

PULMONARY-ALLERGY DRUGS
ADVISORY COMMITTEE MEETING

SEPTEMBER 6, 2002

CLINICAL BRIEFING DOCUMENT

NDA 21-395
SPIRIVA[®]
(TIOTROPIUM BROMIDE)
INHALATION POWDER
FOR COPD

APPLICANT:
BOEHRINGER INGELHEIM
PHARMACEUTICALS, INC.

Table of Contents

Cover Page.....	1
<u>Table of Contents</u>	2
I. Introductory Statement	4
II. Overview	7
A. Brief Overview of the Clinical Program.....	7
B. Efficacy Evaluations	7
C. Safety	9
D. Dosing.....	10
E. Special Populations.....	10
III. Introduction and Background	12
A. Drug Established and Proposed Trade Name, Drug Class, Sponsor’s Proposed Indication(s), Dose, Regimens, Age Groups.....	12
B. State of Armamentarium for Indication	12
C. Important Milestones in Product Development	12
D. Other Relevant Information	13
E. Important Issues with Pharmacologically Related Agents	13
IV. Human Pharmacokinetics and Pharmacodynamics	15
A. Pharmacokinetics	15
B. Pharmacodynamics	20
V. Description of Clinical Data and Sources	31
A. Overall Data	31
B. Tables Listing the Clinical Trials.....	31
C. Postmarketing Experience	33
VI. Clinical Review Methods	34

A.	How the Review was Conducted	34
B.	Overview of Materials Consulted in Review	34
C.	Overview of Methods Used to Evaluate Data Quality and Integrity	34
D.	Were Trials Conducted in Accordance with Accepted Ethical Standards.	34
E.	Evaluation of Financial Disclosure	34
VII.	Integrated Review of Efficacy	36
A.	Brief Statement of Conclusions	36
B.	General Approach to Review of the Efficacy of the Drug.....	36
C.	Detailed Review of Trials by Indication.....	37
D.	Efficacy Conclusions	48
VIII.	Integrated Review of Safety	51
A.	Brief Statement of Conclusions	51
B.	Description of Patient Exposure	51
C.	Methods and Specific Findings of Safety Review	52
D.	Adequacy of Safety Testing.....	67
E.	Four-Month Safety Update	67
IX.	Appendix: Detailed Reviews of Individual Studies.....	69
	One-Year Placebo-Controlled Studies:.....	69
	Six-Month Placebo- and Active-Controlled Studies.....	104
	One-Year, Active-Controlled Studies.....	136

CLINICAL BRIEFING DOCUMENT

Executive Summary

I. Introductory Statement

The Pulmonary – Allergy Drugs Advisory Committee (PADAC) is being convened on September 6, 2002, in order to discuss the New Drug Application submitted to the FDA by Boehringer Ingelheim Pharmaceuticals, Inc. for Spiriva[®] (tiotropium bromide) Inhalation Powder (NDA #21-295). Tiotropium is a long-acting anticholinergic agent that is proposed for use in chronic obstructive pulmonary disease (COPD). No formulation of tiotropium has previously been approved for any use in humans in the US. Spiriva is a dry powder formulation of tiotropium bromide, which is intended for administration by oral inhalation, using a re-usable, hand-held, breath-actuated device called the HandiHaler[®]. The proposed dose is one (18mcg) capsule QD. The Phase 3 clinical development program constituted six, multicenter, clinical studies of 6 to 12 months in duration. Two of the studies were placebo-controlled, two were active- and placebo-controlled, and two were active-controlled studies.

The Applicant has proposed the following indication for Spiriva:

“Spiriva is indicated for the long term, once daily, maintenance treatment of bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.”

Inclusion of the word “dyspnea” in the “Indications” section of the product label would mark a departure from the language commonly used in the product labels of other medications approved in the US for COPD. The “Indications” section of these labels commonly refer to the “treatment of bronchospasm” associated with COPD, intentionally focusing on the bronchodilator activity of the drugs, and avoiding the use of language that would imply that the drugs have been shown to treat a specific symptom of the disease, or the disease itself. This custom is based, in part, on the recognition that, while FEV₁ represents a direct measure of bronchospasm, it is only an indirect, or surrogate, measure of the overall disease that is COPD, which is characterized by a constellation of clinical signs and symptoms, physiologic processes, and histopathologic features. The approval of drugs for COPD has been based, therefore, on the demonstration that the drug provides a clinically meaningful degree of bronchodilation for patients with COPD. The post-treatment change in FEV₁ is commonly used to demonstrate this.

In general, the Agency approves drugs only if it can determine that the drug will provide a real benefit to the patient. As stated above, FEV₁ can be considered a “direct” measure of bronchospasm. However, a drug whose sole benefit was an improvement in a physiologic parameter, without clinical benefit discernible to the patient, would generally not be approved unless the physiologic parameter was a validated surrogate for a clinical benefit discernible to the patient. Intrinsic to the approval of COPD drugs indicated for the treatment of bronchospasm (based on an FEV₁ endpoint), has been the implicit assumption that the temporary relief of bronchospasm is associated with a clinically discernible benefit. This raises the question of whether it is appropriate to list specific symptoms of the disease, such as dyspnea, which may improve based on the stated bronchodilator activity of the drug, as “Indications” for a drug.

The Phase 3 clinical development program for Spiriva has attempted to support both the efficacy of the drug as a bronchodilator, and the efficacy of the drug in the treatment of the symptom of dyspnea in patients with COPD. Each of the six “pivotal” studies submitted in support of the

CLINICAL BRIEFING DOCUMENT

Executive Summary

application have addressed the bronchodilator activity by including FEV₁ as a primary or co-primary endpoint, and including other secondary endpoints that assess bronchodilation (e.g. forced vital capacity, peak expiratory flow rates, and “rescue” albuterol use). In this application, the primary endpoint was the change from baseline in the pre-dose (or “trough”) FEV₁ value, rather than a post-dose value, such as peak FEV₁, as is more commonly the case in COPD clinical studies. A benefit of using the “trough” FEV₁ endpoint is that it can provide justification of the proposed dosing interval, by demonstrating continued efficacy at the end of the dosing interval. One potential drawback is that there is less consensus regarding the minimum magnitude of effect that should be considered to be clinically meaningful at this timepoint. The pivotal clinical studies included numerous secondary analyses of FEV₁ and FVC to evaluate the bronchodilator effect in the early post-dosing period (e.g. peak values, and average values from serial post-dosing spirometry).

In regard to the proposed dyspnea claim, two of the six “pivotal” Phase 3 studies included an index of the symptom, the Mahler Transitional Dyspnea Index (TDI), as a co-primary endpoint (Studies 205.130 and 205.137). This variable was also included as one of the secondary efficacy variables in the remaining four studies. In fact, the decision to amend the statistical plan for Studies 205.130 and 205.137 to include the TDI as a co-primary endpoint was made after these studies were completed, before un-blinding, based on post-hoc analyses of the TDI data from the earlier Phase 3 studies.

The purpose of this PADAC meeting is to discuss the adequacy of the safety and efficacy data submitted in the NDA to support approval for marketing of Spiriva. Given the proposal for the unique indication of dyspnea, the topics for discussions will include the development, validation, and statistical analysis of the dyspnea instrument used in these studies (the TDI), the clinical significance of the TDI findings, and a more general discussion of what type and amount of data would constitute substantial, convincing evidence of a clinically meaningful benefit with regard to the symptom of dyspnea in patients with COPD.

During the meeting, the Applicant will present an overview of the NDA to the PADAC. The FDA presentation will include:

- A discussion of the Mahler TDI instrument.
- Salient pharmacokinetic and pharmacodynamic features of tiotropium bromide.
- An overview of the Phase 3 clinical program, including:
 - The extent and findings of the safety database
 - The efficacy findings in regard to bronchodilator effect
 - The efficacy findings in regard to dyspnea effect

During the meeting, members of the PADAC are encouraged to keep in mind the following issues, on which the Agency seeks input.

- 1) The extent to which the data submitted provides convincing evidence of a clinically meaningful bronchodilator effect of Spiriva, when used in the chronic treatment of patients

CLINICAL BRIEFING DOCUMENT

Executive Summary

with COPD. Any specific further data that would be needed in order to provide such evidence.

- 2) Any specific safety concerns regarding the use of Spiriva in this patient population that might prevent approval.
- 3) Any specific safety concerns regarding the use of Spiriva in this patient population that might merit specific attention in the product label.
- 4) The overall adequacy of the safety database, any further safety information that should be obtained, and when such information should be obtained, in relation to approval.
- 5) In general, the type and amount of data that would constitute substantial, convincing evidence of a clinically meaningful benefit for a drug, with regard to the symptom of dyspnea in patients with COPD.
- 6) The extent to which the data submitted provide convincing evidence that Spiriva has a clinically meaningful effect on the symptom of dyspnea in patients with COPD.
- 7) The appropriateness of listing symptoms of COPD, which may improve based on the bronchodilator activity of a drug, as “Indications” for drugs that are approved for the treatment of bronchospasm associated with COPD.

II. Overview

The purpose of this Clinical Briefing Document is to summarize those aspects of the New Drug Application (NDA) for Spiriva[®] (tiotropium bromide) Inhalation Powder (NDA #21-395) that may be relevant to the discussions of the Pulmonary-Allergy Drugs Advisory Committee, during the meeting to be held on September 6, 2002. These aspects include human pharmacokinetic and pharmacodynamic data, reviews of the important clinical studies, and integrated discussions of both the safety and the efficacy of the drug. Although they play an important role in regulatory decision-making, issues related to the Chemistry, Manufacturing, and Controls and the Preclinical Toxicology aspects of the NDA are not included in this Clinical Briefing Document because they will not be a topic of discussion at the PADAC meeting.

Throughout the document, data sources within the NDA submission are referenced in square brackets. It is recognized that the members of the PADAC do not have access to the full NDA submission, from which these references are drawn.

A. Brief Overview of the Clinical Program

A total of 4,124 subjects participated in the clinical program. This included 224 healthy volunteers, 3,411 COPD patients, 471 asthma patients, and 18 patients with renal impairment. Of these, a total of 2,117 subjects were exposed to tiotropium by inhalation of the powder capsule formulation. This included 57 healthy volunteers, 1,723 COPD patients, and 337 asthma patients. A total of 1,701 subjects were exposed to the 18mcg dose of tiotropium.

The Phase 3 program consisted of six, multicenter, controlled “pivotal” studies in patients with COPD. For inclusion in these “pivotal” studies, patients were required to be 40 years old or older, have a smoking history of >10 pack-years, have a clinical diagnosis of COPD, and meet certain spirometry criteria ($FEV_1 \leq 60\%$ or 65% [depending on the study] of predicted and $FEV_1 \leq 70\%$ of FVC). Baseline responsiveness to bronchodilator was not tested or required. A total of 2,663 patients with COPD were enrolled in these six studies, approximately 1,300 of whom were treated with tiotropium. These studies were:

- Two, 1-year, placebo-controlled studies,
- Two, 1-year, active (ipratropium bromide MDI) controlled studies, and
- Two, 6-month, placebo- and active (salmeterol xinafoate MDI) controlled studies.

For further details regarding the clinical development program, the reader is referred to the section of this Clinical Briefing Document entitled “Description of Clinical Data and Sources.”

B. Efficacy Evaluations

The Phase 3 clinical studies used standard spirometric variables to assess for bronchodilator efficacy. In all six studies, the primary efficacy endpoint was the “trough FEV_1 response,” defined as the mean FEV_1 change from baseline at the end of the dosing interval. Both the baseline and the trough FEV_1 were calculated as the mean of two pre-treatment FEV_1 readings measured in the morning prior to administration of study medication. This primary efficacy endpoint is somewhat atypical for studies of bronchodilator drugs, which usually examine the early post-dosing bronchodilator effect (e.g. peak FEV_1) or the average FEV_1 (e.g. the area under the FEV_1 -Time curve) as the primary efficacy analysis.

CLINICAL BRIEFING DOCUMENT

Overview

One benefit of using the trough FEV₁ as the primary efficacy endpoint is that this variable provides insight into the drug's efficacy at the end of the dosing interval, thus providing support for the proposed dosing interval. One limitation with using this primary efficacy endpoint is that there is little consensus regarding what magnitude of effect constitutes a clinically important effect at the very end of the dosing interval. Customarily, in evaluating the results of a primary efficacy analysis both statistical and clinical significance are considered. In justifying a proposed dosing interval for a bronchodilator drug, the Agency has generally expected that some efficacy is maintained for the bulk of the dosing interval. However, a specific effect size at the end of the dosing interval has not been required.

Numerous secondary efficacy endpoints, including early post-dose spirometry and supplemental "rescue" albuterol use were also employed in order to examine the bronchodilator efficacy of this product. One finding from these secondary endpoints is interesting because it represents a unique pharmacodynamic feature of tiotropium bromide. That feature is the delayed onset of maximal bronchodilator response. For most orally inhaled bronchodilators, the degree of bronchodilation achieved with the first dose is not different from that of subsequent doses. With tiotropium bromide, a degree of bronchodilation is achieved with the first dose; however, the bronchodilator effect increases with multiple dosing, reaching a maximal effect at approximately Day 8. Additional secondary efficacy endpoints employed in these studies included occurrences of COPD exacerbations and patient-reported outcomes such as the Saint George's Respiratory Questionnaire and the Medical Outcomes Study SF-36.

In two of the six "pivotal" studies, the Mahler Transitional Dyspnea Index (TDI) focal score was included as a co-primary efficacy variable in order to support a proposed indication for the treatment of dyspnea in COPD patients. The TDI focal score is the sum of the individual scores of the three components of the TDI (the "functional impairment," "magnitude of task," and "magnitude of effort" components).¹ Four of the six "pivotal" studies included TDI assessments as secondary efficacy variables. In those studies, the mean values of the TDI focal scores were analyzed. After reviewing the TDI data from these studies, the Applicant decided to alter the primary efficacy endpoints for the two remaining "pivotal" studies, which were completed but for which the blind had not been broken (Studies 205.130 and 205.137). These protocols were amended to include both the trough FEV₁ response and the TDI focal score as co-primary efficacy variables. Rather than the mean value analyses used in the other studies, a "responder" analysis of the TDI focal score was specified.

At various stages during the clinical development of tiotropium bromide, the Agency informed the Applicant that, for inclusion anywhere in the product label, the TDI instrument and the proposed analysis of the TDI data must be supported by substantial evidence. Specifically, the instrument itself must be validated, the proposed "responder" threshold (sometimes referred to as the "minimal clinically important change") must be validated, and the clinical significance of any

¹ See page 45 of this document for further description of the TDI instrument.

CLINICAL BRIEFING DOCUMENT

Overview

difference in rates of “response” between active and placebo must be established. One topic for the PADAC’s discussion will be the extent to which these requirements have been met, and the extent to which the data definitively demonstrate a clinically meaningful drug effect on the symptom of dyspnea.

C. Safety

The table below summarizes the numbers of patients exposed to tiotropium, and the duration of exposure, in the six “pivotal” Phase 3 studies.

Patient Exposure to Tiotropium in the Six “Pivotal” Phase 3 Studies				[iss.pdf/p113-4]
	Total	≥101 days	≥200 days	≥ 330 days
One-year, placebo-controlled studies	550	501 (91%)	482 (88%)	302 (55%)
One-year, ipratropium-controlled studies	356	325 (91%)	316 (89%)	260 (73%)
Six-month, salmeterol- and placebo-controlled studies	402	353 (88%)	354 (88%)	not applicable

The mean age for all patients was 65 years in the one-year, placebo-controlled studies, and 64 years in the one-year, ipratropium-controlled studies and the six-month, salmeterol and placebo-controlled studies. Nearly all patients were Caucasian, and 65% to 85% were male. The mean baseline FEV₁ ranged from 1.0 to 1.25 liters, or 38-44% of predicted.

In the pivotal clinical trials safety was monitored with the following assessments:

- clinical adverse events,
- vital signs,
- physical examination,
- clinical laboratory testing, and
- electrocardiograms.

ECGs were performed at baseline and every 90 days for the duration of the study. However, the protocols did not specify the timing of the ECGs in relation to study drug administration and the case report forms did not capture that information. Therefore it cannot be assumed that the ECGs were obtained at C_{max}, as would be most desirable. However, timed ECGs were performed in a Phase 2 multiple-dose, dose-ranging study in which doses up to 44mcg were examined for up to 29 days.

The pivotal clinical studies did not include Holter monitoring. Holter monitoring was included in one Phase 2 study in which a total of 81 COPD patients were treated with tiotropium 18mcg QD for six weeks.

The safety findings are discussed in the section of this Clinical Briefing Document entitled “Integrated Review of Safety.” The following comments briefly summarize the safety findings. The incidence of death was similar in all treatment groups, and the causes of death were consistent with what might be expected in this patient population. Two causes of death were reported in the tiotropium group but not in the comparator groups. They were myocardial

CLINICAL BRIEFING DOCUMENT

Overview

infarction (4 deaths) and arrhythmia (1 death). In the one-year, placebo-controlled studies, five of the seven deaths among the tiotropium patients, but only one of the seven deaths in the placebo patients, were attributable to cardiac ischemia or arrhythmia. Fewer patients in the tiotropium groups reported serious adverse events, as compared with both the placebo and the active comparator groups. The incidence of discontinuation due to adverse events was also lower in the tiotropium groups as compared to both the placebo and active comparator groups. In the one-year, placebo-controlled studies, the most notable adverse events (AEs) were related to the gastrointestinal system (dry mouth, dyspepsia, abdominal pain, constipation, and vomiting). The occurrence of AEs in the category of “Gastrointestinal System Disorders” was 38.5% in the tiotropium group and 29.1% in the placebo group. Among these, by far the most common was dry mouth, with an incidence of 16% in the tiotropium group, and 2.7% in the placebo group. The one-year, ipratropium controlled studies demonstrated that the incidence of dry mouth was greater in the tiotropium group (12.1%) than in the ipratropium group (6.1%). Upper respiratory tract infections were also more common in the tiotropium group than in the placebo group (41.1% vs. 37.2%). There were subtle indications that tiotropium may be associated with an increased frequency of adverse cardiac effects, specifically in the category of “heart rate and rhythm disorders.” This is discussed in the subsection of the Integrated Review of Safety entitled “Adverse Events Related to the Pharmacologic Actions of the Drug.”

D. Dosing

The proposed dose of tiotropium bromide inhalation powder is 18mcg QD. This is the dosing regimen that was studied in the Phase 3 clinical program. In general, there are two aspects to a proposed dosing regimen that must be established, the dose and the dosing interval. Insight into the appropriateness of the proposed dosing interval may be taken from the results of the primary efficacy variable utilized in the Phase 3 studies, the “trough” FEV₁. The clinical development program also included single- and multiple-dose dose-ranging studies in COPD patients, using a variety of formulations and doses of tiotropium. The relevant dose-ranging studies are summarized in the section of this Clinical Briefing Document entitled “Human Pharmacokinetics and Pharmacodynamics.”

