CENTER FOR DRUG EVALUATION AND *RESEARCH*

APPLICATION NUMBER:

21-395

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
STABILITY STUDY

NDA Number:	**21-395**
Applicant:	**Boehringer Ingelheim**
Name of Drug:	**SPIRIVA™ (Tiotropium Bromide) Inhalation Powder**
Document Reviewed:	**Stability data reports – Dated 7/31/03 and 8/22/03**
Statistical Reviewer:	**Feng Zhou, M.S., HFD-715**
Chemistry Reviewer:	**Alan Schroeder, Ph.D., HFD-570**

1. Introduction

The sponsor submitted a stability report with the stability data of the [redacted] NDA stability batches and [redacted] stability batches of the drug product Tiotropium Inhalation Powder (NDA 21-395). The powder is packaged in hard capsule 18 µg [redacted] blisters (original [redacted] and original [redacted] modified with perforation, both are [redacted] configuration package materials). The purpose of the report is to support its shelf life with data up to [redacted] at 25°C/60% R.H., up to [redacted] at 30°C/70% R.H., and up to [redacted] according to the ICH Guideline "Stability testing of new drug substances and drug products" and FDA guidance "Stability testing of drug substances and drug products".

The NDA 21-395 was approvable with some CMC issues. The sponsor has since shortened the proposed expiry to 18 months. This stability review is to evaluate the stability batches under the sponsor new specification limits to support its 18 month shelf life under 25°C/60% R.H. storage condition.

2. Sponsor's Stability Analysis

The sponsor submitted the first stability data up to [redacted] of the [redacted] registration batches of the drug product Tiotropium Inhalation Powder, hard capsule 18 µg packed in [redacted] blisters (original [redacted] batches 001789, 001790, and 001791) on December 12, 2001 with the NDA submission. On August 22, 2003, the sponsor submitted the same batches with [redacted] stability data. On July 31, 2003, the sponsor submitted the [redacted] stability data of the [redacted] supportive stability batches of the drug product Tiotropium Inhalation Powder, hard capsule 18 µg packed in [redacted] blisters [redacted] (batches 519894, 519897, and 518866) (See Table 2 for details). The sponsor performed statistical analyses with specification limits (old) showed in Table 1 and the analysis results supported a [redacted] shelf life under 25°C/60% R.H. condition.

Table 1. List of Specification limits the Sponsor Used to Establish Its Shelf Lives

Test Parameter	*Acceptance Criteria*
Active Ingredient Content	
Uniformity of Delivered Dose	
Active Ingredient Degradation	
	<=
	<=
	<=
Total Degradation	<=
Aerodynamic Particle Size Distribution	

Table 2. Summary of Stability Data Points Submitted by the Sponsor

Batch No.	*Packaging material*	*Storage Conditions*	*Testing Frequency and Storage period (mon.)*
001789	Topical blister	25°C / 60% r.h.	
	(	30°C / 70% r.h.	
001790	Topical blister	25°C / 60% r.h.	
	(	30°C / 70% r.h.	
001791	Topical blister	25°C / 60% r.h.	
		30°C / 70% r.h.	
519894	Topical blister	25°C / 60% r.h.	
		30°C / 70% r.h.	
519894	Topical blister	25°C / 60% r.h.	
		30°C / 70% r.h.	
519894	Topical blister	25°C / 60% r.h.	
		30°C / 70% r.h.	

3. Reviewer's Stability Analysis

This reviewer analyzed the data in accordance with FDA's "Guidelines for Submitting Documentation for the Stability of Human Drugs and Biologics" using the stability data of batches 001789, 001790, and 001791 and the stability data of batches 519894, 519897, and 518866 and the new specification limits listed in Table 3. The results of this reviewer's analysis are presented in Table 4 and Table 5. Data of the primary NDA batches and supportive batches under 25°C/60%RH storage condition support an 18-month expiration date except the Aerodynamic particle size distribution parameter.

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Table 3. List of New Specification Limits Used to Establish Its Shelf Lives

Test Parameter	*Acceptance Criteria*
Active Ingredient Content (mean)	
Uniformity of Delivered Dose	
Active Ingredient Degradation	
	<=
	<=
	<
Total Degradation	<
Aerodynamic Particle Size Distribution	

Table 4. Summary of Statistical Analyses for the Stability Batches of Tiotropium Inhalation Powder, Hard Capsule 18µg Packed in 3listers (Stored Under 25°C/60%RH Condition

Test	*Specification*	*Minimum Expiration Date*	*Model Selection*	*Fitted Line*	*Batch*
Active Ingredient Content					1789 1790 1791
Delivered Dose					POOLED
Active Ingredient Degradation					POOLED
					1789 1790 1791
					1789 1790 1791
Total Degradation					1789 1790 1791
					1789 1790 1791
Aerodynamic Particle Size Distribution					POOLED POOLED 1789 1790 1791

KEY:

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Table 5. Summary of Statistical Analyses for the Stability Batches of Tiotropium Inhalation Powder, Hard Capsule 18µg Package in [redacted] Blisters [redacted] Stored Under 25°C/60%RH Condition

