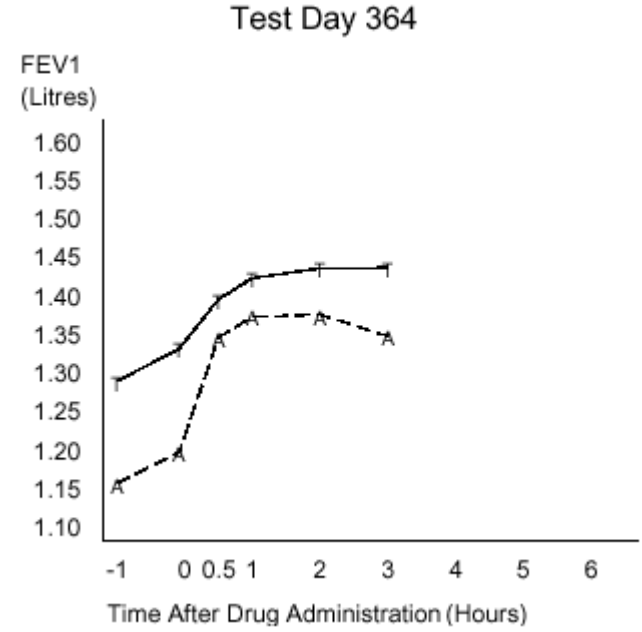
[T= tiotropium A=ipratropium Source: U00-3113.pdf/p66]

From Day 8 onward, the two pre-dose mean FEV_1 (- 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 FEV_1 was not statistically different between groups at the 30 minute and 1 hour timepoints. Tiotropium was, in general, statistically superior to ipratropium on FEV_1 measures beyond one hour. The figures below illustrate the serial FEV_1 values on test day 92 (Week 13), and test day 364 (Week 52).

Appendix:
Study 205.122A/205.126A



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



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

Tiotropium was statistically superior to ipratropium for the average (0-3hour) FEV_1 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) FEV_1 response on days 8, 50, 182, and 273, but not on days 1, 92, or 364.

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).

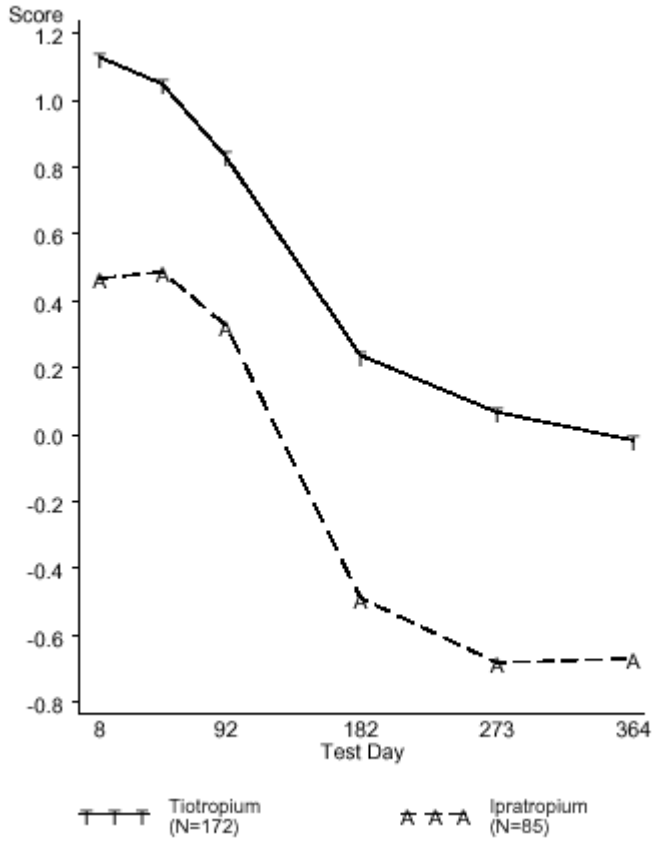
The mean evening PEFR during the baseline period was higher for the tiotropium group (264.91 vs. 255.33 liters/min) [U00-3113.pdf/p85]. The evening PEFR data is expressed as the mean values of weekly means for each week of treatment [U00-3113.pdf/p87-8]. Tiotropium was statistically superior to ipratropium 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 Transitional 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.