E. Special Populations

As mentioned above, the majority of the patients in the pivotal studies were men, and nearly all were Caucasian. Drug-demographic safety interactions are discussed in the section of the Integrated Review of Safety entitled “Interactions.” In the one-year, placebo-controlled studies, the AEs “dry mouth” and “constipation” occurred with greater frequency in older patients in the tiotropium group, but not the placebo group. In these studies, the AE “urinary tract infection” occurred with greater frequency in older patients in both treatment groups, although the apparent age effect was more marked in the tiotropium group. The occurrence of “dry mouth” was also more common in women in the tiotropium group, but not in the placebo group. Because very few patients in the pivotal studies were non-white, analyses for drug-race safety interactions were not informative. However, pharmacokinetic studies in African-American and Caucasian asthma patients indicate similar urinary excretion. There were no patients on tiotropium who became pregnant during the clinical development program. Because the Applicant is seeking an indication for COPD, a disease of older adults, the Applicant has not studied the drug in pediatric patients.

CLINICAL BRIEFING DOCUMENT

Overview

III. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

This NDA is submitted in support of Spiriva® (tiotropium bromide) Inhalation Powder, a long-acting anticholinergic bronchodilator intended for use in patients with COPD. In early development, the drug was identified as Ba679. This product consists of two discrete elements [summary.pdf/p44]. The first element is a hard gelatin capsule containing a pre-metered dose of the drug substance and lactose as a dry powder. The second element is the HandiHaler® inhalation device. The HandiHaler is a reusable, hand-held, breath-actuated device used to inhale the dry powder. The active component of Spiriva is tiotropium. Tiotropium is a quaternary ammonium compound.

The proposed language for the Indication is: *“for the long term, once daily, maintenance treatment of bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.”*

The proposed dose is one inhalation (18mcg) QD. The Indication section of the label will not refer to specific age groups. COPD is a disease of adults. The pivotal clinical studies performed in support of this application appropriately contained an inclusion criterion of age ≥40 years. This will be described in the Clinical Studies section of the label.

B. State of Armamentarium for Indication

The only currently approved category of drugs for COPD are the bronchodilators. Currently approved bronchodilators include several short-acting beta₂-adrenergic agonists (e.g. albuterol, pirbuterol, bitolterol, metaproterenol, and terbutaline), two long-acting beta₂-adrenergic agonists (salmeterol and formoterol), a short-acting anti-cholinergic agent (ipratropium), and theophylline. These drugs are available in various formulations, including solutions and metered dose inhalers for oral inhalation, as well as various formulations for oral ingestion. Other classes of agents, such as corticosteroids and mucokinetic agents, have been investigated for their utility in the pharmacologic management of COPD but none of these are approved for COPD in the US.

If approved, tiotropium bromide inhalation powder would represent the first once-daily oral inhalation drug indicated for COPD. The proposal to include a claim that tiotropium bromide is indicated for the treatment of dyspnea related to COPD would also be unique. No other drug is approved for the treatment of dyspnea, or any other specific symptom associated with COPD in the US.

C. Important Milestones in Product Development

This drug was developed under IND 46,687, which was originally submitted to the Agency on November 30, 1994. The indication listed at the time of the original submission was

CLINICAL BRIEFING DOCUMENT

Introduction and Background

“bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis, emphysema, and moderate to severe asthma.” [indnda.pdf/p1] In an Annual Report dated April 29, 1999, the Applicant notified the Agency that clinical development in patients with asthma had been discontinued. In a submission dated October 8, 2001, the Applicant stated that studies of the product in adults with asthma have failed to demonstrate effectiveness.

An End-of-Phase-2 meeting was held on December 3, 1996. In 1999, two pre-NDA meetings were held. The first, on May 10, 1999, focused on CMC issues. Two days later, on May 12, 1999, a General pre-NDA meeting was held to discuss issues relevant to the other review disciplines. Finally, on July 24, 2000, the Agency met with the Applicant to discuss the Applicant’s plans regarding the pursuit of a unique indication for this drug. Based on its review of the completed Phase 3 studies, the Applicant wished to discuss the possibility of pursuing a “dyspnea” indication. At that time, two additional large, 6-month studies were ongoing (Studies 205.130 and 205.137). The Applicant intended to amend the protocols for these studies in order to designate two co-primary endpoints: FEV₁ and the Mahler Transitional Dyspnea Index (TDI), in hopes of justifying the dyspnea indication. At that meeting, and in a subsequent communication (October 11, 2000) sent to the Applicant in response to an additional submission (Dated August 22, 2000) the Agency advised the Applicant that the dyspnea indication would be unique and would require substantial supportive evidence. The Agency informed the Applicant that substantial validation would be required in regard to the use of the TDI instrument, as well as justification of the clinical significance of the proposed definition of a “responder” and the clinical significance of the differences demonstrated in the percentages of “responders” in each treatment group. The Agency also requested that the NDA include comparisons of mean TDI scores, in addition to the planned “responder” analysis.

No previous NDAs have been submitted for this product.

D. Other Relevant Information

As of November 9, 2001, Spiriva (tiotropium bromide) Inhalation Powder is not marketed in any country [summary.pdf/p43]. Registration dossiers have been filed in 18 countries, and approval has been obtained in two countries, The Netherlands and New Zealand. In Europe, the Mutual Recognition Procedure is being adopted, with Netherlands serving as the Reference Member Site.

E. Important Issues with Pharmacologically Related Agents

Tiotropium is a long-acting, anticholinergic bronchodilator. Ipratropium bromide is a short-acting, anticholinergic bronchodilator that is manufactured by Boehringer Ingelheim and is approved for use in patients with COPD. The drug substance is marketed as a metered dose inhaler in two formulations: as the sole active agent (Atrovent Inhalation Aerosol), and as a combination product with albuterol sulfate (Combivent Inhalation Aerosol). Ipratropium bromide is also approved as an inhalation solution and a nasal spray. Ipratropium bromide has proven to be relatively safe in the COPD patient population. According to the product label for Atrovent Inhalation Aerosol, the product should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction. These precautions are based

CLINICAL REVIEW

Introduction and Background

on the potential systemic anticholinergic effects of the drug, and cases of precipitation or worsening of narrow-angle glaucoma and acute eye pain have been reported. Cases of hypotension and allergic-type reactions have also been reported. The most common adverse events occurring in 90-day active-controlled trials were cough (5.9%), nervousness (3.1%), nausea (2.8%), dry mouth (2.4%), gastrointestinal distress (2.4%), dizziness (2.4%), headache (2.4%), and exacerbation of symptoms (2.4%).

IV. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

1. *Summary*

The bioavailability of tiotropium is poor after oral administration (2-3%), and somewhat greater after oral inhalation (19.5%). The C_{max} after oral inhalation occurred at 5 minutes, the time of the first sample. The drug remains measurable in the blood for 2-4 hours after single-dose oral inhalation. The volume of distribution of tiotropium is quite large, 32 liters/kg. Approximately 74% of the drug is eliminated in the urine as the parent compound. Active renal secretion is likely, based on the observation that renal clearance of the drug exceeds the creatinine clearance. The fate of the remaining 26% of the dose has not been established, but it may be metabolized by a combination of non-enzymatic hydrolysis and cytochrome P450-mediated metabolism (predominantly CYP2D6, and to a lesser extent, 3A4). Although much of the drug is eliminated in the urine quickly (e.g. 44% of the administered dose by 4 hours after single dose administration), the drug persists in the urine for many days, with a terminal elimination half-life of 5 to 6 days. Despite this long half-life, daily administration for 14 days resulted in accumulation of only 2 to 3 fold. This finding, consistent with the large volume of distribution, suggests a multi-compartment model, whereby the drug is distributed to more than one physiologic compartment, from which it is slowly released back into the circulation. Older patients and subjects with impaired renal function exhibit increased plasma concentrations of tiotropium.

2. *Background*

During drug development, tiotropium was quantified using two analytical methods [biosum.pdf/p15]. The radioreceptor assay, which had a limit of quantification of 400ng/mL, was used in the initial studies to quantify the tiotropium in the urine. Subsequently, this test was replaced by a liquid chromatographic/mass spectrometric assay, which was able to measure concentrations down to 5pg/ml in human plasma and 10pg/mL in human urine. Using this assay tiotropium was measurable in the plasma up to 2-4 hours and in the urine for many days following a single dose of 18mcg.

During drug development, drug doses and concentrations were initially expressed in terms of the salt (tiotropium bromide monohydrate). Later in development, in order to comply with a European Directive, a decision was made to label the product in terms of the active entity in the molecule (i.e. the tiotropium cation) for the Phase 3 supplies and commercial drug product. In order to be able to use whole numbers, the actual drug content in the capsules was adjusted (+2.5%) [biosum.pdf/p30]. In addition, the dry powder inhalation capsules used during Phase 1 and 2 actually contained 10% more tiotropium bromide monohydrate than was expressed in the label claim [biosum.pdf/p32]. This was the Applicant's practice at that time, based on its experience with other inhalation capsules, which suggested that only about 90% of the content of an inhalation capsule actually leaves the capsule and the device during inhalation (i.e. delivered dose). Finally, it should be noted that the dry powder inhalation studies were performed with two different devices, the FO2 device (also called the Inhalator Ingelheim) and the HandiHaler

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

device. The Applicant states that these two devices showed identical functional properties and did not differ relevantly in their flow characteristics [biosum.pdf/p34].

The pharmacokinetics of tiotropium were studied in 15 clinical studies in a total of 600 subjects. These include 142 healthy male subjects in eight Phase 1 studies, 18 subjects (3 female, 15 male) with renal impairment (mild to severe), and 434 patients with COPD or asthma in six studies [biosum.pdf/p29]. The studies involved single and multiple tiotropium doses, ranging from 4.5mcg to 282mcg for dry powder inhalation, from 2.4mcg to 14.4mcg for IV infusions, and from 8.0mcg to 64mcg for oral solutions.

Five of the six studies in patients with lung disease included sparse data sets with more extensive urine samplings [biosum.pdf/p16]. The sixth included single- and multiple-dose administration and frequent blood and urine collections (Study #205.133; Report #U00-3029).

The PK studies included the following routes of administration [biosum.pdf/p77]:

- Intravenous: Studies 205.105 (Report U99-1315), 205.107 (Report U98-2282), and 205.134 (Report U00-1289).
- Oral (solution): Studies 205.105 (Report U99-1315) and 205.106 (Report U97-2337)
- Oral inhalation:
 - Piezoelectric dispersion of solution: 205.101 (Report U93-0252)
 - BINEB device (dispersion of solution, later modified to the RESPIMAT device): 205.112 (Report U97-2462)
 - Dry powder inhalation: Studies 205.102 (Report U93-0704), 205.103 (Report U93-0939), 205.104 (Report U93-0940), 205.105 (U99-1315), 205.108 (Report U96-3068), 205.117 (Report U99-3169), 205.120 (Report U94-0198), 205.127 (Report 00-0077), 205.133 (Report U00-3029), and 205.201 (Report U98-3174)

The following table summarizes the clinical studies in which pharmacokinetic assessments were made.

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

Clinical Studies with Pharmacokinetic Assessments				[biosum.pdf/p39-65]
Study # (Report #)	Design/ Duration	Diagnosis/ # of Subjects	Route	Treatments
205.101 (U93-0252)	R, SB, PC/ Single Dose	Healthy males aged 21-50 years/ N=6 per treatment group	Inhalation Solution (via piezo electric)	0.8, 4, 8, 20, 40, 80, or 160mcg, or pbo
205.102 (U93-0774)	R, SB, PC/ Single Dose	Healthy males aged 21- 50 years/ N= 6 per treatment group	Inhalation (inhalet via FO2 device)	35.2, 70.4, 140.8, or 281.6mcg, or pbo
205.103 (U93-0939)	R, DB, PC, XO/ 7 days	Healthy males aged 21-50 years/ N=12	Inhalation (inhalet via FO2 device)	70.4 or 140.8mcg, or pbo
205.104 (U93-0940)	R, DB, PG 14 days	Healthy males aged 21-50 years/ N=15	Inhalation (inhalet via FO2 device)	8.8, 17.6, or 35.2mcg
205.105 (U99-1315)	R, OL, PG Single dose	Healthy males aged 21-50 years/ N=12 per treatment group	Inhalation (via HandiHaler), Oral solution, and Intravenous solution	108mcg inhaled; 64mcg oral soln.; 14.4mcg IV soln.
205.106 (U97-2337)	One day at each dose level	Healthy males aged 21-50 years/ N=4-6 at each dose level	Oral solution	8, 16, 32, or 64mcg, or pbo
205.107 (U98-2282)	DB, PC, increasing dose 3 days	Healthy males aged 21-50 years/ N=17	Intravenous solution	Single dose 2.4 or 14.4mcg, two subsequent daily doses of 4.8 or 9.6mcg; or pbo
205.108 (U96-3068)	R, DB, PC, PG 4 weeks	COPD patients N=169 (33-35 per group)	Inhalation (inhalet via FO2 device)	4.4, 8.8, 17.6, or 35.2mcg, or pbo
205.112 (U97-2426)	PC, DB within group, multiple rising dose 14 days	Healthy males aged 21-50 years/ N=36 (9 per group)	Inhalation Solution (Respimat device)	8, 16, or 32mcg, or pbo
205.114/ 205.117 (U99-3169)	R, DB, PC, PG 49 weeks	COPD N=470	Inhalation (HandiHaler device)	18mcg or pbo
208.120 (U94-0198)	R, DB, PC, XO Single dose	COPD N=35	Inhalation (inhalet via FO2 device)	8.8, 17.6, 35.2, or 70.4mcg, or pbo
205.127 (U00-0077)	R, DB, PC, PG 3 weeks	COPD N=202	Inhalation (inhalet via FO2 device and solution via Respimat)	Respimat: 1.25, 2.5, 5, 10, or 20mcg; Inhalet: 18mcg; or pbo
205.133 (U00-3029)	OL 14 days	COPD N=29	Inhalation (HandiHaler Device)	18mcg
205.134 (U00-1289)	OL Single dose	Volunteers w/ renal impairment N=24	Intravenous solution	4.8mcg
205.139	DB, PC, XO Single dose	COPD N=28	Inhalation (inhalet via HandiHaler)	9, 18, or 36mcg, or pbo
205.201 (U98-3174)	R, DB, PC, PG 21 days	Asthma N=204	Inhalation (inhalet via HandiHaler)	4.5, 9, 18, or 36mcg, or pbo

R= randomized; SB= single blind; DB= double blind; PC= placebo controlled; PG= parallel group; OL= open label; pbo=placebo

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

3. Absorption

Tiotropium was administered to humans as intravenous infusion, oral solution, and by inhalation. Inhalation was accomplished by various means including piezoelectric dispersion, dry powder inhalation capsules, and aerosolization of aqueous solution [biosum.pdf/p16]. Tiotropium was shown to be poorly absorbed after oral ingestion of a solution (absolute bioavailability of 2-3% for a 64mcg dose) (Study #205.105, Report #U99-1315). Administration as an orally inhaled dry powder resulted in greater bioavailability (19.5% after an inhaled dose of 108mcg [3 doses of a 36mcg dry powder capsule using the HandiHaler device] in Study #205.105, Report #U99-1315) [biosum.pdf/p16]. After oral inhalation of a single dose of dry powder formulation, tiotropium may be detected in the blood at the time of the first sample (levels of 17-19pg/mL 5 minutes following inhalation of 18mcg) [biosum.pdf/p18]. Tiotropium remains measurable until 2-4 hours after oral inhalation of a single dose. Interestingly, the second once-daily dose generates consistently higher AUC values than expected from the first dose. The Applicant states that this is not likely due to limited assay sensitivity for the first dose, since a similar finding was observed after intravenous dosing (Study #205.107, Report #U98-2282). The Applicant postulates that the finding may be due to incomplete saturation of binding sites (including muscarinic receptors) after the first dose, and a very slow dissociation constant of the tiotropium binding site complex. Once all binding sites are at least near to saturation, more tiotropium can escape from the tissue and the drug appears faster in the systemic circulation [biosum.pdf/p18].

Tiotropium concentrations after oral inhalation differ in healthy subjects, younger COPD patients, and older COPD patients. Five minutes after a single inhalation of 17.6mcg in these subjects, the geometric mean tiotropium concentrations were 24.6pg/mL (Study 205.104), 15.3pg/mL, and 9.63pcg/mL (Study 205.133), respectively [biosum.pdf/p83].

Although much of the drug is rapidly eliminated in the urine (e.g. 44% by 4 hours, 48% by 8 hours, and 54% by 24 hours), tiotropium remains present in the urine for many days, and thus has a very long elimination half-life (5-6 days) (Study #205.105, Report #U99-1315). After multiple administration, pharmacokinetic steady state was reached after 2-3 weeks.

4. Distribution

In rats, autoradiography studies after intratracheal (Study #not given, Report #U90-0448) and intravenous (Study #PK-99011, Report #U99-0210) administration indicated that tiotropium distributes in higher amounts in the lung, liver, kidney, stomach, and gastrointestinal tract, with particularly long persistence in lung tissue after intratracheal administration [biosum.pdf/p18]. In addition, tissue sampling performed in Study #PK-99011 demonstrated notable distribution in the brown fat, pancreas, salivary gland, prostate, hypophysis, and thyroid gland [U99-0210.pdf/p15]. In three autoradiography studies in rats, distribution to the brain was not detected (Study #, Report #U90-0448), detected at low levels (Study #PK-99011, Report #U99-0210), or detected at higher levels (Study #PK-98005, Report #U99-0205) [biosum.pdf/p19]. Experiments in rats demonstrated that tiotropium crosses the placenta and is excreted in the milk of lactating rats [biosum.pdf/p19].

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

In an *in vitro* human plasma binding study, 72% of the drug was bound to plasma proteins. In humans, the volume of distribution after a 14.4mcg intravenous infusion was 2665 Liters or 32 L/kg (Study #205.105, Report #U99-1315) [biosum.pdf/p78]. This large volume of distribution indicates extensive tissue binding.

5. Metabolism and Elimination

Tiotropium is an ester of the N-quaternary alcohol N-methylscopin with dithienylglycolic acid, which is cleaved in solution at physiologic pH with a half-life of up to 17 hours, and more slowly at lower pH. There is evidence to suggest that this ester hydrolysis is non-enzymatic [biosum.pdf/p66].

Tiotropium is predominantly eliminated via renal secretion of unchanged drug. After intravenous administration in healthy young men, 73.6% of the dose was recovered in the urine (Study #205.105, Report #U99-1315). The fate of the remaining quarter of the intravenous dose in young healthy subjects is not known. It is expected that a portion of the drug is metabolized by hydrolysis or by the cytochrome P450 system; however, mass balance studies were not performed. The Applicant suggests that binding of tiotropium to its binding sites may prevent cleavage. Once it is released from its binding site and appears in the circulation, it is rapidly cleared. Renal clearance after both intravenous and inhalation exposure exceeded calculated creatinine clearance, indicating that tiotropium is actively excreted by a transporter. It is not known which cation transporter is responsible for the active renal secretion. The Applicant states that *in vitro* studies using cyclosporine, a competitive inhibitor of p-glycoprotein, suggest the transporter is not p-glycoprotein [biosum.pdf/p20].

Urinary data in healthy subjects demonstrate that tiotropium was excreted with a geometric mean elimination half-life of 5.71 days after single-dose intravenous administration and 4.84 days after single-dose inhalation. Urinary excretion indicated an accumulation by a factor of 2-3 from the first to the fourteenth inhalation [biosum.pdf/p21]. Thus, the AUC after 14 days is 2-3 times higher than after a single dose.

Tiotropium does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A in human liver microsomes [biosum.pdf/p22]. However, *in vitro* studies showed that quinidine, a CYP 450 2D6 and 3A4 inhibitor, can inhibit the metabolism of tiotropium [biosum.pdf/p25]. The submission dated April 18, 2002 (Four-Month Safety Update), contained the following information. Poor metabolizers of CYP 2D6 had a 33% higher tiotropium AUC_{0-4h} after intravenous administration in comparison to extensive metabolizers [4/18/02 submission, iss.pdf/p269].