Test	Specification	Minimum Expiration Date	Model Selection	Fitted Line	Batch
Active Ingredient Content	[redacted]	[redacted]	[redacted]	[redacted]	518866 519894 519897
Delivered Dose	[redacted]	[redacted]	[redacted]	[redacted]	POOLED
Active Ingredient Degradation	[redacted]	[redacted]	[redacted]	[redacted]	518866 519894 519897
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	POOLED
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	518866 519894 519897
Total Degradation	[redacted]	[redacted]	[redacted]	[redacted]	518866 519894 519897
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	518866 519894 519897
Aerodynamic Particle Size Distribution	[redacted]	[redacted]	[redacted]	[redacted]	POOLED 518866 519894 519897
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	518866 519894 519397

KEY: [redacted]

For Aerodynamic Particle Size Distribution in [redacted] the minimum estimated expiration date was [redacted] based on the batch 518866, which was supportive batch with [redacted] data. Figure 1 shows the expiry date analysis for Aerodynamic Particle Size Distribution in [redacted] The regression line passed the lower bound at [redacted] timepoint. The estimated expiration date was over [redacted] based on the other five batches. Based on the FDA's minimum requirement of three batches, this reviewer can accept the estimated expiration-dating period using the data up to [redacted]

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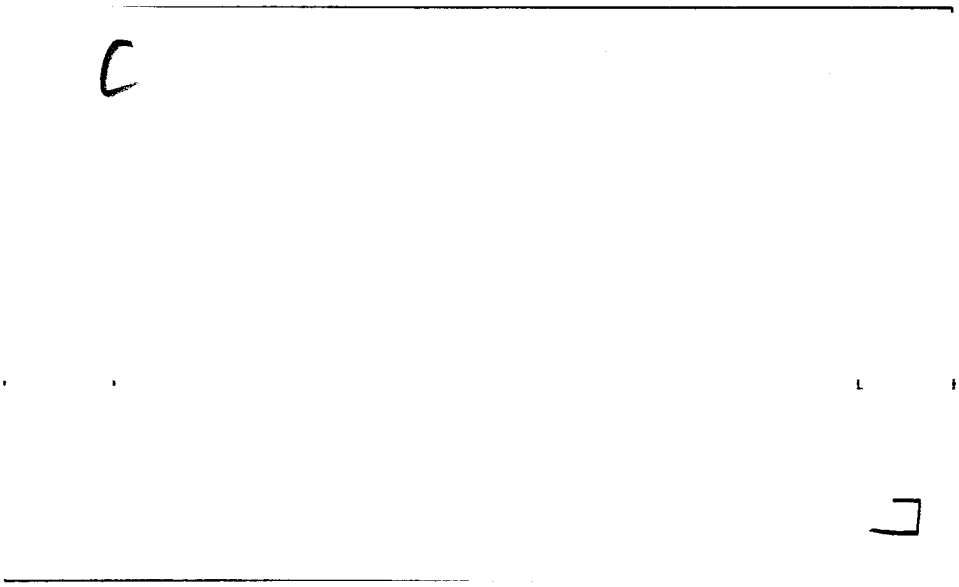
Figure 1. Expiry Date Analysis for Tiotropium Inhalation Powder, Hard Capsule
18µg Package in [redacted] Blisters ([redacted]) Stored Under 25°C/60%RH Condition



4. Conclusion

The results of this reviewer's analysis using the data of [redacted] primary NDA batches and [redacted] supportive stability batches of the drug product Tiotropium Inhalation Powder (NDA 21-395), hard capsule 18 µg packed in [redacted] blisters [redacted] and [redacted] both are [redacted] under 25°C/60%RH storage condition show that the sponsor's stability data support an 18-month expiration date.

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/s/

Feng Zhou
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Karl Lin
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Concur with review

10/12/02

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21395
Name of drug:	Spiriva (tiotropium bromide) Inhalation Powder 18 mcg QD
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Indication:	COPD
Documents reviewed:	\\CDSESUB1\N21395\N_000\2001-12-12\clinstat\copd\U00-0132\U00-0132.pdf
Project manager:	Anthony Zeccola
Clinical reviewer:	Eugene Sullivan, M.D.
Dates:	Received 12/12/2001; user fee (10 months) 10/12/2002.
	Additional volumes dated 03/25/2002 and 04/02/2002.
Statistical reviewer:	Lisa Kammerman, Ph.D.
Statistics team leader:	Lisa Kammerman, Ph.D.
Biometrics division director:	S. Edward Nevius, Ph.D.