Appendix:
Study 205.122A/205.126A

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

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 a 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

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 FEV_1 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 FEV_1 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 FEV_1 (increases of 15% or more) occurred within 15 minutes.

Appendix:
Study 205.122A/205.126A

Following the first dose of study medication, *ipratropium* was statistically superior to tiotropium for FEV_1 at 30 minutes. On most test days the two groups were not statistically different at 30minutes or 1 hour post dose. However, tiotropium was superior to ipratropium for FEV_1 beyond 1 hour on most test days, and tiotropium was superior on the FEV_1 $AUC_{0\text{-}3hours}$ 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)

Appendix:
Study 205.122A/205.126A

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 ≥ 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.

Appendix:
Study 205.122B/205.126B

2. Study 205.122B/205.126B: :"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 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%)

Appendix:
Study 205.122B/205.126B

Subject Disposition and Reasons for Withdrawal, Study 205.122B/126B		[U00-3114.pdf/p54]
	Tiotropium	Ipratropium
Other	3 (1.8%)	2 (2.4%)

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 FEV_1 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 FEV_1 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 FEV_1 (Visit 2) and trough FEV_1 (subsequent visits) were calculated as the mean of two pre-treatment

Appendix:
Study 205.122B/205.126B

FEV_1 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*.

The baseline mean FEV_1 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 FEV_1 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.

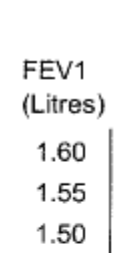
Secondary Endpoints

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 FEV_1 until Hour 4. [U00-3114.pdf/p63] On that day, the mean FEV_1 in the tiotropium group was statistically superior to ipratropium at hours 4, 5, and 6 ($p \leq 0.0024$; 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 FEV_1 data following the first dose.

Appendix:
Study 205.122B/205.126B



.4.pdf/p61]

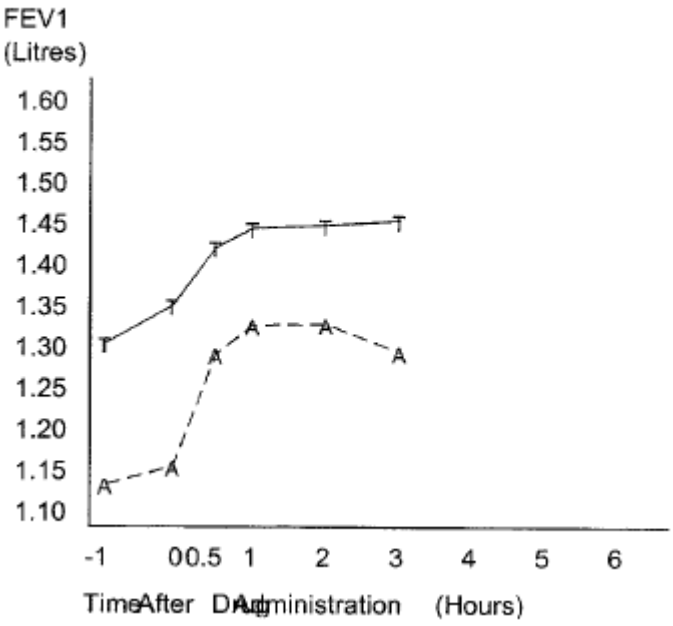
minutes and –5 minutes) values were
), with effect sizes of 0.09 to 0.20 liters
serial FEV_1 values on test day 92 (Week

Test Day 92

p61]

Test Day 364

p62]



Appendix:
Study 205.122B/205.126B

Tiotropium was statistically superior to ipratropium for the average (0-3hour) FEV_1 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) FEV_1 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 FEV_1 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 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.