Pharmacokinetic studies to assess special populations indicate the following [biosum.pdf/p22-4]:

- Gender does not significantly influence drug plasma or urinary excretion of tiotropium.
- Elderly COPD patients (>65 years) demonstrate decreased renal clearance of tiotropium and increased plasma concentrations. In Study 205.133, the renal clearance was 326mL/min in younger COPD patients (mean age: 53 years), versus 163mL/min in the older patients (mean age: 74 years). The AUC_{0-4h} values were 18.2pg.h/mL in the younger group and 26.1pg.h/mL in the older group.

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

- Patients with renal impairment demonstrate lower renal clearance and higher plasma concentrations. Tiotropium plasma concentrations (AUC_{0-4h}) were 39, 81, and 94% higher in mild, moderate, and severe renal impairment when compared to control subjects.
- The effect of hepatic impairment was not studied. The Applicant states that such studies were not performed because renal excretion dominated the elimination of tiotropium in healthy volunteers.
- The Applicant states that the effect of chronic pulmonary disease on the absorbed fraction of the inhaled dose is not exactly known because this effect is hard to separate from the confounding effects of age and formulation on the urinary excretion. A study in asthma patients suggested that increased severity of lung disease is associated with decreased urinary excretion. This effect was not demonstrated in studies with COPD patients.
- African American and Caucasian asthma patients excreted very similar amounts of tiotropium after once daily inhalations of 4.5, 9, 18, or 36mcg of tiotropium.

6. Drug-Drug Interactions

The Applicant states that tiotropium is not expected to influence the metabolism of other drugs because of “the very small dose of tiotropium and the lack of inhibition of CYP 450 isoenzymes by tiotropium.” [biosum.pdf/p25] The Applicant also states that it is unlikely that other drugs will influence the metabolism of tiotropium, although the possibility of such interactions “cannot be completely excluded.” It is possible that a drug that inhibited the renal cation transporter could result in increased plasma tiotropium concentrations. The submission dated April 18, 2002 (Four-Month Safety Update), included data from a pharmacokinetic study in which repeated supratherapeutic doses of cimetidine to inhibit these transporters increased the tiotropium AUC_{0-4h} by 20%, while repeated 300mg doses of ranitidine had no effect (Study 205.222) [4/18/02 submission, iss.pdf/p269].

The effect of food on the oral bioavailability was not examined.

Factors that can increase systemic exposure are impaired renal function, concomitant cimetidine (inhibitor of transporter, 20%), and 2D6 poor metabolizers (33%) [4/18/02 submission, iss.pdf/p269].

B. Pharmacodynamics

1. Efficacy Dose-Ranging

The Applicant indicates that a total of 22 studies have been completed to evaluate the pharmacology of tiotropium [hpsum.pdf/p10]. This section of the Clinical Briefing Document will focus on the dose-ranging studies used to support the proposed dose. The COPD dose-ranging studies are listed in the table below.

COPD Dose-Ranging Studies (Inhalation Powder)							[hpsum.pdf/p12 and ise.pdf/p88]
Study # Country/ Dates	Design	Treatments (Tiotropium)	Device	Duration	# of Subjects	Population	Primary Endpoint
205.119	Dose-ranging	10mcg	RESPIMAT	Single	6	COPD	FEV ₁

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

COPD Dose-Ranging Studies (Inhalation Powder)							[hpsum.pdf/p12 and ise.pdf/p88]
Study # Country/ Dates	Design	Treatments (Tiotropium)	Device	Duration	# of Subjects	Population	Primary Endpoint
Netherlands 11/91-4/92	Open label XO	20mcg 40mcg 80mcg 160mcg		Dose	(2F/ 4M)		
205.120 Netherlands 10/92-5/93	Dose-ranging R, DB, PC, XO	10mcg 20mcg 40mcg 80mcg Placebo	INHALATOR INGELHEIM (FO ₂)	Single Dose	35 (3F/ 32M)	COPD	FEV ₁
205.139 Japan 7/98-5/99	Dose-ranging R, DB, PC, XO	11.3mcg ¹ 22.5mcg ¹ 45mcg ¹ Placebo	HANDIHALER	Single Dose	27	COPD	FEV ₁
205.108 US 1/95-9/95	Dose-ranging Multicenter, R, DB, PC, PG	4.4mcg ² QD 8.8mcg ² QD 17.6mcg ² QD 35.2mcg ² QD Placebo QD	INHALATOR INGELHEIM (FO ₂)	4 Weeks	169 (73F/ 96M)	COPD	FEV ₁

Summaries of the COPD Dose-Ranging Studies

- Study 205.119: “Pilot dose-escalation study of Ba 679 BR in chronic obstructive pulmonary disease.” (Report #U92-0750)
 - This was an open-label, single-dose, five-period, cross-over study performed in The Netherlands between 11/91 and 4/92 [U92-0750.pdf/p16]. A total of six patients with COPD received the following doses of tiotropium inhalation solution, using the RESPIMAT device: 10mcg, 20mcg, 40mcg, 80mcg, and 160mcg. The duration of the washout period between doses was determined based on the pharmacodynamic effect. The washout was specified to be at least 48 hours after the last observed efficacy (defined as FEV₁ ≥15% above baseline). For inclusion into the study, patients were required to demonstrate reversible airway obstruction, defined as a >15% improvement in FEV₁ 30 minutes after inhalation of ipratropium bromide, and to report coughing and excess mucus production on most days for at least 3 months of the year for at least 2 successive years. The primary endpoints were the peak FEV₁, the time to peak FEV₁, and the area under the 24-hour FEV₁ curve (divided by 24).
 - The mean peak FEV₁ change from baseline showed dose ordering for doses up to 80mcg (21% for 10mcg, 30% for 20mcg, 32% for 40mcg, 47% for 80mcg, and 43% for 160mcg) [U92-0750.pdf/p18]. The mean time to peak FEV₁ change from baseline, which ranged from 110 to 148 minutes, did not show dose-ordering [U92-0750.pdf/p43]. The FEV₁ AUC_{0-24h}/24 showed approximate dose-ordering (with the exception of the 40mcg dose, which was inferior to the 20mcg dose on this parameter) [U92-0750.pdf/p43].
 - The serial FEV₁ curves demonstrate an interesting finding. In all dose groups, the FEV₁ declined gradually to a nadir at 23 hours. However, in all dose groups the 24-hour FEV₁ measurement was remarkably higher than the 23-hour measurement. Because of this finding, hourly spirometry was continued from 24 to 29 hours in the 160mcg dose cohort. Each of these measures was notably higher than the 23-hour nadir. **Reviewer’s Note:**

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

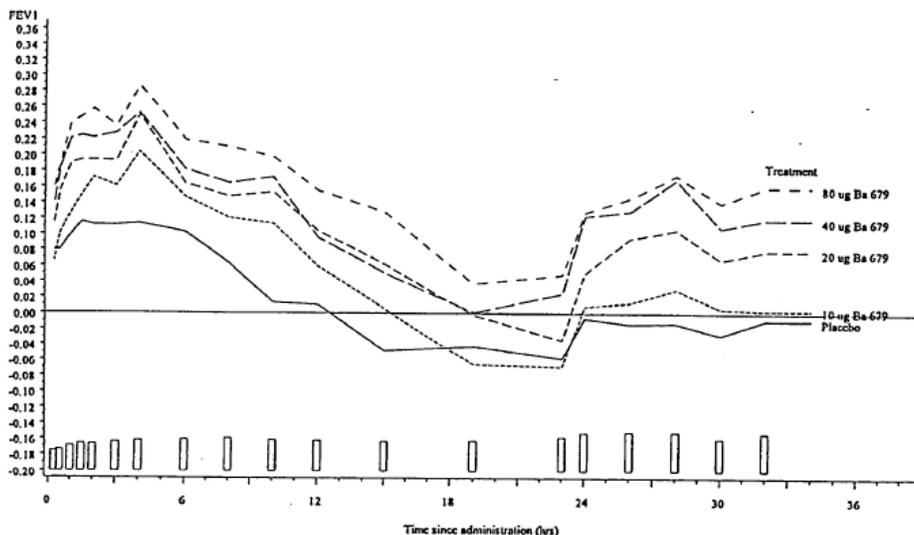
This is an unusual finding. However, interpretation is difficult in the absence of a placebo group.

- This was a pilot study that demonstrated a dose-response bronchodilator effect of tiotropium . However, it is difficult to draw conclusions relevant to this NDA based on this study because: 2) the dose escalation was not blinded; 2) the washout periods were not likely sufficiently long to allow elimination of previous doses; and 3) the formulation and delivery device differ substantially from the proposed drug product. The study drug was administered as an inhalation solution, using the RESPIMAT device. The significance of the unusual finding of improvements in FEV₁ between the 23-hour and 24-hour measurements is not known.
- 205.120: “Dose-response and time-response study of Ba 679 BR in patients with chronic obstructive pulmonary disease.” (Report #U94-0198)
 - This was a randomized, double-blind, placebo-controlled, single dose study performed in The Netherlands, between October, 1992 and May, 1993 [U94-0198.pdf/p26]. A total of 35 patients (32 male, 3 female) with COPD received the following doses of tiotropium dry powder capsule using the Inhalator Ingelheim device (also known as the FO2 device): 10mcg, 20mcg, 40mcg, and 80mcg, and placebo. The washout period between dosing was 72 hours. For inclusion into the study, patients were required to demonstrate reversible airway obstruction, defined as a >15% improvement in FEV₁ 30 minutes after inhalation of ipratropium bromide. The primary efficacy variable was FEV₁, focusing on peak response, and average FEV₁ over a various time periods (8, 12, 24, and 32 hours).
 - The baseline FEV₁ on the first test day was significantly different from other test days (p=0.001), indicating carry-over effect. **Reviewer’s Comment: Given the pharmacokinetics of this drug, it is not surprising that carry-over effects would be demonstrated in a study using a 72-hour washout period.** In addition to performing analyses that did not attempt to adjust for carry-over effects, the Applicant performed two additional analyses in order to adjust for carry-over effects. In one analysis, a parallel group comparison was performed based only on the test day 1 data. In a separate analysis, comparisons were made using a data set that excluded visits following a visit in which the subject received a 20, 40, or 80mcg dose of tiotropium.
 - As seen in Study 205.119, the FEV₁ increased in the period following the 23-hour measurement. The figure below illustrates this data. Note that the data illustrated in this figure do not reflect adjustments for carry-over effects.

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

Figure 5.1.1.1 - A: Increase in Adjusted Mean* FEV₁ From Test-Day Baseline - Intent-To-Treat Data Set



Note that in the data set illustrated in the figure above, which does not attempt to adjust for carry-over effect, the post-23-hour increase in FEV₁ is seen to a small degree in the placebo group, although the effect was much more pronounced in the drug treated groups, particularly at doses above 10mcg. The figures below, using adjustments for carry-over effects (either Test Day 1 only data, or a data set that excludes test days following test days in which doses of tiotropium greater than 10mcg were given), suggest that this phenomenon is not seen with placebo and is a drug-related finding.

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

Figure 5.1.1.2 - A: Increase in Adjusted Mean * FEV₁ From Test-Day Baseline, Excluding Test Days Which Follow Ba 679 BR 20 µg, 40 µg or 80 µg - Intent-To-Treat Data Set

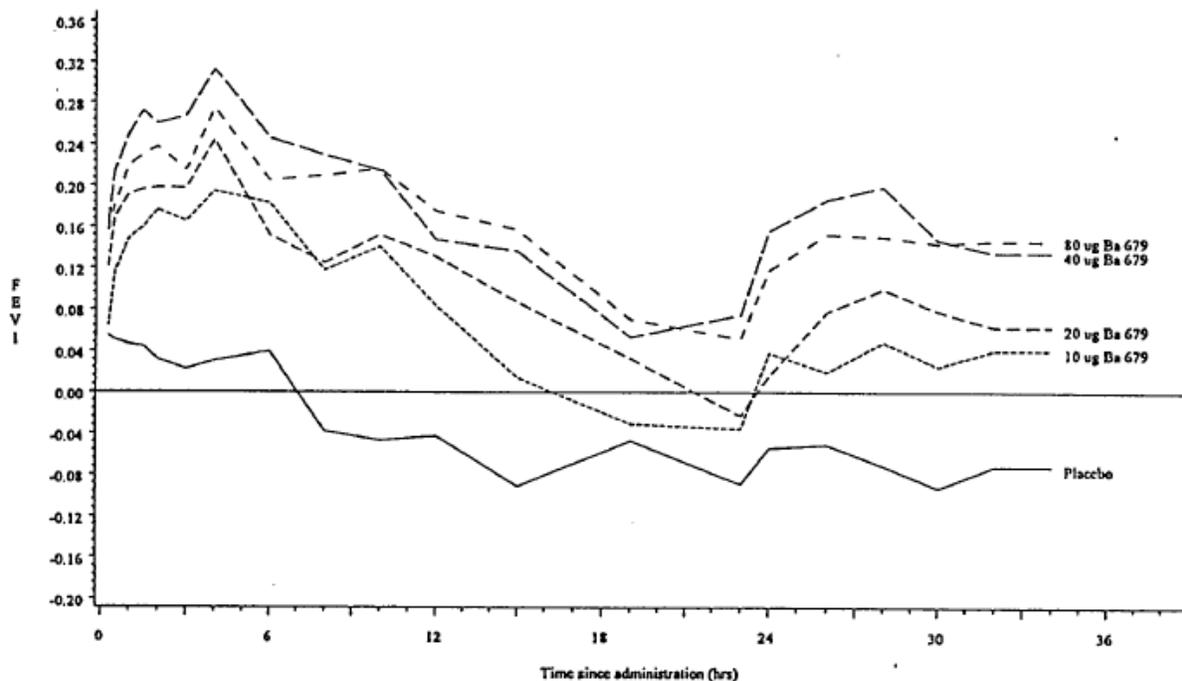
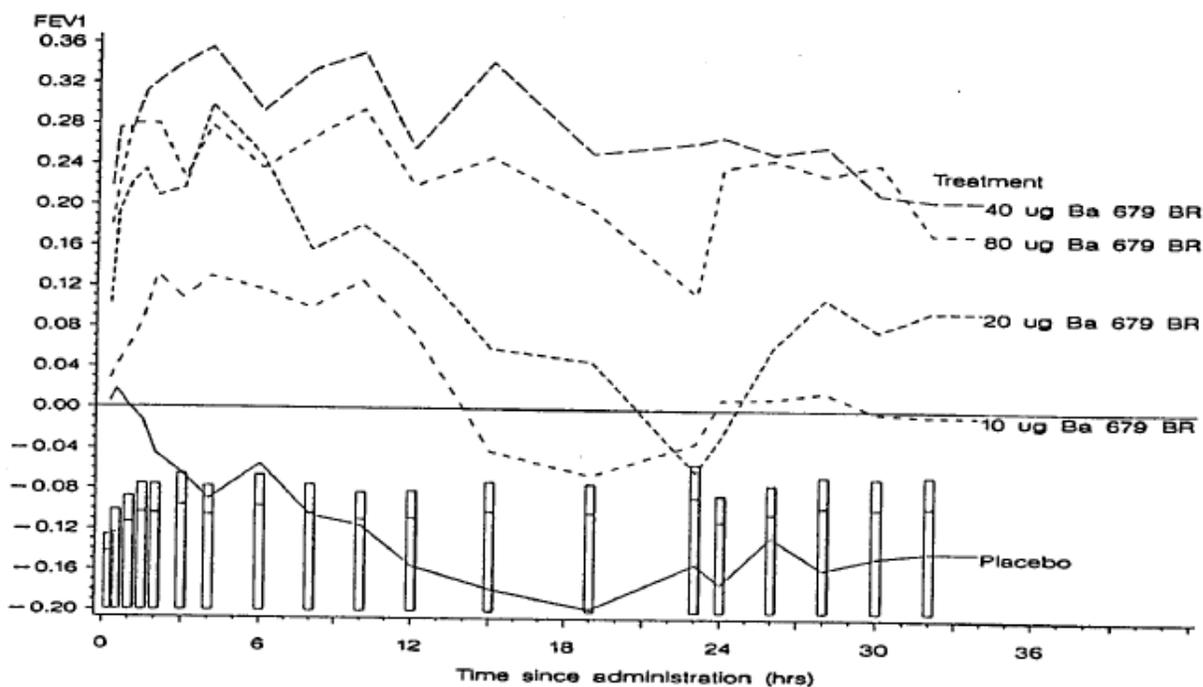


FIGURE 5.1.1.3 - A: Increase in Adjusted Mean FEV₁ from Test-Day Baseline by Treatment on First Test Day Only



CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

- The serial FEV₁ data suggest a dose-response effect in the dose range of 10mcg to 40mcg. The 80mcg dose does not seem to provide added benefit above the 40mcg dose.
 - The incidence of adverse events was comparable across the five treatment groups. There was no evidence of systemic anticholinergic effects (dry mouth, increased heart rate). Increases in systolic and diastolic blood pressure were noted in all treatment groups, including placebo. However, carry-over effects could not be ruled out.
- 205.139: “Dose ranging study of Ba 679 BR inhalation powder following single inhalation in COPD patients.” (Report #U00-0156)
 - This was a randomized, placebo-controlled, four-period, cross-over study performed in Japan between July 27, 1998, and May 22, 1999 [U00-0156.pdf/p10]. A total of 27 patients with COPD received the following doses of tiotropium inhalation powder, using the HandiHaler device: 11.3mcg, 22.5mcg, 45mcg, or placebo. *Note: The Applicant states that the labeling method for tiotropium inhalation powder differs in Japan. The doses labeled 11.3mcg, 22.5mcg, and 45.0mcg in Japan are equivalent to the doses labeled 9mcg, 18mcg, and 36mcg elsewhere [U00-0156.pdf/p28].* Twenty-four hour serial spirometry was performed at each dose level. The duration of the washout period between doses was ≥ 7 days. For inclusion into the study, patients with COPD were required to demonstrate reversible airway obstruction, defined as a $>10\%$ improvement in FEV₁ at 1 hour after inhalation of an anticholinergic agent (Tersigan® Aerazol). The primary endpoint was the peak FEV₁. Secondary endpoints included FEV₁ AUC_{0-24h}, time to peak FEV₁, time to response (defined as an increase in FEV₁ of $\geq 15\%$).
 - Carry-over effects were not observed [U00-0156.pdf/p86]. However, the drug was detected in some urine samples *before dosing* [U00-0156.pdf/p84]. Peak FEV₁ was significantly higher in all active treatment groups, as compared with placebo. A dose response effect was demonstrated for peak FEV₁ and FEV₁ AUC_{0-24hours}. Although the incremental improvement in peak FEV₁ between the 22.5mcg dose and the 45mcg dose was minimal, the increment in FEV₁ AUC_{0-24hours} was more apparent [U00-0156.pdf/p68,70]. A significant dose-response effect was not seen in regard to time to response or time to peak response [U00-0156.pdf/p71]. No safety concerns were reported (adverse events, laboratory measurements, vital signs, oxygen saturation, ECG).