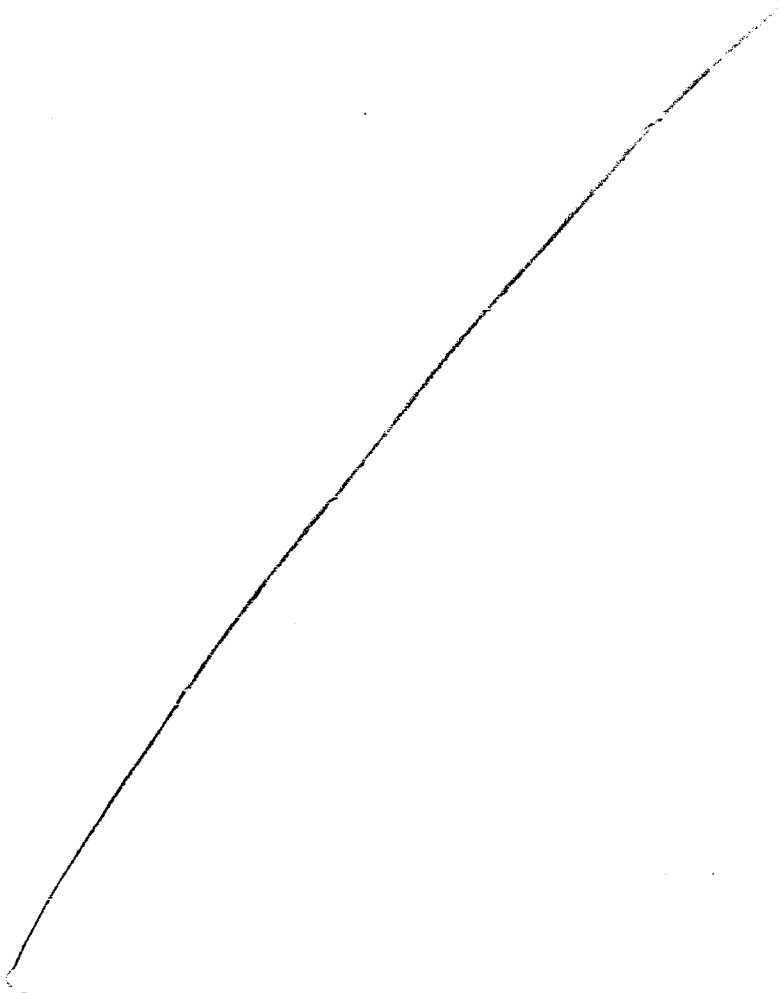
Keywords: NDA review, clinical studies, patient reported outcome

Background

Spiriva would be the first drug product, if approved, to be indicated for the maintenance treatment of dyspnea associated with chronic obstructive pulmonary disease (COPD). The Pulmonary and Allergy Drugs Advisory Committee discussed this indication at a meeting on September 6, 2002.

Because the results of the spirometry data from the NDA support the efficacy of this product for the treatment of bronchospasm, the approvability of the product does not rely on whether efficacy has been demonstrated for the treatment of dyspnea.

My review evaluates the development and validity of the Transition Dyspnea Index (TDI). The applicant is using the TDI and its results to support the dyspnea indication. Dr. J. Gebert (HFD-715) is reviewing the indication for the maintenance treatment of bronchospasm associated with COPD.



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/s/

Lisa A. Kammerman
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S. Edward Nevius
10/12/02 12:50:35 PM
BIOMETRICS
Concur with review.

9/30/02

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21395
Name of drug:	Spiriva (tiotropium bromide) Inhalation Powder 18 mcg QD
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Indication:	COPD
Documents reviewed:	\\CDSESUB1\N21395\N_000\2001-12-12\clinstat\copd\U00-0132\U00-0132.pdf
Project manager:	Anthony Zeccola
Clinical reviewer:	Eugene Sullivan, M.D.
Dates:	Received 12/12/2001; user fee (10 months) 10/12/2002. Additional volumes dated 03/25/2002 and 04/02/2002.
Statistical reviewer:	James Gebert, Ph.D.
Statistics team leader:	Lisa Kammerman, Ph.D.
Biometrics division director:	S. Edward Nevius, Ph.D.

Keywords: NDA review, clinical studies, analysis of covariance

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

The sponsor has demonstrated efficacy for once a day dosing of tiotropium against placebo for changes from baseline at endpoint trough FEV_1 in Studies 205.117, 205.128, 205.130 and 205.137. The sponsor also demonstrated efficacy for once a day dosing of tiotropium against ipratropium for changes from baseline at endpoint trough FEV_1 in Studies 205.126A and 205.126B.

Furthermore, the sponsor has claimed to have demonstrated efficacy for once a day dosing of tiotropium against placebo for the percentage of patients having a response of greater than 1 in Mahler's Transitional Dyspnea Index (TDI) Focal Score at endpoint in studies 205.130 and 205.137 which was pre-specified as a co-primary efficacy analysis. In these studies, the alternative covariance analysis of TDI Focal Score values also showed a significant difference from placebo of more than one. A value of one is considered to be a clinical meaningful difference by Dr. Mahler, who developed the index. These results were supported by the results of the analysis of the COPD shortness of breath symptom scores in these two studies.

The Pulmonary and Allergy Drug Advisory Committee on September 6, 2002 felt that since the studies were not originally designed with TDI Focal Score as a primary efficacy variable and that the sponsor did not adequately train the interviewers to insure reliable assessments that TDI data did not support an indication for dyspnea. The Committee expressed doubt that TDI was appropriate for a clinical trial setting. Furthermore, the Committee felt that the sponsor had not adequately justified 1 as being a clinically important improvement. The Committee seemed to have mixed views on the appropriateness of the TDI instrument with some members believing that the patient should be the assessor.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

This review will only focus on two one-year, placebo-controlled studies in patients with COPD (Studies 205.117 and 205.128); two one-year, ipratropium-controlled studies in patients with COPD (Studies 205.126A and 205.126B); and two six-month, placebo and salmeterol controlled studies in patients with COPD (Studies 205.130 and 205.137). These are the Phase 3 studies.

After favorable results for TDI Focal Score in the one-year placebo and ipratropium studies, the sponsor made the analysis of percentage of patients responding (TDI Focal Score greater than 1) as a co-primary efficacy variable in Studies 205.130 and 205.137.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Tiotropium is a quaternary ammonium compound developed as a long-acting anticholinergic bronchodilator for treatment of patients with reversible obstructive airway disease.

Tiotropium 18 mcg inhalation capsules are inserted into a Handihaler device and inhaled into the lungs.

This reviewer requested new datasets to facilitate his review of this submission on March 7, 2002. These new datasets were supplied in the sponsor's April 2, 2002 submission.