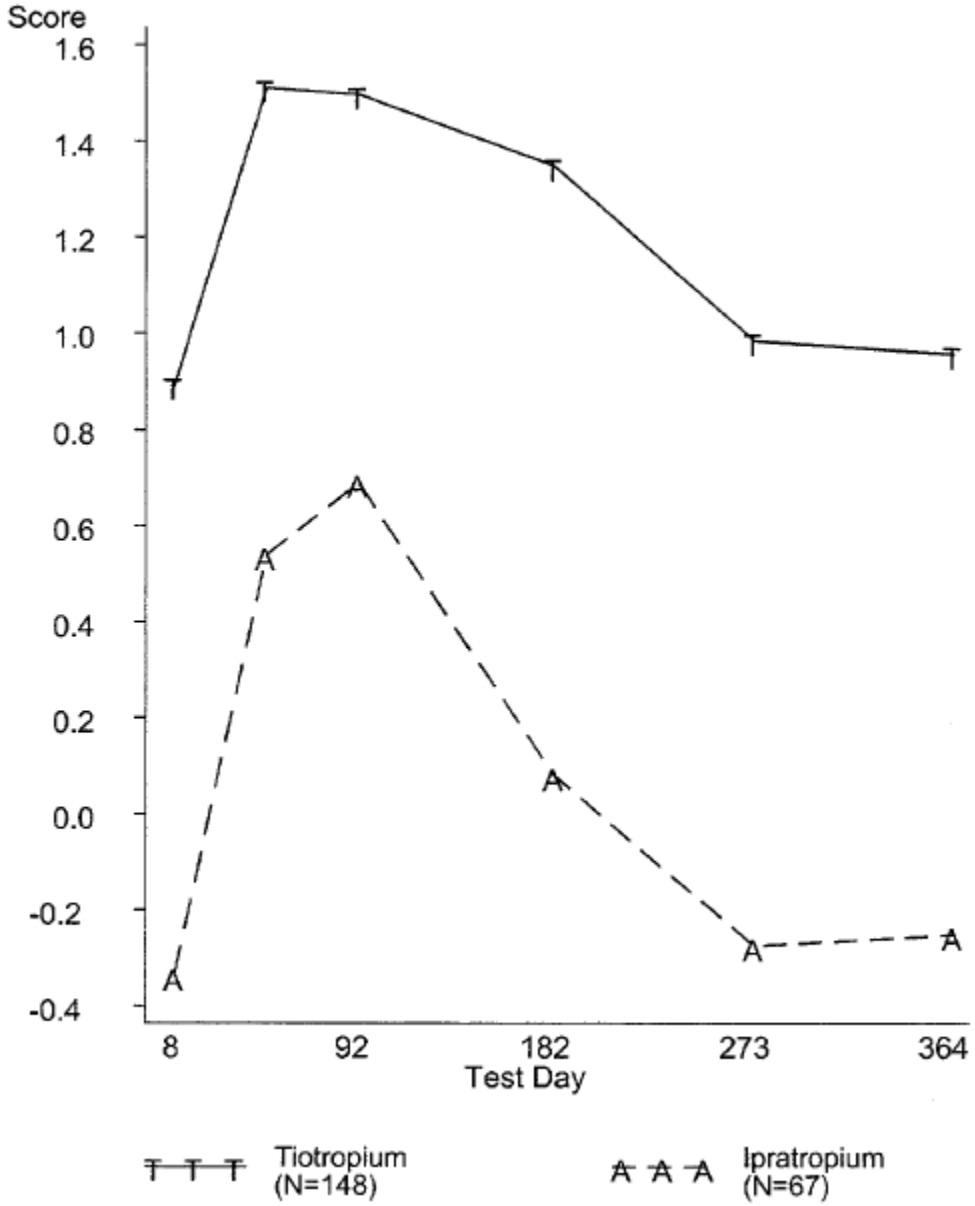
Patient Reported Outcomes

The Mahler Baseline Dyspnea Index and Transitional 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.

Appendix:
Study 205.122B/205.126B

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

Appendix:
Study 205.122B/205.126B



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.

Appendix:
Study 205.122B/205.126B

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

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 FEV_1 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 FEV_1 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 FEV_1 (increases of 15% or more) occurred within 15 minutes.

Appendix:
Study 205.122B/205.126B

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 FEV_1 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 FEV_1 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 Applicant'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)

Appendix:
Study 205.122B/205.126B

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 that 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 ≥ 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 document.