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

- The serial FEV₁ curves in other single-dose dose-ranging studies indicated a rise in the FEV₁ at 24 hours (see discussions above). In this study a similar phenomenon was demonstrated. This effect was seen in all groups, including placebo, suggesting that it may represent, in part, a normal circadian variation. However, the figure below suggests that the effect was greater in the active treatment groups, suggesting an element of drug effect [U00-0156.pdf/p74].

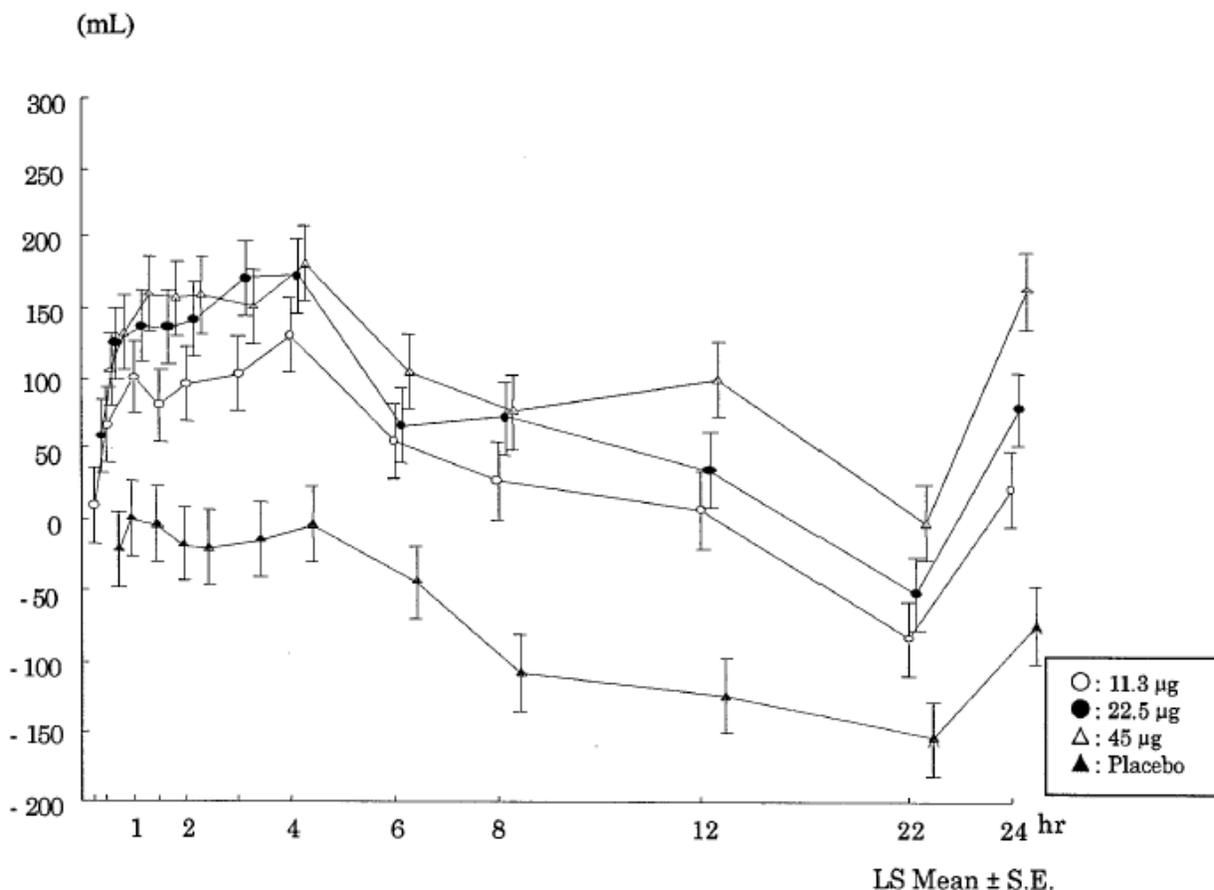


FIGURE 11.4.1.2: 3 Time Course of Changes in FEV_{1.0} (LS Mean)

- 205.108: “Randomized, multiple-dose, double-blind, parallel group study to determine the optimal dose of Ba 679 BR Inhaled as a dry powder in patients with chronic obstructive pulmonary disease.” (Report #U96-3068)
 - This was a multicenter, randomized, double-blind, placebo-controlled, multiple-dose, parallel group study performed in the US between January 16, 1995, and September 19, 1995 [U96-3068.pdf/p24]. A total of 169 patients with COPD received one of the following doses of tiotropium inhalation powder (expressed as the tiotropium cation), using the HandiHaler device for the four-week treatment period: 4.4mcg, 8.8mcg, 17.6mcg, or 35.2mcg, or placebo. *Note: The doses of active drug expressed in terms of tiotropium bromide monohydrate are 5.5mcg, 11mcg, 22mcg, and 44mcg.* Study

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

medication was dosed once daily, at 12 noon. Spirometry was conducted weekly at 8:00AM, 10:00AM, and 12 noon. During the weekly visits during the treatment period, study drug was administered following the 12 noon spirometry, and serial spirometry was conducted hourly for six hours post-drug administration. The primary variable was FEV₁, “with emphasis on the last four hours of the dosing interval” [U96-3068.pdf/p32]. Secondary endpoints included FEV₁ during the first six hours after the first dose and after multiple daily dosing at the end of each of the four weeks.

- All doses were statistically more effective than placebo [U96-3068.pdf/p71]. No statistically significant differences were seen among doses. The six-hour serial spirometry on the first treatment day shows evidence of a dose-response effect, however, the incremental benefit from the 17.6mcg and 35.2mcg doses is slight [U96-3068.pdf/p66]. The trough FEV₁ data following multiple daily dosing indicates little consistent difference among the doses in the range of 4.4mcg to 17.6mcg [U96-3068.pdf/p67]. The trough FEV₁ for the 35.2mcg dose is consistently higher than the other doses. The Applicant fitted a maximum efficacy (E_{max}) model to the dose-response data including all trough FEV₁ measurements from Week 2 onward [hpsum.pdf/p52]. In this model, the 8.8mcg dose provided 75%, the 17.6mcg dose provided 86%, and the 35.2mcg dose provided 92% of the maximum effect.
- There were no dose-dependent increases in the incidence or severity of any adverse event [U96-3068.pdf/p94]. Dry mouth was the only event that appeared to be drug-related.

The four studies summarized above utilized either an inhalation solution or an inhalation powder formulation. The following study examined dose-ranging using an inhalation solution formulation and one dose level of an inhalation powder formulation.

- 205.127: “Pharmacodynamic and pharmacokinetic dose ranging study of tiotropium bromide administered via Respimat device in patients with chronic obstructive pulmonary disease (COPD): A randomized, 3-week, multiple-dose, placebo-controlled, intraformulation double-blind, parallel group study.” (Report #U00-0077)
 - This was a multicenter, randomized, double-blind, placebo-controlled, multiple-dose, parallel group study performed in the France between 1998 and 1999 [U00-0077.pdf/p18]. A total of 202 patients with COPD received one of the following doses of tiotropium inhalation solution, using the Respimat device: 1.25mcg, 2.5mcg, 5mcg, 10mcg, or 20mcg, or tiotropium inhalation powder 18mcg using the HandiHaler device, or placebo. The treatment period was 3 weeks. Study medication was dosed once daily, between 8:00AM and 10:00AM. Spirometry was conducted at each weekly visit at: 120, 60, and 5 minutes prior to dosing, immediately following dosing, and at 60, 120, 180, and 240 minutes after dosing. The primary variable was FEV₁, at Day 23, “with emphasis on the last two hours of the dosing interval” [U00-0077.pdf/p47]. Secondary endpoints included FEV₁ during the first four hours post-dose.
 - Trough FEV₁ data (defined as the mean of the three pre-dosing values) from Day 7, Day 14, and Day 21 did not suggest a consistent dose-response effect for the Respimat groups [U00-0077.pdf/p62]. The trough FEV₁ was consistently higher in the 18mcg HandiHaler

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

- group than in the other treatment groups. Interestingly, the placebo response was consistently greater in the Respimat placebo as compared to the HandiHaler placebo.
- Dry mouth appeared to be drug-related, and occurred more frequently in the higher dose groups [U00-0077.pdf/p86].

The COPD efficacy dose-ranging studies summarized above were submitted, in part, to support the proposed dose, which is 18mcg QD. They are somewhat difficult to interpret for this purpose because of several factors. These factors include inadequate washout periods in crossover studies, different formulations and delivery devices used, differences in the actual drug content due to changes in labeling conventions (See Section III, A above), and non-blinded dosing (in one case). The only COPD dose-ranging study that used the proposed HandiHaler device was the single-dose study from Japan. The only multiple-dose, dose-ranging study utilized the Inhalator Ingelheim (FO2) device, rather than the HandiHaler. Nonetheless, these studies generally demonstrate a dose-response pharmacodynamic relationship. The added efficacy benefit of the highest dose examined was small or non-existent. The single-dose DPI study that used a 7-day washout, and the multiple-dose DPI study supported suggested that a dose of approximately 18mcg was superior to lower doses, and nearly as effective as a dose of approximately 36mcg. This would support the proposed dose of 18mcg.

2. Tolerability Dose Ranging

Seven human pharmacology studies were performed to assess the pharmacodynamic properties and tolerability of tiotropium, in relation to dose in healthy volunteers. These included various formulations routes of administration (inhalation powder in Studies 205.102, 205.104, and 205.104, inhalation solution in Studies 205.101 and 205.112, oral ingestion in study 205.106, and IV infusion in Study 205.107) [hpsum.pdf/p14]. Two of the five inhalation studies evaluated single dose administration and three of the five evaluated multiple dose administration. The single-dose inhalation studies examined doses up to 281.6mcg and the multiple-dose inhalation studies used doses up to 140.8mcg. In these studies, no effects were noted on pupil diameter, vital signs, ECG, or clinical laboratory tests [hpsum.pdf/p15]. Dose-related reports of dry mouth and reductions in salivary secretion were noted after multiple daily doses of 70.4 and 140mcg of the inhalation powder and after 32mcg of the inhalation solution from the RESPIMAT device. Reports of dry mouth and taste perversion were dose-related. Dry mouth was reported in 60-100% of subjects receiving multiple daily doses of 32 to 142mcg, and was reported in 0-22% of subjects receiving 8 to 17.6mcg. Taste perversion was reported in 17-83% of subjects following single doses of ≥ 40 mcg, and was not reported at lower single doses. After multiple daily dosing, taste perversion was reported by up to 83% of subjects, in a dose-dependent fashion. Dry mouth was not reported in the IV dosing studies. These observations in healthy volunteers were considered in dose selection [hpsum.pdf/p54]. The excessive incidence of dry mouth at doses at and above 32mcg suggested that a lower dose would be preferable.

In the dose-ranging studies performed in COPD patients, no drug effects were seen in regard to vital signs, ECG, or clinical laboratory values. With the exception of dry mouth, adverse events were comparable across all treatments, including placebo. Dry mouth was not observed in the

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

single-dose studies. In the multiple-dose studies, 5.2% of patients reported dry mouth, with an onset ranging from 1 to 29 days (mean 10.6 days, median 3 days) and duration of 8 to 52 days (mean 29.7 days, median 28 days) [hpsum.pdf/p16]. The time to onset and duration of this adverse effect did not appear dose-related. Taste perversion was not reported in the COPD dose-ranging studies.

3. Pharmacologic Properties Related to Possible Safety Concerns (Pupillary Effects)

Because of possible ocular effects of this drug, the Applicant performed a randomized, placebo-controlled, double-blind, parallel group study examining the effects of topical ocular administration of tiotropium (Study 205.138) [hpsum.pdf/p56-7]. A total of 48 healthy male volunteers participated in this study. Six subjects received one of the following single doses of tiotropium in one eye: 0.02, 0.04, 0.08, 0.16, 0.28, or 0.4 μ g, and twelve subjects received placebo. The Applicant indicates that pupil diameter, pupillary reflex, intraocular pressure, accommodation, vital signs, and clinical laboratory values did not reveal any clinically relevant, drug-induced changes.

4. Onset of Pharmacodynamic Steady State

The onset of pharmacodynamic steady state was examined Study 205.129 (Report #U99-1072), which was performed in a subset of subjects in one of the one-year, double-blind, ipratropium-controlled, parallel-group studies (Study 205.122A/205.126A, reviewed in Section XI of this document) [hpsum.pdf/p57]. In this sub-study, 31 subjects (25 men, 6 women; n=20 treated with tiotropium and n=11 treated with ipratropium) underwent more frequent spirometry than was required in Study 205.122A/205.126A [U99-1072.pdf/p16]. Additional spirometry was performed on one hour prior to and just prior to dosing, and at 30, 60, 120, 180, 240, 300, and 360 minutes post-dosing on Days 1, 2, 3, 8, and 50. After completion of the six-hour post-dose serial spirometry, the subjects inhaled 2 puffs of ipratropium or placebo and additional pulmonary function tests were conducted at 30, 60, and 120 minutes after this. Of the 31 randomized subjects, only the 28 subjects with complete data were used in the efficacy analysis [U99-1072.pdf/p42].

As demonstrated in the table below, data for the trough, peak, and average FEV₁ indicate that the maximum effect (“steady state”) was achieved on Day 8, and remained stable at Day 50.

Study 205.129: Mean (SE) FEV ₁ Trough, Peak, and Average Response (Liters) (Completers Data Set) [U99-0172.pdf/p48]			
Response	Test Day	Tiotropium (N=17)	Ipratropium (N=11)
Trough	Baseline	1.04 (0.09)	1.07 (0.12)
	2	0.17 (0.03)	0.05 (0.03)
	3	0.14 (0.03)	0.05 (0.06)
	8	0.19 (0.02)	0.00 (0.07)
	50	0.19 (0.04)	0.06 (0.08)
Peak	Baseline	0.35 (0.02)	0.33 (0.04)
	2	0.40 (0.03)	0.33 (0.06)
	3	0.35 (0.03)	0.36 (0.06)
	8	0.37 (0.02)	0.33 (0.08)
	50	0.39 (0.04)	0.34 (0.04)
Average	Baseline	0.27 (0.02)	0.20 (0.03)
	2	0.30 (0.03)	0.23 (0.06)

CLINICAL BRIEFING DOCUMENT

Human Pharmacokinetics and Pharmacodynamics

Study 205.129: Mean (SE) FEV₁ Trough, Peak, and Average Response (Liters) (Completers Data Set) [U99-0172.pdf/p48]			
Response	Test Day	Tiotropium (N=17)	Ipratropium (N=11)
	3	0.25 (0.03)	0.22 (0.05)
	8	0.29 (0.02)	0.20 (0.06)
	50	0.28 (0.04)	0.22 (0.06)

Daily AM PEFR reached maximum effect (“steady state”) at Day 6.

CLINICAL BRIEFING DOCUMENT

Description of Clinical Data and Sources

V. Description of Clinical Data and Sources

A. Overall Data

The clinical data submitted in support of this NDA are derived from the studies performed as part of the Applicant's clinical development program. The application does not rely on reports in the medical literature or other sources of data.

B. Tables Listing the Clinical Trials

The clinical program submitted in support of efficacy included six "pivotal" studies and five "supportive" studies [S8/ise.pdf/p88]. These are summarized in the two tables below.

CLINICAL BRIEFING DOCUMENT

Description of Clinical Data and Sources

Summary of Pivotal Studies

Study Number (Report #)	Study Type	Treatment Groups	Location	Duration	Design	Number of Subjects	Primary Endpoint
205.114/ 205.117 (U99-3169)	Safety/ Efficacy	Tiotropium 18mcg capsule QD Placebo Capsule QD	US	1 year (49 weeks)	R, DB, PC, PG	470	Trough FEV ₁ response at 13 weeks (mean of values at 23 and 24 hours)
205.115/ 205.128 (U99-3170)	Safety/ Efficacy	Tiotropium 18mcg capsule QD Placebo Capsule QD	US	1 year (49 weeks)	R, DB, PC, PG	451	Trough FEV ₁ response at 13 weeks (mean of values at 23 and 24 hours)
205.122A/ 205.126A (U00-3113)	Safety/ Efficacy	Tiotropium 18mcg capsule QD + Placebo MDI QID Placebo capsule QD + Ipratropium MDI 40mcg QID	Netherlands	1 year (52 weeks)	R, DB, PG Active comparator	288	Trough FEV ₁ response at 13 weeks (mean of values at 23 and 24 hours)
205.122B/ 205.126B (U00-3114)	Safety/ Efficacy	Tiotropium 18mcg capsule QD + Placebo MDI QID Placebo capsule QD + Ipratropium MDI 40mcg QID	Netherlands and Belgium	1 year (52 weeks)	R, DB, PG Active comparator	247	Trough FEV ₁ response at 13 weeks (mean of values at 23 and 24 hours)
205.130 (U01-1236)	Safety/ Efficacy	Tiotropium 18mcg capsule QD + Placebo MDI BID Placebo capsule QD + Salmeterol MDI BID Placebo capsule QD + Placebo MDI BID	Multinational	6 months	R, DB, PC Active comparator	623	TDI focal score (responder analysis) AND Trough FEV ₁ Response
205.137 (U01-1231)	Safety/ Efficacy	Tiotropium 18mcg capsule QD + Placebo MDI BID Placebo capsule QD + Salmeterol MDI BID Placebo capsule QD + Placebo MDI BID	Multinational	6 months	R, DB, PC Active comparator	584	TDI focal score (responder analysis) AND Trough FEV ₁ Response

CLINICAL BRIEFING DOCUMENT

Clinical Review Methods

Supporting Studies							
Study # Country/ Dates	Design	Treatments (Tiotropium)	Device	Duration	# of Subjects	Population	Primary Endpoint
205.119 Netherlands 11/91-4/92	Dose-ranging Open label XO	10mcg 20mcg 40mcg 80mcg 160mcg	RESPIMAT	Single Dose	6 (2F/ 4M)	COPD	FEV ₁
205.120 Netherlands 10/92-5/93	Dose-ranging R, DB, PC, XO	10mcg 20mcg 40mcg 80mcg Placebo	INHALATOR INGELHEIM (FO ₂)	Single Dose	35 (3F/ 32M)	COPD	FEV ₁
205.139 Japan 7/98-5/99	Dose-ranging R, DB, PC, XO	11.3mcg ¹ 22.5mcg ¹ 45mcg ¹ Placebo	HANDIHALER	Single Dose	27	COPD	FEV ₁
205.108 US 1/95-9/95	Dose-ranging Multicenter, R, DB, PC, PG	4.4mcg ² QD 8.8mcg ² QD 17.6mcg ² QD 35.2mcg ² QD Placebo QD	INHALATOR INGELHEIM (FO ₂)	4 Weeks	169 (73F/ 96M)	COPD	FEV ₁
205.123 UK 5/97-7/98	AM/PM Dosing Multicenter, R, DB, PC, PG	18mcg QAM 18mcg QPM Placebo QAM Placebo QPM	HANDIHALER	6 Weeks	121 (46F/ 75M)	COPD	FEV ₁

C. Postmarketing Experience

There are no postmarketing data available because the drug has not been marketed in any country [summary.pdf/p43].

VI. Clinical Review Methods

A. How the Review was Conducted

The six studies that were designated by the Applicant as “pivotal” studies were reviewed individually in-depth in regard to study design issues and efficacy conclusions. These in-depth reviews may be found in the Appendix to this Clinical Briefing Document. Safety data from the individual studies were reviewed less rigorously. Rather, the safety assessment was primarily derived from the integrated safety data provided in the Applicant’s Integrated Summary of Safety. Individual pharmacokinetic and pharmacodynamic studies were reviewed primarily for evidence to support the proposed dose and dosing interval.