2.2 DATA ANALYZED AND SOURCES

This review will only focus on two, one-year, placebo-controlled studies in patients with COPD (Studies 205.117 and 205.128); two, one-year, ipratropium-controlled study in patients with COPD (Studies 205.126A and 205.126B); and two, six-month placebo and salmeterol controlled studies in patients with COPD (Studies 205.130 and 205.137).

Data for these studies were in the sponsor's December 12, 2001 and April 02, 2002 submissions. The April 02, 2002 data was requested by this reviewer to facilitate analyses of the primary efficacy variable.

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

Studies 205.130 and 205.137 were multicenter, multinational, randomized, double-blind, double-dummy, parallel group studies with a two-week baseline period and a six-month treatment period comparing tiotropium inhalation capsules, salmeterol inhalation aerosol and placebo in patients with COPD. The only difference between these studies was that 12-hour serial PFTs were done at Day 1 and at 2, 8, 16 and 24 weeks of treatment in Study 205.130 whereas only 3-hours of serial PFTs were done at those times in Study 205.137.

To enter the study subjects had to have an $FEV_1 \leq 60$ % of predicted normal and an $FEV_1 \leq 75\%$ of FVC. They had to have a smoking history of more than 10 pack years.

During the two-week baseline period but not the treatment period, they were allowed to be on Atrovent by oral inhalation or Atrovent Nasal Spray, and long-acting adrenergics such as salmeterol or formoterol. If stabilized, they were allowed to continue their oral inhaled corticosteroids, low dose oral corticosteroids (equivalent to 20mg or less of prednisone daily), theophylline (excluding 24 hour preparations), and mucolytic agents not containing broncholdilators.

COPD symptoms (wheezing, shortness of breath, coughing and tightness of chest) were assessed by the physician at clinic visits using a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe).

The co-primary efficacy measures were changes from baseline trough FEV_1 at endpoint and percentage of patients having a TDI Focal Score greater than 1 at endpoint. Trough FEV_1 at endpoint was the average of the FEV_1 taken at 60 minutes before dosing and 10 minutes before dosing at endpoint visit.

Changes from baseline in trough FEV_1 at endpoint was analyzed by an analysis of covariance with treatment and centers as factors and baseline FEV_1 as covariate. Baseline FEV_1 was the average of the pre-dose values at 60 and 10 minutes before treatment on Day 1.

The percentage of patients having a TDI Focal Score greater than 1 was analyzed by a logistic regression with baseline dyspnea index focal score as covariate. {The protocol stated that both centers and baseline dyspnea focal score would be used.} The TDI Focal Scores were also analyzed by an analysis of covariance with treatments and centers as factors and baseline dyspnea index focal score as covariate.

If data was missing because of worsening of COPD, the least favorable observation was carried forward, otherwise the LOCF rule was used. In particular, if a patient had missing data because of worsening of COPD and a serial FEV_1 value was the lowest value and lower than the trough FEV_1 at that visit, it would be the carried forward value.

The TDI Focal Score is the sum of improvement scores of three components of dyspnea: Functional Impairment, Magnitude of Effort, and Magnitude of Task (each measured on a 4 point scale). Therefore the TDI Focal score has values from –9 to +9. The developer of the scale, Dr. Mahler, is of the opinion that a score of even 1 represents a clinically meaningful improvement. The improvement in the components of TDI was measured from Baseline scores in the corresponding component.

COPD symptoms were analyzed by an analysis of covariance with treatments, center, and baseline.

Patients excluded from the ITT analysis of trough FEV_1 had either no on-treatment FEV_1 assessments or had no baseline FEV_1 data. For the Baseline Dyspnea Index (BDI) data if the patient responded with a W (Amount Uncertain) or X(Unknown) the value was set to missing. If the patient responded with Y (Impaired for Reasons Other than Shortness of Breath), the BDI value was set to Grade 4 (No impairment). For the TDI if the patient responded with Y, the value was set to 0 (no change). If one of the three categories for TDI or BDI was missing the TDI Focal Score was missing. Patients were excluded from the ITT analysis of TDI Focal Score if there were no on-treatment or baseline data. Another important factor leading to more exclusions in the ITT analysis of TDI Focal Score was that TDI score were first assessed on Day 57 whereas FEV_1 was assessed on Days 1 and 15.

The sponsor used LOCF rules to impute data except that when data was missing for lack of efficacy the least favorable data was used.

Studies 205.117 and 205.128 were multicenter, multinational (Netherlands and Belgium only), randomized, double-blind, parallel group studies with a two-week baseline period and a one year treatment period comparing tiotropium inhalation capsules and placebo in patients with COPD. These were similar to Studies 205.130 and 205.137 with the exception that the FEV_1 entrance criteria was an $FEV_1 \leq 65$ % of predicted normal. The analysis of covariance of endpoint trough FEV_1 was the primary analysis for these studies.

Studies 205.126A and 205.126B were multicenter, multinational, randomized, double-blind, double-dummy, parallel group studies with a two-week baseline period and a one year treatment period comparing tiotropium inhalation capsules and ipratropium in patients with COPD. The analysis of covariance of endpoint trough FEV_1 was the primary analysis for these studies.

2.3.1.1 Study 205.130

The study report for this study was called document number U01-1236-1.

There were 623 patients (209 to tiotroprium, 213 to salmeterol and 201 to placebo) randomized into the trial at 39 centers in 12 countries. Of the 623 randomized patients, 506 (81.2%) completed all nine visits, 184 (88.0%) in the tiotropium group, 177 (83.1%) in the salmeterol group and 145 (72.1%) in the placebo group. Fewer patients in the tiotropium group [7 (3.3%)] failed to complete the study due to worsening of COPD, compared to salmeterol 22 (10.3%) and placebo 30(14.9%).

There were 26 (4.2%) patients who were excluded from all efficacy analyses. There were 584 patients (202 tiotropium, 203 salmeterol, and 179 placebo) in the ITT analysis of trough FEV_1. There were only 511 patients (184 tiotropium, 179 salmeterol, and 148 placebo) in the ITT analysis of TDI Focal Score.

The treatment groups were comparable in demographic variables, baseline pulmonary function, and Baseline Dyspnea Index Focal Score. The table below provides the baseline FEV_1 and Baseline Dyspnea Index Focal Score treatment means for the ITT populations for the respective variables.

Centers 12, 14, 27, 29, 34, and 39 were pooled into one center for analyses. All these centers had less than 6 evaluable patients. Pooling was done before unblinding.

	Tiotropium		Salmeterol		Placebo	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
FEV_1	202	1.09 (0.03)	203	1.07 (0.03)	179	1.03 (0.03)
Baseline Dyspnea Index Focal Score	184	6.65 (0.15)	179	6.62 (0.16)	148	6.21 (0.19)

The following table includes the results of the analysis of changes from baseline in trough FEV_1 at endpoint using an analysis of covariance with treatments, centers and baseline FEV_1.

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value	95% CI
Tiotropium	202	0.11 (0.01)	TIO-PLA	0.14 (0.02)	0.0001	(0.10, 0.18)
Salmeterol	203	0.05 (0.01)	TIO-SAL	0.05 (0.02)	0.0088	(0.01, 0.09)
Placebo	179	-0.03 (0.02)	SAL-PLA	0.09 (0.02)	0.0001	(0.05, 0.11)

[1] The means are differences from baseline and are adjusted for center effects and the baseline mean.

The following table provides the percentages of patients having a TDI Focal Score greater than 1 (called a responder) at endpoint.

	Tiotropium	Salmeterol	Placebo
N	184	179	148
Number (%) of responders	77 (42%)	63 (35%)	39 (26%)

The following table presents the odds ratios and 95% confidence intervals from a logistic analysis of responders on treatment and baseline focal score as covariate. Tiotropium was significantly different from placebo.

Tiotropium/Placebo	1.965 (p=0.0049)	(1.228, 3.144)
Tiotropium/Salmeterol	1.324 (NS)	(0.866, 2.026)
Salmeterol/Placebo	1.484 (NS)	(0.919, 2.396)

The following table provides the results of the analysis of TDI Focal Score at endpoint. This is an alternative analysis for TDI.

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value	95% CI
Tiotropium	184	0.39 (0.28)	TIO-PLA	1.02 (0.41)	0.0134	(0.21, 1.82)
Salmeterol	179	-0.39 (0.28)	TIO-SAL	0.78 (0.39)	0.0447	(0.02, 1.53)
Placebo	148	-0.63 (0.31)	SAL-PLA	0.24 (0.41)	0.5596	(-0.57, 1.05)

[1] The means are adjusted for center effects and the baseline mean.

Shortness of breath was also assessed by diary symptom severity assessments. These showed a significant difference between tiotropium and placebo averaged over two weeks for most time periods.

2.3.1.2 Study 205.137

The study report for this study was called document number U01-1231-1.

There were 584 patients (193 to tiotroprium, 192 to salmeterol and 199 to placebo) randomized into the trial at 48 centers in 15 countries. Of the 584 randomized patients, 460 (78.8%) completed all nine visits, 156 (80.8%) in the tiotropium group, 152 (79.2%) in the salmeterol group and 152 (76.4%) in the placebo group. There were 13 (6.7%) in the tiotropium group , 19 (9.9%) in the salmeterol group, and 15(7.5%) in the placebo group who failed to complete the study due to worsening of COPD

There were 18 (3.1%) patients who were excluded from all efficacy analyses. There were 552 patients (184 tiotropium, 185 salmeterol, and 183 placebo) in the ITT analysis of trough FEV_1 There were only 486 patients (164 tiotropium, 161 salmeterol, and 161 placebo) in the ITT analysis of TDI.

Centers 4, 9, 19, 21, 26, 33, 34, 35, 45, 47, 49, and 50 were pooled into one center. All these centers had less than 6 evaluable patients. Pooling was done before unblinding.

The treatment groups were comparable in demographic variables, baseline pulmonary function and Baseline Dyspnea Index Focal Score. The table below provides the baseline FEV_1 and Baseline Dyspnea Index Focal Score treatment means for the ITT populations for the respective variables.

	Tiotropium		Salmeterol		Placebo	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
FEV_1	184	1.14 (0.03)	185	1.06 (0.03)	183	1.13 (0.03)
Baseline Dyspnea Index Focal Score	164	6.43 (0.20)	161	6.47 (0.20)	161	6.88 (0.19)

The following table includes the results of the analysis of changes from baseline in trough FEV_1 at endpoint using an analysis of covariance with treatments, centers and baseline FEV_1. Tiotropium was significantly different from placebo.