B. Overview of Materials Consulted in Review

This Clinical Briefing Document is based on the materials submitted in the original NDA submission, the 120-Day Safety Update, and the various amendments submitted by the Applicant either on its own initiative or in response to the Division’s requests for specific information. These amendments are listed on the first page of this Review.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Pulmonary and Allergy Drug Products requested that the Agency’s Division of Scientific Investigations perform an audit of two clinical centers. The clinical centers to be audited were chosen based on participation in Study 205.130 or 205.137 (the two studies submitted in support of the dyspnea claim), number of subjects enrolled, and the magnitude of benefit reported in regard to the TDI. Two large US centers that reported greater benefit of study drug were selected. DSI has concluded that one of the two study sites adhered to all pertinent federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. At the second study site, which enrolled 13 patients into Study 205.130, one potentially important protocol violation was noted. At this site, the TDI questionnaire was improperly administered. Rather than having study site personnel ask questions of the patient and complete the questionnaire, the patients themselves read the questionnaire and completed the form. This is not the validated method of administration. A review of the case report forms by the DSI Inspector indicated that this may have caused some confusion for the patients, potentially impacting the validity of the scoring. One patient made several significant corrections to his/her answers, two patients provided divergent descriptions of their status in the TDI compared with the SGRQ. Because this was a large, multicenter study, this finding at a single study center is unlikely to impact the conclusions of the study. However, it must be recognized that this type of protocol violation may have occurred at additional study centers, which were not audited.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The Applicant has indicated that all clinical trials were conducted in accordance with accepted ethical standards [gcp.pdf].

E. Evaluation of Financial Disclosure

Section 19 of the NDA addresses the Applicant’s compliance with the Final Rule on Financial Disclosure by Clinical Investigators. The Applicant notes that, as a privately held company, it

CLINICAL BRIEFING DOCUMENT

Clinical Review Methods

has no equity available to investigators and does not provide compensation to investigators based on the outcome of studies conducted on its behalf. In addition, no investigators can have or own a proprietary interest in a product, trademark, licensing agreement or patent owned by the company. The Application contains a signed FDA Form 3454 for each of the six “pivotal” clinical studies. These forms certify that the Applicant did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study, than none of the investigators disclosed a proprietary interest in the product or a significant equity interest in the Sponsor, and that no investigator received significant payments of other sorts, as defined in 21 CFR 54.2 (f). One investigator in Study 205.130 was reported to be involved in a financial arrangement with the Applicant. The Applicant states that because payment was made in August, 1998, prior to the FDA Regulation date February 2, 1999, no form 3455 is submitted [financial.pdf/p13]. Based on this information, as well as the multi-center nature of the pivotal clinical studies, it is unlikely that financial interests could have influenced or biased the results of these studies.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

VII. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The evidence derived from the six pivotal clinical trials appears to establish the efficacy of tiotropium as a bronchodilator in patients with COPD. The data regarding the effect of this drug on the symptom of dyspnea in this patient population is less convincing. These are the subject matter for discussion at the September 6, 2002, PADAC meeting.

The pharmacodynamic properties of tiotropium are unusual for an orally inhaled drug. As discussed in the Human Pharmacokinetics and Pharmacodynamics section of this document, the bronchodilator effect seen after a single dose increases with multiple daily dosing, reaching “steady state” by Day 8. The text and figures used to illustrate the pharmacodynamic properties of tiotropium in the product label should capture this feature.

B. General Approach to Review of the Efficacy of the Drug

Conclusions regarding the efficacy of tiotropium bromide inhalation powder (18mcg QD) were developed following detailed review of the efficacy findings of each of the individual pivotal Phase 3 studies. There were six such studies, as outlined in the table below. These studies included two one-year placebo-controlled studies (205.114/205.117 and 205.115/205.128), two six-month placebo- and active-controlled studies (205.130 and 205.137), and two one-year active-controlled studies (205.122A/205.126A and 205.122B/205.126B).

Pivotal Clinical Studies							
Study Number (Report #)	Study Type	Treatment Groups	Location	Duration	Design	Number of Subjects	Primary Endpoint
205.114/ 205.117 (U99-3169)	Safety/ Efficacy	– Tiotropium 18mcg capsule QD – Placebo Capsule QD	US	1 year (49 weeks)	R, DB, PC, PG	470	Trough FEV ₁ response at 13 weeks (mean of values at 23 and 24 hours)
205.115/ 205.128 (U99-3170)	Safety/ Efficacy	– Tiotropium 18mcg capsule QD – Placebo Capsule QD	US	1 year (49 weeks)	R, DB, PC, PG	451	Trough FEV ₁ response at 13 weeks (mean of values at 23 and 24 hours)
205.122A/ 205.126A (U00-3113)	Safety/ Efficacy	– Tiotropium 18mcg capsule QD + Placebo MDI QID – Placebo capsule QD + Ipratropium MDI 40mcg QID	Netherlands	1 year (52 weeks)	R, DB, PG Active comparator	288	Trough FEV ₁ response at 13 weeks (mean of values at 23 and 24 hours)
205.122B/ 205.126B (U00-3114)	Safety/ Efficacy	– Tiotropium 18mcg capsule QD + Placebo MDI QID – Placebo capsule QD + Ipratropium MDI 40mcg QID	Netherlands and Belgium	1 year (52 weeks)	R, DB, PG Active comparator	247	Trough FEV ₁ response at 13 weeks (mean of values at 23 and 24 hours)
205.130 (U01-1236)	Safety/ Efficacy	– Tiotropium 18mcg capsule QD + Placebo MDI BID	Multinational	6 months	R, DB, PC Active comparator	623	TDI focal score (responder analysis) AND

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

Pivotal Clinical Studies							
Study Number (Report #)	Study Type	Treatment Groups	Location	Duration	Design	Number of Subjects	Primary Endpoint
		<ul style="list-style-type: none"> - Placebo capsule QD + Salmeterol MDI BID - Placebo capsule QD + Placebo MDI BID 					Trough FEV ₁ Response
205.137 (U01-1231)	Safety/ Efficacy	<ul style="list-style-type: none"> - Tiotropium 18mcg capsule QD + Placebo MDI BID - Placebo capsule QD + Salmeterol MDI BID - Placebo capsule QD + Placebo MDI BID 	Multinational	6 months	R, DB, PC Active comparator	584	TDI focal score (responder analysis) AND Trough FEV ₁ Response

Currently approved medications for COPD are indicated for the relief of bronchospasm due to COPD. As such, the basis for approval of these drugs has been adequate and well controlled studies demonstrating bronchodilator efficacy. Consistent with this traditional approach, all of the pivotal clinical studies in this NDA specified as the primary (or co-primary) variable an established measure of bronchodilator activity (FEV₁). In addition, numerous secondary variables supporting bronchodilator activity were employed. The unique aspect to this NDA is that the Applicant has proposed that this drug be labeled for the treatment of dyspnea as well as bronchospasm due to COPD. In order to support this proposal, the primary endpoints of two of the pivotal studies were changed after study completion but prior to un-blinding (Studies 205.130 and 205.137). The co-primary variables for these studies were FEV₁ and an index of subjective dyspnea, the Mahler Transitional Dyspnea Index. This Integrated Review of Efficacy will discuss the efficacy findings of the pivotal clinical studies in regard to the bronchodilator efficacy of the drug and in regard to putative effects on subjective dyspnea.

C. Detailed Review of Trials by Indication

1. Data Addressing Bronchodilator Efficacy

ONE-YEAR, PLACEBO-CONTROLLED STUDIES

Two, nearly identical, large, randomized, double-blind, placebo-controlled, parallel group studies examined the safety and efficacy of tiotropium versus placebo administered for approximately 1 year (49 weeks) (Study 205.114/205.117 and Study 205.115/205.128). These two studies differed only in that the former included pharmacokinetic assessments, whereas the latter did not. Detailed reviews of these studies are located in the Appendix to this Clinical Briefing Document. In these studies, a total of 921 patients with COPD were, following a 2-week baseline period, randomized to receive tiotropium or placebo once daily in the morning. Eligible patients had a history of COPD, a smoking history of ≥10 pack-years, age ≥40 years, and FEV₁ ≤65% of predicted and ≤70% of FVC. Baseline bronchodilator reversibility was not assessed. Spirometry was performed at baseline, and after 1, 7, 13, 37, and 49 weeks of treatment. On these test days

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

spirometry was performed at one-hour prior to dosing, immediately prior to dosing, and at 30, 60, 120, and 180 minutes after dosing. The pre-specified primary efficacy endpoint was the “trough FEV₁ response” at the end of the first 13 weeks of treatment. The “trough FEV₁ response” was defined as the change from baseline in the mean of the two FEV₁ values at the end of the dosing interval (approximately 23 and 24 hours post-dosing). Secondary efficacy endpoints included the trough FEV₁ response at other timepoints, the average and peak FEV₁ response for the first 3-hours post-treatment on each test day, individual FEV₁ and FVC values, weekly mean PEFr measured by the patient at home twice daily, physician’s global evaluation, COPD symptom scores (wheezing, shortness of breath, coughing, and tightness of chest), rescue albuterol use, number of nocturnal awakenings during the first 13 weeks, number and length of COPD exacerbations and hospitalizations for respiratory disease, the Saint George’s Respiratory Questionnaire (SGRQ), and pharmacoeconomic variables.

Most of the patients in these studies were White (91.9% and 96.7%), and the majority were men (66.7% and 66.4%). At screening, these patients had a mean FEV₁ of approximately 1 liter, and a ratio of FEV₁/FVC of approximately 45%.

Primary Endpoint: Trough FEV₁ Response (liters), Week 13 (Studies 205.114/205.117 and 205.115/205.128)			
Study	Tiotropium	Placebo	p-value
205.114/205.117	0.11	-0.03	0.0001
205.115/205.128	0.13	-0.01	0.0001

Both of these studies demonstrated that tiotropium was superior to placebo on the pre-specified primary endpoint, trough FEV₁ response after 13 weeks of treatment (p=0.0001). The mean trough FEV₁ response in the tiotropium group was 0.11 liters (compared with –0.03 liters in the placebo group) in Study 205.114/205.117, and 0.13 liters (compared with –0.01 liters in the placebo group) in Study 205.115/205.128. These data indicate that tiotropium has a statistically significant bronchodilator effect at the end of the proposed dosing interval. It should be noted that the Division has not previously taken a position regarding the magnitude of effect that would be considered to be clinically meaningful for the end-of-dosing interval FEV₁. In assessing acute bronchodilator efficacy, a threshold of at least 12% and at least 200ml is commonly used to determine a clinically meaningful bronchodilator effect. However, it would not seem reasonable to use this threshold for the end of the dosing interval. *Thus, the analysis of the primary endpoint established that the bronchodilator effect of tiotropium remains statistically significant at the end of the dosing interval. The magnitude of that effect is small compared to what would be expected if this measure were taken at peak effect, but is probably clinically meaningful at the end of the dosing interval.*

Secondary spirometry endpoints included trough FEV₁ response after 1, 7, 25, 37, and 49 weeks of treatment. At each of these timepoints, tiotropium was statistically superior to placebo (p=0.0001), with effect sizes (tiotropium minus placebo) of 0.11 to 0.16 liters. These data further support the conclusions regarding end-of-dosing interval efficacy that were drawn from the primary efficacy endpoint analysis.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

Insight into the early post-dose bronchodilator effect of tiotropium can be drawn from the 3-hour serial spirometry performed on each test day. In both studies, tiotropium was superior to placebo in regard to the mean average FEV₁ response during the 3-hour serial spirometry, on all test days (p=0.0001). Because this parameter is an average of several spirometry measures, interpretation of the effect size is less intuitive.

Perhaps more helpful is the information derived from the analyses of the peak FEV₁ data. In both studies, tiotropium was superior to placebo in regard to the mean peak FEV₁ response on all test days (p=0.0001). However, the mean treatment effect size (i.e. tiotropium effect minus placebo effect) was small, ranging from 0.15 liters on test day 1, to 0.19-0.22 liters on subsequent test days. It should be noted that in assessing for what is considered a clinically meaningful degree of bronchodilation (using the threshold of 12% and at least 200ml), it is not customary to consider placebo responses. Thus, the absolute increase in FEV₁, without subtraction of placebo effect, is customarily used. In these studies, the mean peak FEV₁ response was 0.24 liters on test day 1, and ranged from 0.25 to 0.31 liters on subsequent test days. This would support the assertion that, despite the relatively small difference between tiotropium and placebo, tiotropium is associated with a clinically meaningful degree of bronchodilation on all test days.

One further insight into the pharmacodynamics of tiotropium can be obtained from the peak FEV₁ data. While the mean peak FEV₁ on test day 1 was 0.24 liters in the tiotropium groups, the mean peak FEV₁ at each of the four individual test day 1, post-dose assessments was <0.20 liters. This unusual circumstance is due to the fact that patients reached their personal peak FEV₁ values at differing time points (see table below).

Percentage of Patients Who Reached Their Peak FEV₁ at Each Timepoint (Test Day 1)				
[Submission dated 7/16/02; page 8]				
Timepoint	Tiotropium		Placebo	
	205.114/205.117	205.115/205.128	205.114/205.117	205.115/205.128
30 minutes	14.7%	18.8%	26.2%	30.0%
1 hour	20.4%	19.2%	25.1%	25.0%
2 hours	29.7%	29.2%	26.7%	19.4%
3 hours	35.1%	32.8%	22.0%	25.6%

Other measures of pulmonary function also supported the bronchodilator efficacy of tiotropium. In both studies, tiotropium was also statistically significantly superior to placebo for the trough, average, and peak FVC responses on all test days. The FVC data from both studies suggested that the bronchodilator efficacy increased between Day 1 and Day 8. Daily morning and evening peak flow measurements were performed and recorded by the patients. For the morning peak flow measurements, tiotropium was statistically superior to placebo during approximately one-half of the weeks in one study (205.114/205.117), and during nearly all of the weeks in the other, with effect sizes ranging from 8 to 31 liters/minute. Tiotropium was statistically superior to placebo in regard to evening peak flow measurements, with effect sizes ranging from 13 to 40 liters/minute.

Other evidence in support of the efficacy of tiotropium as a bronchodilator includes the reported use of as-needed supplemental albuterol. During each week of treatment, patients in the

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

tiotropium group used statistically significantly fewer doses of as-needed albuterol. On average, patients in the tiotropium group used approximately 5-6 fewer doses of albuterol per week, compared with patients in the placebo group. Although in one study (205.114/205.117) patients in the tiotropium group reported statistically fewer nocturnal awakenings due to COPD symptoms during 7 of the 13 weeks this was assessed, in the second study, no effect on this variable was seen.

Despite the efficacy of tiotropium as a bronchodilator, in both studies there was no difference between tiotropium and placebo in regard to the number of patients with COPD exacerbations, time to COPD exacerbation, number of COPD exacerbation days, number of patients with hospitalization due to COPD, or number of hospitalizations due to COPD.

The studies also included two health-related quality of life assessments, the “disease-specific” St. George’s Hospital Respiratory Questionnaire (SGRQ) and the non-disease specific Medical Outcomes Study SF-36. Differences between groups rarely reached the generally accepted threshold for a minimal clinically meaningful effect on the SGRQ, which was administered at baseline, and after 7, 13, 25, 37, and 49 weeks of treatment. The study reports did not describe analyses of the total SF-36 scores. Results for the “physical health” domains within the SF-36 were not consistent between studies.

Finally, in both studies the scores on the Physician’s Global Evaluation were statistically superior in the tiotropium group on all test days. However, the clinical significance of the treatment effect seen (0.25 to 0.59 on a scale of 1-8) is not known.

ONE-YEAR, ACTIVE-CONTROLLED STUDIES (205.122A/205.126A and 205.122B/205.126B)

Two, identical, large, randomized, double-blind, active-controlled, parallel group studies examined the safety and efficacy of tiotropium (QD) versus ipratropium bromide (QID) administered for approximately 1 year (52 weeks) (Study 205.122A/205.126A and Study 205.122B/205.126B). Detailed reviews of these studies are located in the Appendix to this Clinical Briefing Document. In these studies, a total of 535 patients with COPD were, following a 2-week baseline period, randomized to receive either tiotropium inhalation capsules QD or ipratropium bromide MDI QID (2:1 randomization). Eligible patients had a history of COPD, a smoking history of ≥ 10 pack-years, age ≥ 40 years, and $FEV_1 \leq 65\%$ of predicted and $\leq 70\%$ of FVC. Baseline bronchodilator reversibility was not assessed. Spirometry was performed at baseline, and after 1, 7, 13, 26, 39, and 52 weeks of treatment. On test days during the first 13 weeks, spirometry was performed at one-hour prior to dosing, immediately prior to dosing, and at 30, 60, 120, 180, 240, 300, and 360 minutes after dosing. On the remaining test days, the serial spirometry ended after the 180-minute measure. The pre-specified primary efficacy variable was the “trough FEV_1 response,” 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-dosing). The protocol did not state which specific treatment visit would serve as the primary efficacy endpoint. Secondary efficacy endpoints included the average and peak FEV_1 response for the first 6-hours post-treatment at Weeks 1, 7, and 13, and the first 3-hours post treatment on the remaining test days, individual FEV_1 and FVC values, weekly mean PEF measured by the

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

patient at home twice daily, an Energy-Fatigue Questionnaire, rescue albuterol use, the Saint George's Respiratory Questionnaire (SGRQ), and pharmacoeconomic variables.

The great majority of patients were men (81.7% and 87.3%, in each study), and all patients except one were white. The baseline mean FEV₁ for all patients was approximately 1.2 liters, with an FEV₁/FVC ratio of approximately 45%.

Before discussing the efficacy results of these studies, two issues should be noted. First, in these studies the primary efficacy variable (trough FEV₁) 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 dose and subsequent morning dose of ipratropium, little if any bronchodilator effect is likely to be detected on morning pre-dose spirometry. The second issue is that, for US regulatory purposes, a new drug does not need to demonstrate superiority over existing drugs. Therefore, although the primary endpoint may be intrinsically biased to favor a longer-acting drug over a shorter-acting drug, in this circumstance, for regulatory decision-making, the ipratropium treatment group may be considered analogous to placebo. Presuming that treatment with ipratropium has no detrimental effect in terms of COPD efficacy endpoints, demonstrated superiority over ipratropium may be construed as superiority over placebo.

In both studies, tiotropium was statistically superior to ipratropium for the trough FEV₁ response at all test days. The difference in trough FEV₁ response between groups ranged from 0.11 liters to 0.18 liters.

Because these studies did not include a placebo treatment group, the post-dosing serial spirometry offer little data relevant to regulatory decision-making. This data will not be discussed further here, but is discussed for each study in the Appendix to this document. Home morning and evening PEFr values were statistically superior in the tiotropium group during all of the weeks of one study (205.122B/205.126B), and during most of the weeks in the other. The effect sizes for these measures were variable.