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value	95% CI
Tiotropium	184	0.07 (0.02)	TIO-PLA	0.11 (0.02)	0.0001	(0.07, 0.15)
Salmeterol	185	0.05 (0.02)	TIO-SAL	0.02 (0.02)	0.3934	(-0.02,0.06)
Placebo	183	-0.03 (0.02)	SAL-PLA	0.09 (0.02)	0.0001	(0.05,0.13)

[1] The means are differences from baseline and are adjusted for center effects and the baseline mean.

The following table provides the percentages of patients having a TDI Focal Score greater than 1 (called a responder) at endpoint.

	Tiotropium	Salmeterol	Placebo
N	164	161	161
Number (%) of responders	73 (45%)	77 (48%)	53 (33%)

The following table presents the odds ratios and 95 % confidence intervals from a logistic analysis of responders on treatment and Baseline Focal Score as covariate. Tiotropium had significantly more responders than placebo.

Tiotropium/Placebo	1.691 (P=0.0232)	(1.075, 2.662)
Tiotropium/Salmeterol	0.877 (NS)	(0.566, 1.357)
Salmeterol/Placebo	1.929 (p=0.0046)	(1.224, 3.038)

The following table provides the results of the analysis of TDI focal score at endpoint

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value	95% CI
Tiotropium	164	0.80 (0.28)	TIO-PLA	1.21 (0.39)	0.0021	(0.44, 1.99)
Salmeterol	161	0.85 (0.29)	TIO-SAL	-0.05 (0.39)	0.9031	(-0.82, 0.72)
Placebo	161	-0.42 (0.29)	SAL-PLA	1.26 (0.39)	0.0015	(0.49, 2.04)

[1] The means are adjusted for center effects and the baseline mean.

2.3.1.3 Study 205.117

The study report for this study was called document number U99-3169. The first 13-week portion of the study was called study 205.114, which was denoted as the efficacy portion of the study. The nine-month extension of the study was called Study 205.117.

There were 470 patients (279 to tiotroprium and 191 to placebo) randomized into the trial at 25 centers in the U.S. Of the 470 randomized patients, 374 (79.6%) completed all visits, 235 (84.2%) in the tiotropium group and 139 (72.8%) in the placebo group.

There were 442 patients (268 tiotropium and 174 placebo) in the ITT analysis of trough FEV_1. There were only 429 patients (258 tiotropium and 171 placebo) in the ITT analysis of TDI Focal Score.

The treatment groups were comparable in demographic variables, baseline pulmonary function and Baseline Dyspnea Index Focal Score. The table below provides the baseline FEV_1 and Baseline Dyspnea Index Focal Score treatment means for the ITT populations for the respective variables.

Centers 2, 12, and 24 were pooled into one center for analyses. All these centers had less than 10 evaluable patients. Pooling was done before unblinding.

	Tiotropium		Placebo	
	N	Mean (SE)	N	Mean (SE)
FEV_1	268	1.03 (0.03)	174	0.99 (0.03)
Baseline Dyspnea Index Focal Score	258	5.96 (0.12)	171	6.09 (0.17)

The following table includes the results of the analysis of changes from baseline in trough FEV_1 at endpoint using an analysis of covariance with treatments, centers and baseline FEV_1. Tiotropium was significantly different from placebo.

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value	95% CI
Tiotropium	268	0.11 (0.01)	TIO-PLA	0.16 (0.02)	0.0001	(0.12, 0.20)
Placebo	174	-0.05 (0.02)				

[1] The means are differences from baseline and are adjusted for center effects and the baseline mean.

Since the sponsor considered the data up to 13-weeks as the primary efficacy data, the results of the primary efficacy analysis will be presented for this time period.

The following table includes the results of the analysis of changes from baseline in trough FEV_1 at Day 92 or endpoint before Day 92 using an analysis of covariance with treatments, centers and baseline FEV_1.

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value	95% CI
Tiotropium	268	0.11 (0.01)	TIO-PLA	0.14 (0.02)	0.0001	(0.10, 0.18)
Placebo	174	-0.03 (0.02)				

[1] The means are differences from baseline and are adjusted for center effects and the baseline mean.

The following table provides the results of the analysis of TDI Focal Score at endpoint

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value
Tiotropium	258	0.86 (0.17)	TIO-PLA	1.15 (0.26)	0.0001
Placebo	171	-0.29 (0.21)			

[1] The means are adjusted for center effects and the baseline mean.

2.3.1.4 Study 205.128

The study report for this study was called document number U99-3170-1. The first 13-week portion of the study was called study 205.115, which was denoted as the efficacy portion of the study. The nine-month extension of the study was called Study 205.128.

There were 451 patients (271 to tiotroprium and 180 to placebo) randomized into the trial at 25 centers in the U.S. Of the 451 randomized patients, 341 (75.6%) completed all visits, 212 (78.2%) in the tiotropium group and 129 (71.7%) in the placebo group.

There were 404 patients (250 tiotropium and 154 placebo) in the ITT analysis of trough FEV_1. There were only 403 patients (249 tiotropium and 154 placebo) in the ITT analysis of TDI Focal Score.

The treatment groups were comparable in demographic variables, baseline pulmonary function and Baseline Dyspnea Index Focal Score. . The table below provides the baseline FEV_1 and Baseline Dyspnea Index Focal Score treatment means for the ITT populations for the respective variables.

Centers 44, 48 and 49 were pooled into one center. All these centers had less than 10 evaluable patients. Pooling was done before unblinding.