The use of as-needed albuterol was not different between groups in one study (205.122B/205.126B), and was statistically lower in the tiotropium group for 36 of the 52 weeks of the other study. The effect on COPD exacerbations was not consistent. In one study (205.122A/205.126A), no difference between groups was observed in regard to the number of patients with COPD exacerbation, time to first COPD exacerbation, number of COPD exacerbations, number of COPD exacerbation days, number of patients with hospitalizations due to COPD, or number of hospitalization days for COPD. However, in the second study, the tiotropium group had significantly fewer subjects with COPD exacerbations, fewer COPD exacerbations, and fewer COPD exacerbation days. Also in that study, the time to first COPD exacerbation was longer in the tiotropium group. Hospitalizations due to COPD were not different.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

The studies also included two health-related quality of life assessments, the “disease-specific” St. George’s Hospital Respiratory Questionnaire (SGRQ) and the non-disease specific Medical Outcomes Study SF-36. Differences between groups rarely reached the generally accepted threshold for a minimal clinically meaningful effect on the SGRQ, which was administered at baseline, and after 7, 13, 25, 37, and 49 weeks of treatment. The SF-36 did not demonstrate statistical differences between groups. Finally, the studies included a three-question “Energy Fatigue Questionnaire,” administered on test days 8, 50, 92, 182, 273, and 364. There were no statistically significant differences between groups on this questionnaire.

SIX-MONTH PLACEBO- AND ACTIVE-CONTROLLED STUDIES (205.130 and 205.137)

Two, nearly identical, large, randomized, double-blind, placebo- and active (salmeterol inhalation aerosol) controlled, parallel group studies examined the safety and efficacy of tiotropium versus placebo administered for six months (Study 205.130 and Study 205.137). These two studies differed only in that the former included post-dosing serial spirometry for 12 hours after dosing, whereas the latter included 3-hour post-dosing serial spirometry. Detailed reviews of these studies are located in the Appendix to this Clinical Briefing Document. In these studies, a total of 1207 patients with COPD were, following a 2-week baseline period, randomized to receive either tiotropium (18mcg QD), salmeterol xinafoate inhalation aerosol (50mcg BID), or placebo. Eligible patients had a history of COPD, a smoking history of >10 pack-years, age ≥ 40 years, and $FEV_1 \leq 60\%$ of predicted and $\leq 70\%$ of FVC. Baseline bronchodilator reversibility was not assessed. Spirometry was performed at baseline, and after 2, 8, 16, and 24 weeks of treatment. On these test days spirometry was performed at one-hour prior to dosing, 10 minutes prior to dosing, and at 30minutes, 1, 2, 3, 4, 6, 8, 10, and 12 hours after dosing in Study 205.130. In Study 205.137, post-dose serial spirometry included only 3 hours after dosing. The pre-specified primary efficacy endpoints were the “trough FEV_1 response” and the focal score of the Mahler Transitional Dyspnea Index (TDI), at the end of the 24 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-dosing). Secondary efficacy endpoints included the TDI focal score on other test days, the trough FEV_1 response on other test days, the average and peak FEV_1 response on each test day, individual FEV_1 and FVC values, weekly mean PEFr measured by the patient at home twice daily, physician’s global evaluation, COPD symptom scores (wheezing, shortness of breath, coughing, and tightness of chest), rescue albuterol use, the shuttle walking test with Borg dyspnea rating scale, number and length of COPD exacerbations and hospitalizations for respiratory disease, the number of patients with at least one COPD exacerbation, the number of patients with at least one hospitalization for respiratory disease, the Saint George’s Respiratory Questionnaire (SGRQ), patient preference, and pharmacoeconomic variables.

The majority of patients were men (74.6% and 77.9% in Study 205.130 and 205.137, respectively), and nearly all patients were white (99.5%). The mean age of the patients was approximately 64 years, and the mean screening FEV_1 was approximately 1.1 liters.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

Before discussing the efficacy results of these studies, one important issue should be noted. Although these studies included three treatment arms, the pre-specified primary comparison was that of tiotropium versus placebo. This is appropriate because, from the regulatory perspective, it is this comparison that is most important. Therefore, this Integrated Review of Efficacy will focus on the comparison of tiotropium versus placebo. However, the study report also discusses the comparison of tiotropium versus salmeterol. In considering the findings of the tiotropium versus salmeterol comparison, one must keep in mind that one of the co-primary efficacy variables (trough FEV₁) 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, salmeterol, is indicated for use twice daily. Given the relatively long interval between the evening dose and subsequent morning dose of salmeterol, little if any bronchodilator effect is likely to be detected on morning pre-dose spirometry.

In both studies, tiotropium was statistically superior to placebo for the trough FEV₁ response after 24 weeks of treatment. The mean trough FEV₁ response in the tiotropium group was 0.14 liters in Study 205.130, and 0.11 liters in Study 205.137. These data indicate that tiotropium has a statistically significant bronchodilator effect at the end of the proposed dosing interval. It should be noted that the Division has not previously taken a position regarding the magnitude of effect that would be considered to be clinically meaningful for the end-of-dosing interval FEV₁. In assessing acute bronchodilator efficacy, a threshold of at least 12% and at least 200ml is commonly used to determine a clinically meaningful bronchodilator effect. However, it would not seem reasonable to use this threshold for the end of the dosing interval. *Thus, the analysis of this co-primary endpoint established that the bronchodilator effect of tiotropium remains statistically significant at the end of the dosing interval. The magnitude of that effect is small compared to what would be expected if this measure were taken at peak effect, but is probably clinically meaningful at the end of the dosing interval.*

Tiotropium was also statistically superior to placebo on each of the serial spirometry measurements on all test days in both studies. Consistent with this, tiotropium was statistically superior to placebo in regard to the mean trough, average, and peak FEV₁ response on all test days in both studies. On the first test day, the mean peak FEV₁ response was 0.31 liters (Study 205.130) and 0.27 liters (Study 205.137). The difference between the tiotropium mean peak FEV₁ response and the placebo mean peak FEV₁ response was 0.19 and 0.16 liters on test day 1 in these two studies. The serial spirometry FVC data was consistent with the FEV₁ data. The patient-recorded daily PEFr data also supported the efficacy of tiotropium as a bronchodilator. In both studies, the mean weekly morning and mean weekly evening PEFr values were statistically superior in the tiotropium group, as compared to the placebo group. The differences between tiotropium and placebo ranged from 14.9 to 27 liters/minute for the morning PEFr, and from 21 to 33 liters/minute for the evening PEFr.

Interestingly, in only one of the two studies was tiotropium statistically superior to placebo in regard to the number of puffs of as-needed albuterol used by the patients (Study 205.130).

In Study 205.130, there were statistically fewer COPD exacerbations and COPD exacerbation days in the tiotropium group as compared to placebo, but there was no statistically significant

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

difference between these two groups in regard to the number of subjects with at least one COPD exacerbation. In Study 205.137 there were no significant differences between tiotropium and placebo in regard to the various expressions of COPD exacerbations. There were no notable differences between tiotropium and placebo in regard to hospitalizations for COPD in either study.

Tiotropium was statistically superior to placebo in regard to the Physician's Global Evaluation on all test days except Week 24 in Study 205.137. In regard to the total SGRQ scores, the difference between tiotropium and placebo did not reach the generally accepted threshold of a minimal clinically important difference (4 units) on any test day in either study.

SUMMARY OF BRONCHODILATOR EFFICACY RESULTS

Existing drugs for COPD are indicated for the relief of bronchospasm associated with COPD. As such, the standard for approval has been demonstration, through adequate and well-controlled trials, of a bronchodilator effect. The most commonly used index of bronchodilator effect has been the FEV₁. In most cases, the primary analyses of FEV₁ have focused on peak changes. In this application, the primary focus has been on the "trough FEV₁ response." This endpoint has the benefit of incorporating important information regarding end-of-dosing-interval bronchodilator efficacy. The limitation of this endpoint is that there is less experience and consensus regarding what constitutes a minimal clinically meaningful effect.

In the six Phase 3 studies submitted with this application, tiotropium was statistically superior to placebo (or an active control that may be considered a proxy for placebo) in regard to the trough FEV₁ response. The treatment effect size on this endpoint, while less than what might be desired of a peak effect size, may be clinically significant. Secondary analyses of serial spirometry during the early post-dosing period appear to demonstrate that tiotropium is statistically superior to placebo in regard to peak and average FEV₁. Analyses of the mean peak FEV₁ values in the one-year, placebo-controlled studies suggest that the mean peak effect may be clinically meaningful. It is interesting to note that the time to reach peak FEV₁ seems to vary substantially among individual subjects. Other secondary efficacy variables, such as home PEF values and supplemental "as-needed" albuterol use, also appear to support the bronchodilator activity of tiotropium. No consistent, clinically meaningful effect was demonstrated on other indicators of COPD disease activity, such as COPD exacerbations, COPD hospitalizations, and health-related quality of life assessments.

LABELING ISSUES REGARDING BRONCHODILATOR EFFECT

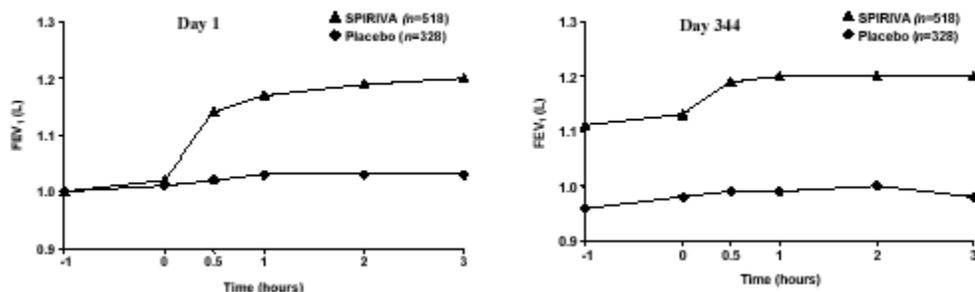
The product labels for orally inhaled bronchodilators customarily provide information (text and figures) that describes the pharmacodynamic effect of the drug. Typical information that is conveyed includes peak effect, time to peak effect, and duration of action. For this drug, these concepts are not easy to convey. One difficulty is the fact that the bronchodilator effect is not maximal after the initial dose. While it is important to convey the single-dose performance characteristics in the label, because the drug would be indicated for chronic use (maintenance treatment), rather than as a "rescue" medication, it would be equally important to convey the performance characteristics expected with chronic use. One difficulty conveying the chronic use characteristics is that, due to its demonstrated efficacy throughout the dosing interval, the pre-

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

dose FEV₁ after chronic use is greater than the pre-treatment baseline. Thus, describing the bronchodilator effect as a change from pre-dose values would underestimate the actual clinical benefit. Because of this issue, the text of the label should be fairly general in this regard, with figures used to illustrate the pharmacodynamic effects. The Applicant proposes the following figures to convey this information [proposed.pdf/p5].

Figure 1: Mean FEV₁ Over Time (prior to and after administration of study drug) on Days 1 and 344 for the Combined One-Year Placebo-Controlled Studies*



*Means are adjusted for center and baseline effects.

For these figures, the Applicant has pooled data from two studies.

The Applicant also proposes text that states that tiotropium provided *significant* improvements in lung function *within 30 minutes* following the first dose [proposed.pdf/p4]. The term significant when used in regard to bronchodilators usually indicates an improvement of 12% and at least 200ml in the FEV₁. In the two 1-year, placebo-controlled studies, while the mean peak FEV₁ did increase by 240ml, the mean FEV₁ did not increase by ≥ 200 ml at any of the timepoints during the 3-hour post-dose serial spirometry after the first dose. This was because the time to peak FEV₁ varied among individual patients. In fact, at 30 minutes only 14.7% (Study 205.114/205.117) and 18.8% (Study 205.115/205.128) of patients in the tiotropium group had reached their peak FEV₁.

2. Data Addressing Efficacy in Regard to the Proposed Dyspnea Indication

The Applicant has proposed a unique indication for tiotropium, namely the relief of dyspnea related to COPD. The primary support of this proposed indication is taken from the results of two studies for which an index of dyspnea (the TDI focal score) was pre-specified as one of two co-primary endpoints (Studies 205.130 and 205.137). Supporting data may be drawn from other studies in which various indices of the symptom were captured as secondary endpoints. In the following section of this document, the TDI instrument will be briefly summarized, and the findings of Studies 205.130 and 205.137 will be discussed, along with this additional supporting data. The studies cited in the discussion are reviewed in depth in the Appendix to this document and summarized briefly above.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

The Baseline/Transitional Dyspnea Index

The Baseline/Transitional Dyspnea Index (BDI/TDI) is a multidimensional index of the sensation of dyspnea. Both the BDI and TDI consist of three components. The components are “functional impairment,” “magnitude of task” (needed to evoke dyspnea), and “magnitude of effort” (needed to evoke dyspnea). At baseline, each component is assigned a grade, ranging from 0 to 4. The components may also be graded “W” for “amount uncertain,” “X” for “unknown,” or “Y” for “impaired for reasons other than shortness of breath.” On subsequent visits, the TDI is administered, with each component assigned a score ranging from –3 (major deterioration) to +3 (major improvement). A score of +1 indicates improvement within a BDI grade. The TDI can also be recorded as “Z,” indicating that there was “further impairment for reasons other than shortness of breath.” **Reviewer’s Note: For the purposes of the studies, any data recorded as “W,” “X,” “Y,” or “Z” was set to missing for the purposes of data analysis.** The TDI focal score, which consists of the sum of the three components, can thus range from –9 to +9. The instrument is administered by an observer who has experience in taking a medical history regarding respiratory disease. The interviewer asks open-ended questions about the patient’s experience of breathlessness and then selects a grade for each component by matching the patient’s responses with the specific criteria of the index.

STUDIES 205.130 AND 205.137

In these six-month studies, which are summarized above and reviewed in-depth in the Appendix to this document, one of the co-primary variables was the Mahler Transitional Dyspnea Index (TDI). The Applicant chose to specify as the primary analysis, a “responder” analysis based on a threshold of 1 unit in the focal TDI score. During drug development, the Agency informed the Applicant that the clinical validity of both the TDI instrument and of this threshold must be established in order for this primary analysis to be meaningful. Further, the Applicant was informed that whatever effect was demonstrated in regard to the percentage of “responders” must itself be clinically meaningful in order to merit an indication for dyspnea associated with COPD. Finally, the Applicant was informed that any claims in regard to dyspnea must be supported by a substantial weight of evidence.

At the end of the six-month studies, the percentages of patients with a TDI ≥ 1 unit was 42% and 45% in the tiotropium groups (Studies 205.130 and 205.137, respectively), compared with 26% and 33% in the placebo groups. These differences were statistically significant in both studies. The percentages of responders in the active-comparator group (salmeterol) was 35% and 48% in these two studies.

Percentage of Patients with TDI≥ 1 After 6 Months of Treatment (Studies 205.130 and 205.137)			
Study	Tiotropium	Placebo	Salmeterol
205.130	42%	26%	35%
205.137	45%	33%	48%

There are additional data from these two studies that may shed light on the effect of tiotropium in regard to the symptom of dyspnea. Because this would be a unique indication for tiotropium, some data on the effect of salmeterol on these endpoints is provided for comparison.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

- Responder analyses for the TDI focal score (based on a threshold of 1 unit) were performed after 8 and 16 weeks of treatment. In both studies, tiotropium was statistically superior to placebo in these analyses. The percentages of responders in the tiotropium and placebo groups were 40% vs. 24% and 44% vs. 31% at Week 8, and 43% vs. 27% and 42% vs. 30% at Week 12 in Studies 205.130 and 205.137, respectively. Of note, in one study (205.130) tiotropium was numerically superior to salmeterol on these analyses, and in the other study (205.137), salmeterol was numerically superior to tiotropium.
- Using analyses of mean TDI focal scores rather than “responder” analyses, tiotropium was statistically superior to placebo on each test day in both studies. The effect size was >1 unit on each day except Week 16 in Study 205.130. Of note, in one study (205.130) salmeterol was not statistically superior to placebo on these analyses, but in the other study (205.137) salmeterol was statistically superior to placebo, with effect sizes ranging from 1.26 to 1.66.
- A “COPD Symptom Score,” based on the investigator’s assessment, was assigned at each treatment visit. Tiotropium was statistically superior to placebo in regard to the “shortness of breath” component of this score at most of the treatment visits. The effect size ranged from 0.17 to 0.36 on this 0-3 scale. Salmeterol was also statistically superior to placebo for “shortness of breath” at most treatment visits.
- A “shuttle walk test” (SWT) was administered after the first dose and after 8, 16, and 24 weeks of treatment. The “Modified Borg Dyspnea Scale” was administered before and after each SWT. In both studies, there was no difference between groups in regard to the distance walked in the SWT. Of note, in Study 205.137, on each test day the distance walked was numerically superior in the placebo group, as compared to the tiotropium group. There was no significant difference between tiotropium and placebo in regard to the Modified Borg scores. There was also no significant difference between salmeterol and placebo on the SWT distance or the Modified Borg score.

STUDIES 205.114/204.117 AND 205.115/205.128

In these studies, which are summarized above and reviewed in-depth in the Appendix to this document, the symptom of dyspnea was addressed in two secondary variables, the TDI and the component of the “COPD Symptoms Score” called “shortness of breath.” The TDI was administered on five occasions during these 1-year studies. On all occasions the mean TDI focal score was statistically superior in the tiotropium group. However, the difference between the tiotropium and placebo group was <1 on all but three occasions. Symptoms of COPD were assessed and recorded by the investigator using a 0-3 scale at each visit. The tiotropium group was statistically superior to the placebo group in regard to the score on the “shortness of breath” component at most visits.

STUDIES 205.122A/205.126A AND 205.122B/205.126B

These active-controlled studies are summarized above and reviewed in-depth in the Appendix to this document. They TDI assessments on six occasions during the one-year treatment period. In Study 205.122A/205.126A, the tiotropium group was statistically superior to ipratropium in regard to the mean TDI focal score on four of the six occasions. However, the difference between the two groups was <0.75 units on each of these occasions. In Study 205.122B/205.126B, the tiotropium group was superior to ipratropium in regard to the mean TDI focal score on every occasion, with differences exceeding 1 unit on four of the six occasions.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

SUMMARY OF THE DYSPNEA EFFICACY RESULTS

The Applicant has proposed a unique indication for tiotropium, the treatment of dyspnea associated with COPD. The primary support for this proposal is derived from two, six-month, active and placebo-controlled studies in which the TDI, an index of subjective dyspnea, was pre-specified as one of two co-primary efficacy variables. In those studies, tiotropium was demonstrated to be statistically significantly superior to placebo in the pre-specified primary analysis. This analysis was a “responder” analysis using a threshold of 1 in the TDI as the definition of a “responder.” The utility of this analysis will be discussed in the section below entitled Efficacy Conclusions. Secondary analyses including TDI responder analyses on other test days, and analyses of mean TDI focal score data also showed statistical superiority of tiotropium over placebo. It should be noted that in many of these analyses, the effect of tiotropium was not markedly greater than that of the active control, salmeterol. Finally, in these studies, no difference between groups was seen in regard to the distance walked during a shuttle walk test, or perceived dyspnea during the shuttle walk test, as assessed by the modified Borg scale.

In other long-term, placebo controlled studies, the TDI data was analyzed using mean values. While tiotropium was often statistically superior to its comparator (placebo or ipratropium), the differences were commonly <1 unit.

D. Efficacy Conclusions

The clinical development program for this drug included a total of six large, controlled studies in patients with COPD. Of these, two were 1-year, placebo-controlled studies, two were 1-year, active-controlled studies, and two were 6-month, active- and placebo-controlled studies. The one-year studies primarily focused on establishing substantial evidence of efficacy to support the indication traditionally used for COPD drugs, the relief of bronchospasm associated with COPD. Thus, in these studies the primary efficacy variable was a measure of bronchodilation, FEV₁. One unique aspect of these studies is that the primary endpoint was the pre-dose FEV₁, rather than a post-dose assessment, such as peak FEV₁, as is more commonly used. The benefit of using the pre-dose (or “trough”) value is that by showing statistical superiority to the comparator, the proposed dosing interval is supported. However, there is less of a consensus regarding the minimum magnitude of effect that should be regarded as being clinically meaningful at this timepoint.