	Tiotropium		Placebo	
	N	Mean (SE)	N	Mean (SE)
FEV_1	250	1.00 (0.03)	154	1.00 (0.03)
Baseline Dyspnea Index Focal Score	249	6.11 (0.13)	154	6.34 (0.17)

The following table includes the results of the analysis of changes from baseline in trough FEV_1 at endpoint using an analysis of covariance with treatments, centers and baseline FEV_1. Tiotropium was significantly different from placebo.

Drug	N	Mean (SE)	Comparison	Diff. (SE)	P-value	95% CI
Tiotropium	250	0.12 (0.01)	TIO-PLA	0.15 (0.02)	0.0001	(0.11, 0.19)
Placebo	154	-0.03 (0.02)				

[1] The means are differences from baseline and are adjusted for center effects and the baseline mean

Since the sponsor considered the data up to 13-weeks as the primary efficacy data the results of the primary efficacy analysis will be presented for this time period.

The following table includes the results of the analysis of changes from baseline in trough FEV_1 at Day 92 or endpoint before Day 92 an analysis of covariance with treatments, centers and baseline FEV_1.

Drug	N	Mean (SE)	Comparison	Diff. (SE)	P-value	95% CL
Tiotropium	250	0.13 (0.01)	TIO-PLA	0.14 (0.02)	0.0001	(0.09, 0.18)
Placebo	154	-0.01 (0.02)				

[1] The means are differences from baseline and are adjusted for center effects and the baseline mean

The following table provides the results of the analysis of TDI focal score at endpoint

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value
Tiotropium	249	1.25 (0.18)	TIO-PLA	1.13 (0.28)	0.0001
Placebo	154	0.11 (0.23)			

[1] The means are adjusted for center effects and the baseline mean.

2.3.1.5 Study 205.126A

The study report for this study was called document number U00-3113. The first 13-week portion of the study was called study 205.122, which was denoted as the efficacy portion of the study. The nine-month extension of the study was called Study 205.126.

There were 288 patients (191 to tiotroprium and 97 to ipratropium) randomized into the trial at 14 international centers. Of the 288 randomized patients, 240 (83.3%) completed all visits, 162 (84.8%) in the tiotropium group and 78 (80.4%) in the ipratropium group.

There were 265 patients (176 tiotropium and 89 ipratropium) in the ITT analysis of trough FEV_1. There were only 257 patients (172 tiotropium and 85 ipratropium) in the ITT analysis of TDI Focal Score.

The treatment groups were comparable in demographic variables, baseline pulmonary function and Baseline Dyspnea Index Focal Score. The table below provides the baseline FEV_1 and Baseline Dyspnea Index Focal Score treatment means for the ITT populations for the respective variables.

Centers 14, 15, 16, 19 and 20 were pooled into one center. All these centers had less than 10 evaluable patients. Pooling was done before unblinding.

	Tiotropium		Ipratropium	
	N	Mean (SE)	N	Mean (SE)
FEV_1	176	1.21 (0.03)	89	1.15 (0.04)
Baseline Dyspnea Index Focal Score	172	7.12 (0.18)	85	7.18 (0.26)

The following table includes the results of the analysis of changes from baseline in trough FEV_1 at endpoint using an analysis of covariance with treatments, centers and baseline FEV_1.

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value	95% CI
Tiotropium	176	0.11 (0.02)	TIO-IPO	0.13 (0.03)	0.0001	(0.07, 0.19)
Ipratropium	89	-0.02 (0.03)				

[1] The means are differences from baseline and are adjusted for center effects and the baseline mean

Since the sponsor considered the data up to 13-weeks as the primary efficacy data the results of the primary efficacy analysis will be presented for this time period.

The following table includes the results of the analysis of changes from baseline in trough FEV_1 at Day 92 or endpoint before Day 92 an analysis of covariance with treatments, centers and baseline FEV_1.

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value	95% CI
Tiotropium	176	0.16 (0.02)	TIO-IPO	0.13 (0.03)	0.0001	(0.08, 0.19)
Ipratropium	89	0.03 (0.03)				

[1] The means are differences from baseline and are adjusted for center effects and the baseline mean

The following table provides the results of the analysis of TDI focal score at endpoint.

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value
Tiotropium	172	-0.02 (0.18)	TIO-IPO	0.65 (0.28)	0.0216
Ipratropium	85	-0.67 (0.25)			

[1] The means are adjusted for center effects and the baseline mean.

2.3.1.6 Study 205.126B

The study report for this study was called document number U00-3114. The first 13-week portion of the study was called study 205.122, which was denoted as the efficacy portion of the study. The nine-month extension of the study was called Study 205.126.

There were 247 patients (165 to tiotroprium and 82 to ipratropium) randomized into the trial at 15 international centers. Of the 247 randomized patients, 203 (82.2%) completed all visits, 140 (84.8%) in the tiotropium group and 63 (76.8%) in the ipratropium group.

There were 225 patients (153 tiotropium and 72 ipratropium) in the ITT analysis of trough FEV_1. There were only 215 patients (148 tiotropium and 67 ipratropium) in the ITT analysis of TDI Focal Score.

The treatment groups were comparable in demographic variables, baseline pulmonary function and Baseline Dyspnea Index Focal Score. The table below provides the baseline FEV_1 and Baseline Dyspnea Index Focal Score treatment means for the ITT populations for the respective variables.

Centers 11, 22, 41, 45, 47 and 48 were pooled into one center. All these centers had less than 10 evaluable patients. Pooling was done before unblinding.

	Tiotropium		Ipratropium	
	N	Mean (SE)	N	Mean (SE)
FEV_1	153	1.22 (0.04)	72	1.13 (0.05)
Baseline Dyspnea Index Focal Score	148	7.16 (0.23)	67	7.70 (0.29)

The following table includes the results of the analysis of changes from baseline in trough FEV_1 at endpoint using an analysis of covariance with treatments, centers and baseline FEV_1.

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value	95% CI
Tiotropium	153	0.14 (0.02)	TIO-IPO	0.18 (0.03)	0.0001	(0.13, 0.24)
Ipratropium	72	-0.05 (0.02)				

[1] The means are differences from baseline and are adjusted for center effects and the baseline mean

Since the sponsor considered the data up to 13-weeks as the primary efficacy data the results of the primary efficacy analysis will be presented for this time period.

The following table includes the results of the analysis of changes from baseline in trough FEV_1 at Day 92 or endpoint before Day 92 an analysis of covariance with treatments, centers and baseline FEV_1.

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value	95% CI
Tiotropium	153	0.12 (0.02)	TIO-IPO	0.15 (0.03)	0.0001	(0.09, 0.21)
Ipratropium	72	-0.02 (0.03)				

[1] The means are differences from baseline and are adjusted for center effects and the baseline mean

The following table provides the results of the analysis of TDI focal score at endpoint

Drug	N	Mean[1] (SE)	Comparison	Diff. (SE)	P-value
Tiotropium	148	0.96 (0.28)	TIO-IPO	1.21 (0.47)	0.0102
Ipratropium	67	-0.25 (0.40)			

[1] The means are adjusted for center effects and the baseline mean.

2.3.1.7 Analysis of Special Subgroups

Only TDI showed some suggestion of differential effect among subgroups. The results even for TDI are somewhat problematic.

The sponsor's table 11.2.2.2.3:1 below provides the results of the analysis of TDI by gender for the pooled data from these two salmeterol studies.

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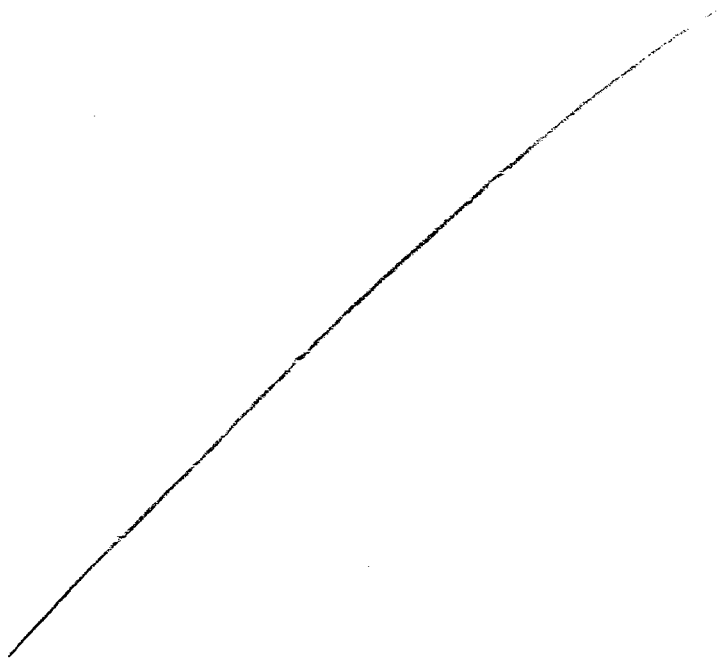

3 Reviewer's Conclusions

The sponsor has demonstrated efficacy for once a day dosing of tiotropium against placebo for changes from baseline at endpoint trough FEV_1 in Studies 205.117, 205.128, 205.130 and 205.137. The sponsor also demonstrated efficacy for once a day dosing of tiotropium against ipratropium for changes from baseline at endpoint trough FEV_1 in Studies 205.126A and 205.126B. These latter two studies were conducted in the Netherlands and Belgium.

Furthermore, the sponsor claims to have demonstrated efficacy for once a day dosing of tiotropium against placebo for the percentage of patients having a response of greater than 1 in Mahler's Transitional Dyspnea Index (TDI) Focal Score at endpoint in studies 205.130 and 205.137 which was pre-specified as a co-primary efficacy analysis. In these studies, the alternative covariance analysis of TDI Focal Score values also showed a significant difference from placebo of more than one. A value of one is considered to be a clinical meaningful difference by Dr. Mahler, who developed the index. These results were supported by the results of the analysis of the COPD shortness of breath symptom scores in these two studies.

This reviewer agrees with the opinions of the Pulmonary and Allergy Drug Advisory Committee. The Pulmonary and Allergy Drug Advisory Committee on September 6, 2002 felt that since the studies were not originally designed with TDI Focal Score as a primary efficacy variable and that the sponsor did not adequately train the interviewers to insure reliable assessments that the sponsor has not demonstrated efficacy to satisfy an dyspnea indication. The Committee expressed doubt that the TDI was appropriate for a clinical trial setting. Furthermore, the Committee felt that the sponsor had not adequately justified 1 as being a clinically important improvement.

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/s/

James Gebert
9/25/02 03:14:25 PM
BIOMETRICS

Lisa A. Kammerman
9/25/02 04:13:23 PM
BIOMETRICS
I concur

S. Edward Nevius
9/30/02 10:28:09 AM
BIOMETRICS
Concur with review.