The 6-month studies were submitted in order to support a proposal for a unique indication for a COPD drug, the treatment of dyspnea associated with COPD. Prior to unblinding the data for these studies, the primary efficacy variable for these studies was altered, to include FEV₁ and TDI focal score as co-primary variables. The following discussion will address the proposed indications, treatment of bronchospasm associated with COPD and treatment of dyspnea associated with COPD, separately.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

The six clinical studies appear to establish the bronchodilator efficacy of tiotropium. Primary analyses of the six studies all demonstrate that treatment with tiotropium at the proposed dose results in statistically significant improvements in FEV₁ at the end of the dosing interval (“trough” FEV₁). In four of the studies the comparator was placebo, and in the remaining two studies the comparator was a short-acting agent whose effect is expected to be negligible at the time the variable was assessed (morning, pre-dose). The magnitude of effect demonstrated at this timepoint is small, but may be clinically meaningful. In secondary analyses of the FEV₁ data, tiotropium was statistically significantly superior to placebo in regard to standard post-dose variables such as average FEV₁ and peak FEV₁. It is noted that the time to reach peak FEV₁ is quite variable among individual patients. Other secondary efficacy variables, such as morning and evening home peak flow measurements and supplemental “as-needed” albuterol use, appear to support the bronchodilator activity of tiotropium in COPD patients. No consistent, clinically meaningful effect was seen on other indicators of COPD disease activity, such as COPD exacerbations, COPD hospitalizations, and health-related quality of life assessments.

The support of a proposed “dyspnea” indication appears to be less convincing. It is true that the in the two six-month studies tiotropium was statistically superior to placebo on the co-primary analysis of the TDI focal score. However, several points regarding the TDI and the analysis of the TDI should be noted.

- The package of materials submitted by the Applicant in order to provide details regarding the development of the TDI was very limited. The instrument was first described in 1984, and it is not clear from the submission that the methodology used to develop the instrument would be considered appropriate using modern day standards. Currently, appropriate development of a patient reported outcome instrument typically involves: 1) convening of “focus groups” of the specific patient population in order to identify items of importance, 2) reducing the number of these items in order to eliminate highly correlated items, 3) determining the most appropriate response choices, and 4) assigning the most appropriate weight to each item.
- Responses to the TDI involve recollection of the baseline status, which may be difficult after many months. For instance, the baseline assessment of “Magnitude of Task” is determined in the Baseline Dyspnea Index (BDI) using four Grades of severity. A score +1 on the TDI for this category, represents an improvement of less than one grade. The ability of patients to make a determination of a change within one grade after 6 or 12 months is not clear. It should be noted however, that in Studies 205.130 and 205.137, the TDI was administered at Weeks 8 and 16, in addition to Week 24.
- There is little consensus in the medical literature regarding the minimal TDI focal score that is considered to be clinically meaningful. Therefore the selection of the most appropriate “responder” threshold is somewhat uncertain. There is no evidence that patients were consulted to determine what they believe is clinically meaningful. The Applicant has proposed that 1 unit is clinically meaningful. It should be noted that this also represents the smallest improvement that a patient could possibly report. This means that there is no degree of improvement that could be reported that would not be considered to be clinically meaningful. Of note, however, according to

CLINICAL BRIEFING DOCUMENT

Integrated Review of Efficacy

analyses performed by the Division's Biometrics Reviewer, tiotropium would have been statistically superior to placebo in the two 6-month studies even if the "responder" threshold were set at 2, rather than 1. Using a response threshold of 2, the percentage of responders in the tiotropium and placebo groups was 33.7% and 23% in Study 205.130, and 40.8% and 29.8% in Study 205.137. For comparison, the using this threshold, the percentage of responders in the salmeterol groups was 30.7% and 46.6% in Study 205.130 and 205.137, respectively.

- The six-month studies were multinational. The issue of cross-culture interpretation and translation is not addressed. The Applicant has not provided data to establish the validity of the TDI when translated into languages other than English and when used in other cultures.
- The effect size demonstrated is questionable to merit a specific indication for dyspnea. In one study 42% of tiotropium patients were classified as "responders," while 26% of placebo patients were "responders." In the second study, the difference between the groups was even smaller (45% vs. 33%). According to "number needed to treat" (NNT) analyses performed by the Division's Biometrics Reviewer, approximately 7.5 patients would need to be treated with tiotropium in order that one patient would note a dyspnea benefit above that expected with the use of placebo. (This figure is derived from the pooled data from the two studies. The NNT was 6.45 in Study 205.130, and 8.6 from Study 205.137).
- The robustness of the dyspnea effect is called into question by the fact that in analyses of mean TDI focal scores in the six pivotal studies the difference between tiotropium and placebo was often less than 1 unit.
- The comparator drug used in the two six-month studies (salmeterol) does not have an indication for dyspnea, yet its performance in the "responder" analyses was not different from that of tiotropium.
- The studies were not designed with TDI as a primary efficacy endpoint. The conduct of the studies reflect this the following ways: 1) there is no indication that the observers, who completed the TDI questionnaire, were blinded to other study data, either at the time of the visit, or over the duration of the study. Knowledge of the patient's clinical data and status as well as possible adverse events (e.g. dry mouth) could have introduced bias into the grading of the TDI. 2) The observer first reviewed the SGRQ results prior to interviewing the patient for the TDI.

VIII. Integrated Review of Safety

A. Brief Statement of Conclusions

The clinical development program included adequate numbers of subjects exposed. The types of safety assessments used in these studies was adequate, and was generally consistent with development programs for other inhalation drug products for a COPD indication. The adverse event data indicated that anticholinergic effects were more frequent in the treated group. Dry mouth was quite common, and was more frequent in women and in older patients. Other anticholinergic effects included constipation and urinary effects. Upper respiratory tract infections were also more common in the tiotropium-treated patients.

The safety database contains subtle suggestions that tiotropium may be associated with increased adverse cardiac effects, particularly in the category of “heart rate and rhythm disorders.” The cardiac safety database contains relatively few 24-hour Holter monitors. Given the potential, based on mechanism of action, pharmacokinetics, and intended patient population, for adverse cardiac effects with this drug, this issue will be raised for discussion at the PADAC meeting.

B. Description of Patient Exposure

1. *Clinical Studies*

The Phase 3 development program included six “pivotal” clinical studies. Four of these were randomized, double-blind, active- or placebo-controlled studies with treatment durations of approximately one year. These studies were conducted in the U.S., Netherlands, and Belgium. The two remaining studies were randomized, double-blind, active and placebo-controlled studies with treatment durations of six months. Three additional studies are described by the Applicant as Phase 3 “characterization” studies. These were: 1) a six-week placebo-controlled study comparing morning to evening dosing (“AM/PM dosing study”; 205.123); 2) a mucociliary clearance study (205.116); and 3) a sleep study (205.124).

Additional clinical studies include eleven human pharmacology studies, three Phase 2 single-dose studies (205.119, 205.120, and 205.139), one Phase 2 multiple-dose, dose ranging study (205.108), one multiple-dose dose-ranging study using tiotropium inhalation solution and inhalation powder, and four studies in patients with asthma.

This Clinical Briefing Document will focus primarily on safety data derived from the six “pivotal” clinical studies. Following the approach taken by the Applicant in the Applicant’s Integrated Summary of Safety, the pooled safety data from the two 1-year placebo controlled studies, the pooled safety data from the two 1-year ipratropium-controlled studies, and the pooled safety data from the two 6-month salmeterol and placebo-controlled studies will be discussed separately. Additional relevant safety information from the remainder of the clinical studies will be discussed as well.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

2. Exposure

A total of 4,124 subjects participated in the clinical program [iss.pdf/p102]. This included 224 healthy volunteers, 3,411 COPD patients, 471 asthma patients, and 18 patients with renal impairment. A total of 2,117 subjects were exposed to tiotropium by inhalation of the powder capsule formulation. This included 57 healthy volunteers, 1,723 COPD patients, and 337 asthma patients. A total of 1,701 subjects were exposed to the 18mcg dose of tiotropium. Of these 1,701 subjects, 48% were exposed to the drug for more than 200 days, and 34% were exposed to the drug for more than 330 days.

The table below summarizes the numbers of patients exposed to tiotropium in the six “pivotal” Phase 3 studies.

Patient Exposure to Tiotropium in the Six “Pivotal” Phase 3 Studies				[iss.pdf/p113-4]
	Total	≥101 days	≥200 days	≥ 330 days
One-year, placebo-controlled studies	550	501 (91%)	482 (88%)	302 (55%)
One-year, ipratropium-controlled studies	356	325 (91%)	316 (89%)	260 (73%)
Six-month, salmeterol- and placebo-controlled studies	402	353 (88%)	354 (88%)	not applicable

The mean age for all patients was 65 years in the one-year placebo-controlled studies, and 64 years in the one-year ipratropium-controlled studies and the six-month salmeterol and placebo-controlled studies. Nearly all patients were caucasian, and 65% to 85% were male [iss.pdf/p127, 133]. In the one-year, placebo-controlled studies, the mean FEV₁ was approximately 1 liter, representing 38-39% of the predicted value. In the one-year, ipratropium-controlled studies the mean baseline FEV₁ was 1.18 to 1.25 liters, representing 41-44% of the predicted value [iss.pdf/p129]. In the six-month, salmeterol- and placebo-controlled studies the mean baseline FEV₁ was 1.07 to 1.12 liters, representing 39-41% of the predicted value [iss.pdf/p134].

C. Methods and Specific Findings of Safety Review

1. Safety Evaluations Performed

In the tiotropium clinical studies safety was monitored using the following assessments: clinical adverse events, vital signs, physical examinations, clinical laboratory results, and electrocardiograms (ECGs). Adverse events were classified using the Boehringer Ingelheim – World Health Organization – Adverse Reaction Terminology List (BI-WHO-ART) [iss.pdf/p82]. The respiratory system events were further divided into “upper” and “lower” respiratory system disorders. One of the (non-pivotal) clinical studies included 24-hour Holter monitoring (Study 205.123, one of the Phase 3 “characterization” studies).

2. Significant/Potentially Significant Events (Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events)

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

The table below summarizes the incidences of deaths, serious adverse events (SAEs), and adverse events leading to discontinuation in the three sets of “pivotal” Phase 3 studies.

Significant/ Potentially Significant Adverse Event Profile													[iss.pdf/p33, 44]	
	1-year, placebo-controlled studies				1-year, ipratropium-controlled studies				6-month, salmeterol and placebo-controlled studies					
	Tiotropium		Placebo		Tiotropium		Ipratropium		Tiotropium		Salmeterol		Placebo	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total Treated	550	100	371	100	356	100	179	100	402	100	405	100	400	100
Deaths	7	1.3	7	1.9	9	2.5	3	1.7	1	0.2	6	1.5	5	1.3
SAEs	99	18	78	21	57	16	46	25.7	37	9.2	50	12.3	55	13.8
AEs leading to discontinuation	53	9.6	50	13.5	35	9.8	22	12.3	29	7.2	60	14.8	64	16.0

A total of 26 deaths occurred among the 1456 patients enrolled in the one-year studies [iss.pdf/p145]. None of the deaths were considered by the investigators to be related to study medication. In general, the causes of death were consistent with what might be expected in this patient population. Two causes of death were reported in the tiotropium groups but not in the comparator groups. These were myocardial infarction (4 deaths) and arrhythmia (1 death). The incidence of death was similar in all groups. In the one-year, placebo-controlled studies, there were 7 (1.3%) deaths in the tiotropium group and 7 (1.9%) in the placebo group. In the one-year, ipratropium-controlled studies there were 9 (2.5%) deaths in the tiotropium and 3 (1.7%) deaths in the ipratropium group. Narrative summaries of all deaths were reviewed by the Medical Reviewer.

The seven deaths among the tiotropium patients in the one-year, placebo-controlled studies were due to [iss.pdf/p149-54]:

- acute myocardial infarction:
 - 67 year-old man, after 227 days of treatment.
- coronary artery disease
 - 49 year-old man developed severe chest pain after 91 days of treatment. Cardiac catheterization revealed single vessel disease (60% lesion). Cardiac medications were begun during a seven day hospitalization, but twelve days later he developed recurrent chest pain and expired.
- cardiac arrhythmia:
 - 85 year-old man found dead after 33 days of treatment. No autopsy.
- sudden death:
 - 59 year-old man found dead in bed after 45 days of treatment.
- cardiac arrest:
 - 61 year-old man with history of hypertension and coronary artery disease (status post coronary artery bypass grafting) experienced cardiac arrest after 15 days of treatment. He was initially resuscitated and placed on a ventilator, but died two days later.
- congestive heart failure/ cardiomyopathy:

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

- 65 year-old woman with a baseline diagnosis of cardiomyopathy, who was hospitalized for congestive heart failure after 339 days of treatment. She was hospitalized for 15 days for diagnostic testing and treatment. She was readmitted 5 days later with congestive heart failure, and died.
- suicide:
 - 51 year-old man with history of post-traumatic stress disorder died of suicide (opiate, cocaine, and diphenhydramine intoxication) after 112 days of treatment.

Thus, five of these seven deaths among the tiotropium patients in the one-year, placebo-controlled trials were attributable to cardiac ischemia or arrhythmia. For comparison, only one of the seven deaths in the placebo group was attributed to cardiac ischemia or arrhythmia. (This was a 65 year-old man with a history of hypertension who died after 240 days of treatment. Details of the circumstances of his death are not provided, but an autopsy revealed atherosclerotic coronary disease without signs of acute myocardial infarction.) The remaining deaths in the placebo group were due to worsening COPD (1 patient), cor pulmonale (1 patient; recorded as “myocardial insufficiency”), and carcinoma (4 patients).

In the one-year, ipratropium-controlled studies there were two deaths in the tiotropium group (out of a total of 7) due to myocardial infarction, and no deaths in the ipratropium group (out of a total of 3) due to myocardial infarction [iss.pdf/p154-9]. The remaining causes of death were carcinoma, pulmonary emboli, respiratory insufficiency, and meningitis in the tiotropium group, and pneumonia, aortic aneurysm rupture, and carcinoma (with treatment-related leukopenia and sepsis) in the ipratropium group.

In the six-month studies there was only one death in the tiotropium group. This was due to ruptured abdominal aortic aneurysm [iss.pdf/p183]. For comparison, there were five deaths in the placebo groups of the six-month studies. These deaths were due to cardiac arrest (two events, one of which occurred in association with COPD exacerbation), respiratory insufficiency, bronchial carcinoma, and “death” (patient was found dead, cause not specified) [iss.pdf/p184-8].

Fewer patients in the tiotropium groups reported serious adverse events, as compared with both the placebo and the active comparator groups. As indicated in the table above, the percent of patients reporting SAEs in the tiotropium group was 18% in the one-year, placebo-controlled studies and 16% in the one-year, ipratropium-controlled studies, compared with 21% of placebo patients and 26% of ipratropium patients [iss.pdf/p159]. In the six-month studies, 9.2% of tiotropium patients, 14% of placebo patients, and 12% of salmeterol patients reported SAEs.

The most common SAEs were COPD exacerbation and pneumonia. None of the SAEs were considered to be related to tiotropium. COPD exacerbation SAEs were less common in the tiotropium groups (5.8% vs. 8.1% in the placebo-controlled one-year studies, 6.5% vs. 12% in the ipratropium controlled studies, and 3.5% vs. 5.8% in the placebo group and 5.9% in the salmeterol group in the 6-month studies) [iss.pdf/p39, 47]. The table below indicates the SAEs that occurred in >1 patient in the tiotropium group and occurred more frequently in the tiotropium group in the one-year, placebo-controlled studies.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

Serious Adverse Events Occurring More Frequently in the Tiotropium Group And Occurring in >1 Patient in the Tiotropium Group (One-year, Placebo-Controlled Studies) (number [%] of patients) [iss.pdf/p161-6]		
Event	Tiotropium Group	Placebo Group
Chest Pain	8 (1.5)	4 (1.1)
Dehydration	5 (0.9)	0 (0)
Neoplasm Malignant	4 (0.7)	0 (0)
Syncope	3 (0.5)	0 (0)
Myocardial Infarction	3 (0.5)	1 (0.3)
Angina Pectoris	2 (0.4)	1 (0.3)
Fibrillation, Atrial	2 (0.4)	1 (0.3)
Prostatic Disorder	2 (0.4)	0 (0)
Diabetes Mellitus, Aggravated	2 (0.4)	0 (0)
Hyperglycemia	2 (0.4)	0 (0)
Accident, Vehicular	2 (0.4)	0 (0)
Manic Reaction	2 (0.4)	0 (0)
Infection	2 (0.4)	0 (0)

As shown in the table above the SAEs that occurred in the tiotropium group but did not occur in the placebo group in the one-year, placebo-controlled studies were: dehydration (5 events), syncope (3 events), prostatic disorder (2 events), vehicular accident (2 events), diabetes mellitus aggravated (2 events), hyperglycemia (2 events), manic reaction (2 events), and infection (2 events). In addition, one event of each of the following occurred in the tiotropium group, but did not occur in the placebo group: allergic reaction, arrhythmia, cardiac arrest, angina pectoris aggravated, coronary thrombus, sick sinus syndrome, tachycardia, tachycardia supraventricular, aneurysm, aortic stenosis, cardiomyopathy, hemoptysis, hypoxia, sinusitis, constipation, ileus, colitis, dysphagia, gastrointestinal disorder NOS, gastroesophageal reflux, esophagitis, goiter, hyperkalemia, colon carcinoma, larynx neoplasm malignant, malignant melanoma, neoplasm malignant, uterine carcinoma, neuritis, anxiety, delirium, depression, suicide attempt, cerebellar infarction, thrombus arterial leg, lymphadenopathy, herpes zoster, hydronephrosis, and renal calculus [iss.pdf/p161-6].

In the six-month studies, SAEs occurring in the tiotropium group but not in the placebo group were: upper respiratory tract infection (2 events), gastroenteritis (2 events), and one episode each of the following: tachycardia supraventricular, skeletal pain, aneurysm, breast neoplasm malignant (female), epididymitis, prostatic disorder, testis disorder, abdomen enlarged, accident household, cor pulmonale, arthritis rheumatoid aggravated, duodenal ulcer, skin ulceration, urticaria, epistaxis, and cataract [iss.pdf/p191-3].

The incidence of discontinuation due to adverse events was lower in the tiotropium groups as compared with both the placebo and the active comparator groups. In the one-year, placebo-controlled studies, 53 (9.6%) of tiotropium patients and 50 (14%) of placebo patients discontinued due to an adverse event [iss.pdf/p167]. In those studies, events leading to discontinuation that were seen in more than two patients in a treatment group are listed in the table below. Dry mouth, the only event that occurred more frequently in the tiotropium group, is shaded.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

Adverse Events Leading to Discontinuation, occurring in more than 2 patients in the one-year, placebo-controlled studies (number [%] of patients) [iss.pdf/p167]		
Event	Tiotropium Group	Placebo Group
COPD Exacerbation	20 (3.6%)	19 (5.1%)
Dyspnea	0 (0%)	5 (1.3%)
Pneumonia	4 (0.7%)	5 (1.3%)
Cardiac Failure	2 (0.4%)	3 (0.8%)
Dry Mouth	3 (0.5%)	1 (0.3%)

In the 6-month studies, 7.2% of tiotropium patients and 16% of placebo patients discontinued due to an adverse event [iss.pdf/p194]. In these studies, COPD exacerbation and dyspnea were the only AEs that led to discontinuation of more than 2 patients in a treatment group. COPD exacerbation was the cause of discontinuation in 3.5% of tiotropium patients and 7.5% of placebo patients, and dyspnea was the cause of discontinuation in 1.2% of tiotropium patients and 3.3% of placebo patients. Dry mouth led to discontinuation in 1 tiotropium patient (0.2%) and in 0 patients in the placebo and salmeterol groups.

3. Other Safety Findings: Adverse Events, Lab Findings, Vital Signs, and ECGs

The table below summarizes the overall incidence of adverse events and the incidence of those adverse events that were considered by the investigator to be possibly drug-related. The overall incidence of adverse events was similar among the groups. Of note, the incidence of drug-related adverse events was greater in the tiotropium group, as compared to placebo and as compared to each of the active comparators examined (ipratropium and salmeterol). This is due to the increased incidence of drug-related dry mouth with tiotropium.

Adverse Event Profile [iss.pdf/p33, 44]														
	1-year, placebo-controlled studies				1-year, ipratropium-controlled studies				6-month, salmeterol and placebo-controlled studies					
	Tiotropium		Placebo		Tiotropium		Ipratropium		Tiotropium		Salmeterol		Placebo	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total Treated	550	100	371	100	356	100	179	100	402	100	405	100	400	100
All Adverse Events	495	90	338	91.1	318	89.3	162	90.5	298	74.1	305	75.3	307	76.8
Drug-related Adverse Events	104	18.9	34	9.2	73	20.5	22	12.3	44	10.9	33	8.1	31	7.8

The tables below summarize adverse events that were reported by $\geq 3\%$ of patients in the tiotropium group and occurred more frequently in the tiotropium group as compared to the placebo group. For purposes of reference, the tables contain data on the incidence of these AEs in the active comparator groups. The active comparator data is drawn from separate studies in the case of the one-year studies, and from the same studies in the case of the 6-month studies. The first table contains the one-year studies, and the second table contains the 6-month studies.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

Adverse Events Reported by $\geq 3\%$ of Patients in the Tiotropium Group and Occurring More Frequently in the Tiotropium Group as Compared with the Placebo Group [One-Year Studies] [issa.pdf/p143-4]									
		1-year, placebo-controlled studies				1-year, ipratropium-controlled studies			
		Tiotropium		Placebo		Tiotropium		Ipratropium	
		N	(%)	N	(%)	N	(%)	N	(%)
Total Treated		550	100	371	100	356	100	179	100
Body as a Whole									
	Accidents	73	13.3	42	11.3	16	4.5	14	7.8
	Chest Pain	38	6.9	17	4.6	19	5.3	4	2.2
	Edema, dependent	25	4.5	13	3.5	10	2.8	9	5.0
	Influenza-Like Symptoms	45	8.2	30	8.1	39	11.0	25	14.0
Gastrointestinal System									
	Abdominal Pain	26	4.7	11	3.0	20	5.6	11	6.1
	Constipation	19	3.5	6	1.6	2	0.6	2	1.1
	Dyspepsia	32	5.8	17	4.6	5	1.4	1	0.6
	Mouth Dry	88	16.0	10	2.7	43	12.1	11	6.1
	Vomiting	19	3.5	9	2.4	3	0.8	3	1.7
Musculoskeletal System									
	Arthritis	26	4.7	17	4.6	15	4.2	7	3.9
	Myalgia	21	3.8	11	3.0	13	3.7	6	3.4
Resistance Mechanism Disorders									
	Infection	23	4.2	12	3.2	5	1.4	5	2.8
	Moniliasis	20	3.6	9	2.4	10	2.8	3	1.7
Respiratory System									
	Coughing	26	4.7	17	4.6	30	8.4	17	9.5
	Epistaxis	20	3.6	7	1.9	4	1.1	2	1.1
	Pharyngitis	49	8.9	27	7.3	23	6.5	5	2.8
	Rhinitis	30	5.5	20	5.4	9	2.5	4	2.2
	Sinusitis	62	11.3	35	9.4	12	3.4	4	2.2
	Upper Respiratory Tract Infection	226	41.1	138	37.2	153	43.0	62	34.6
Skin and Appendages									
	Rash	23	4.2	8	2.2	7	2.0	4	2.2
Urinary System									
	Urinary Tract Infection	40	7.3	19	5.1	14	3.9	4	2.2

In the one-year placebo-controlled studies, the most notable adverse events were related to the gastrointestinal system (abdominal pain, constipation, dyspepsia, dry mouth, and vomiting). The occurrence of AEs in the category of “Gastrointestinal System Disorders” was 38.5% in the tiotropium group and 29.1% in the placebo group [issa.pdf/13]. Of these, by far the most common was dry mouth, with an incidence of 16% in the tiotropium group. Of note, the one-year ipratropium-controlled studies demonstrated that the frequency of dry mouth is greater with tiotropium than with the related drug, ipratropium. Upper respiratory tract infections were also remarkably more common in the tiotropium groups as compared to both the placebo group and the ipratropium group. Other upper respiratory tract AEs, such as epistaxis, pharyngitis, and sinusitis may reflect drying effects of this anticholinergic compound on the airway mucosa. The mechanism that might be responsible for the observed increased incidence of urinary tract infections in the tiotropium group is not known, but may relate to urinary stasis due to anticholinergic effects on the genitourinary system.

The table above includes adverse events reported by $\geq 3\%$ of subjects in a treatment group. The listings of all AEs reported in the one-year, placebo-controlled studies, by treatment group, were reviewed [issa.pdf/p7-34]. The following observations are derived from these listings:

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

- The AE “allergic reaction” occurred in 14 (2.5%) patients in the tiotropium group and 3 (0.8%) patients in the placebo group.
- The AE “tooth caries” occurred in 4 (0.7%) patients in the tiotropium group and 0 patients in the placebo group.
- The occurrence of AEs in the category “Metabolic and Nutritional Disorders” was 6.4% in the tiotropium group and 2.7% in the placebo group. This difference is primarily the result of the following disparities in the occurrence of AEs in this category:
 - 1) “diabetes mellitus”, “diabetes mellitus aggravated,” or “hyperglycemia” was reported in 14 (2.5%) tiotropium patients and was reported in only 1 (0.3%) placebo patients;
 - 2) “dehydration” was reported in five tiotropium patients (0.9%) and was not reported in any placebo patients; **Reviewer’s Comment: It is not clear if the occurrence of dehydration was related to the reported hyperglycemia/diabetes.**
 - 3) “hypercholesterolemia” was reported in 6 (1.1%) tiotropium patients and 1 (0.3%) placebo patients.
- “Urinary retention” occurred in 4 (0.7%) tiotropium patients and 0 placebo patients.
- “Micturation disorder” or “micturation frequency” occurred in 6 (1.1%) tiotropium patients and 0 placebo patients.

Reviewer’s Note: With the exception of hypercholesterolemia, which was slightly more common in the tiotropium group than the placebo group (1.0% vs. 0.3%), the adverse event data from the six-month studies did not confirm these observations [issa.pdf/p201-22].

Adverse Events Reported by ≥3% of Patients in the Tiotropium Group and Occurring More Frequently In the Tiotropium Group as Compared with the Placebo Group [6-month Studies] [iss.pdf/p182]						
	Tiotropium		Placebo		Salmeterol	
	N	(%)	N	(%)	N	(%)
Total Treated	402	100	400	100	405	100
Body as a Whole						
Accidents	17	4.2	10	2.5	21	5.2
Back Pain	16	4.0	12	3.0	16	4.0
Chest Pain	16	4.0	15	3.8	14	3.5
Influenza-Like Symptoms	27	6.7	16	4.0	21	5.2
Gastrointestinal System						
Mouth Dry	33	8.2	9	2.3	7	1.7
Respiratory System						
Pharyngitis	18	4.5	12	3.0	14	3.5
Sinusitis	13	3.2	10	2.5	1	0.2
Upper Respiratory Tract Infection	78	19.4	64	16.0	69	17.0

The AE data from the 6-month studies indicate fewer differences between tiotropium and placebo. Several of the AEs that were more common in the tiotropium group in the 1-year studies were also noted to be more common in the tiotropium group in the 6-month studies. Most notable among these were dry mouth, upper respiratory tract infection, influenza-like symptoms, and pharyngitis.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

In these studies, the investigators were asked to indicate which adverse events were considered to be possibly related to study drug. The most common adverse event that was considered to be possibly drug related was dry mouth [iss.pdf/p37-8, 46-7]. Drug-related dry mouth was reported in 14% of the tiotropium patients in the placebo-controlled studies (compared with 2.2% of placebo patients), in 11% of tiotropium patients in the ipratropium-controlled studies (compared with 5.6% of ipratropium patients), and in 6.5% of tiotropium patients in the 6-month studies (compared with 1% in the placebo and the salmeterol patients). Drug-related dysphonia was also more common in the tiotropium group as compared with placebo in the one-year studies (1.5% vs. 0.3%), but not in the 6-month studies. Finally, drug-related pharyngitis was slightly more common in the tiotropium group (1.1% vs. 0.8% in the placebo-controlled studies, and 1.1% vs. 0% in the ipratropium-controlled studies) in the one-year studies.

Vital signs were measured at the screening visit and on test days at the same intervals as the pulmonary function testing for the first three hours post dose (vital signs were measured just prior to pulmonary function measurements) [iss.pdf/p82]. The mean values for heart rate and blood pressure were similar in the tiotropium and the placebo groups [issa.pdf/p263-5]. The Applicant defined “marked changes” in vital signs as follows [iss.pdf/p229]:

- Systolic BP increase: an increase of ≥ 25 mmHg above baseline
- Systolic BP decrease: below 100mmHg if not at that level at baseline, and a decrease of greater than 10mmHg below baseline
- Diastolic BP increase: above 90mmHg and an increase of greater than 10mmHg from baseline
- Diastolic BP decrease: below 60mmHg if not at that level at baseline and a decrease of >10 mmHg below baseline
- Pulse increase: greater than 100bpm if not at that level at baseline and an increase of $>10\%$ above baseline.
- Pulse decrease: below 60bpm if not at that level at baseline and a decrease of >10 bpm below baseline

The incidence of “marked changes” from baseline (as defined by the Applicant) were generally similar in the tiotropium and placebo groups [iss.pdf/p236-7]. On Test Day 1 in the one-year, placebo-controlled studies, more patients in the tiotropium group developed a marked decrease in systolic blood pressure (defined as: below 100mm Hg if not at that level at baseline, and a decrease of greater than 10mm Hg below baseline [iss.pdf/p229]), as compared with placebo (3.1% vs. 0.5%). Because patients with potentially significant changes in pulse rate due to the anticholinergic effects of the drug might not be captured by the definition of a “marked change” for increased pulse, the Applicant was asked to submit shift tables for pulse rate increases of various magnitudes. This data was submitted on July 31, 2002. In all of the placebo-controlled studies, no remarkable difference was seen between tiotropium and placebo in regard to the percentages of patients who exhibited increases in heart rates of >5 , >10 , >15 , or >20 beats per minute at any test day [Submission dated 7/31/02, pages 4-9].

In the four 1-year Phase 3 studies, laboratory testing was performed at baseline and at three-month intervals throughout the treatment period [iss.pdf/p83]. In the two 6-month Phase 3 studies, laboratory testing was performed at baseline and at the end of the study. Laboratory

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

tests included hematology, clinical chemistry, and urinalysis. The mean values for all parameters both at baseline and conclusion of patient participation were similar between treatment groups [iss.pdf/p244-50]. The incidence of “marked” changes in laboratory values (as defined by the Applicant) from baseline to final evaluation was similar among groups in the one-year and the six-month studies [iss.pdf/p251-6]. In the one-year, ipratropium-controlled studies there was a relatively high percentage of subjects in each group who demonstrated “marked” increase in LDH (12.7% in the tiotropium group and 9.9% in the ipratropium group). Marked elevations in other liver enzymes were not seen, nor were marked changes in hemoglobin or hematocrit to suggest hemolysis as a source of the LDH.

In the one-year, placebo-controlled studies there was no difference between groups in the percentage of patients with clinically significant changes in physical examination (defined by the Applicant) from baseline to final examination. In the one-year, placebo-controlled studies there were 46 (8.4%) such patients in the tiotropium group and 36 (9.7%) such patients in the placebo group [iss.pdf/p257].

Electrocardiogram data are discussed in the section below, entitled “Adverse Events Related to the Pharmacologic Actions of the Drug.”

Paradoxical bronchospasm, defined as a decline in FEV₁ by at least 15% from baseline within 30 minutes of administration of study drug, was less frequent in the tiotropium group than in the placebo group in the one-year, placebo-controlled studies (4.5% vs. 12%) [iss.pdf/p240]. In five of the 25 tiotropium patients who exhibited paradoxical bronchospasm, the event occurred on two test days. In the one-year, ipratropium-controlled studies 15 (4.2%) patients in the tiotropium group and 1 (0.6%) patient in the ipratropium group experienced paradoxical bronchospasm. In the six-month studies 10 (1.0%) patients in the tiotropium group, 22 (2.1%) patients in the salmeterol group, and 33 (3.2%) patients in the placebo group experienced paradoxical bronchospasm. There were no discontinuations of tiotropium due to paradoxical bronchospasm.

4. Pregnancy

No pregnancies were reported during the conduct of any of the clinical studies for tiotropium [Submission date 7/24/02, page 4].

5. Interactions

Drug-Demographic Interactions

In order to assess the effect of age on the safety of tiotropium, adverse events were analyzed according to age groups (≤ 60 years, 61-70 years, and ≥ 71 years) [iss.pdf/p41]. In the one-year placebo-controlled studies, two specific adverse events were noted to occur with increasing frequency in the older age groups in the tiotropium group only, suggesting a drug-age interaction. These were dry mouth, and constipation. A third AE, urinary tract infection, occurred with greater frequency in older patients in both treatment arms, although the effect was more marked in the tiotropium group.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

The adverse event “dry mouth” increased in frequency with age in the tiotropium group. In the one-year, placebo-controlled studies the percent of patients with dry mouth was 11% in the younger age group, 16% in the middle age group, and 21% in the older age group [iss.pdf/p176]. In contrast, the incidence of this adverse event in the placebo group was 3.0%, 1.9%, and 3.5% in the three age groups. This observation was also made in the one-year, ipratropium-controlled studies, in which the percentages of patients with dry mouth also increased with age (7.7%, 15%, and 14%). In contrast, the percentages declined with age in the ipratropium group (8.2%, 6.1%, and 4.2%) in these studies [iss.pdf/p41]. Drug-age interaction was not suggested in the 6-month studies [iss.pdf/p49].

In the one-year, placebo-controlled studies constipation was also more frequent with increasing age in the tiotropium group (2%, 2.8%, and 6%), but not in the placebo group (3.0%, 0.6%, and 1.7%). In these studies, urinary tract infection occurred with increased frequency in the older age groups in the both the tiotropium group (3.3%, 5.2%, and 12%), and the placebo group (2.0%, 3.9%, and 6.1%), although the frequency was greater in the tiotropium group. These observations were not made in the one-year, ipratropium-controlled studies or the six-month studies [iss.pdf/p49].

Reviewer’s Comment: The observation that dry mouth, constipation, and urinary tract infection occur more frequently with increasing age in the tiotropium group, along with the observation of increased systemic drug exposure with increasing age (see discussion of pharmacokinetics in Section IV of this Clinical Briefing Document) suggest that these adverse events represent systemic effects of the drug.

The majority of patients in the pivotal clinical studies were men. The proportions of patients with adverse events was generally similar between genders within each treatment group, with the exception of dry mouth. In the one-year, placebo-controlled studies the frequency of dry mouth in the tiotropium group was 23% among women, and 13% among men. For comparison, the frequencies in the placebo group were 2.9% in women and 2.6% in men [iss.pdf/p177]. This pattern was also seen in the six-month studies, with dry mouth being reported by 14.3% of women and 6.4% of men [iss.pdf/p49]. In the one-year, ipratropium-controlled studies women also reported more dry mouth than men [iss.pdf/p42].

Genitourinary effects also showed evidence of a gender effect in the one-year studies. The adverse events “urinary retention” and “micturation disorder” were reported solely in men, and there was an increase in the frequency of urinary tract infection among men. Urinary retention occurred only in men in the tiotropium group (1.1%) in the one-year, placebo-controlled studies. Micturation disorders occurred only in men receiving either tiotropium (1.1% in the placebo-controlled studies and 0.3% in the ipratropium-controlled studies), or ipratropium (0.6%).

In the six-month studies, pharyngitis and sinusitis were more common in women (7.7% and 7.7%) than in men (3.5% and 1.9%) [iss.pdf/p49].

Because very few patients in these studies were non-white, analyses for drug-race safety interactions were not informative.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

Drug-disease interactions

There was no evidence of a drug-disease severity interaction, based on categories of diseases severity (FEV₁ <35%, FEV₁ 35-49%, and FEV₁ ≥50% predicted) [iss.pdf/p43, 50]. There was no evidence of a drug-smoking status interaction, based on smoking status at entry into the trial [iss.pdf/p43, 50].

Drug-drug interactions

The clinical development program did not include specific drug-drug interaction studies. Subgroup analyses of adverse event data from the “pivotal” Phase 3 studies were performed for baseline users vs. non-users of theophylline, oral corticosteroids, and inhaled corticosteroids. While the incidence of COPD exacerbations was greater in steroid users compared with steroid non-users, the Applicant states that there was no evidence of interaction of tiotropium with oral steroids or inhaled steroids on reported adverse events. In the one-year placebo controlled studies, the incidence of dry mouth in the tiotropium group was greater in theophylline users than in non-users (20% vs. 15%) [iss.pdf/p175]. No such difference was seen in the placebo group. In the 1-year ipratropium-controlled studies, reports of dry mouth were equally distributed in those receiving tiotropium who were theophylline users and non-users. Finally, in the six-month studies, the pattern was reversed, with a lower incidence of dry mouth among tiotropium patients who were theophylline users vs. non-users (2.7% vs. 10%) [iss.pdf/p48].

6. Safety Findings from Other Clinical Studies

COPD Studies

COPD studies discussed in this section include the AM/PM dosing trial (205.123), the mucociliary clearance trial (205.116), the sleep trial (205.124), the dose-ranging trials (205.119, 205.120, and 205.108), a pharmacokinetic trial in the elderly (205.133), and a trial conducted with the Respimat device (205.127) [iss.pdf/p50].

There were three deaths in these studies. The causes of death were myocardial infarction (11 weeks after the last dose of tiotropium in the pharmacokinetic trial in the elderly), respiratory failure (in a placebo patient in the sleep study), and non-Hodgkin’s lymphoma (108 days following the two-week study period of a dose-ranging trial [205.120]). Few SAEs were reported in these relatively short studies. Few adverse events led to discontinuation, and such events were generally less common in the tiotropium groups. In the six-week AM/PM dosing study, one patient receiving PM tiotropium developed cystitis, hematuria, and orchitis requiring hospitalization. Study drug was discontinued [iss.pdf/p206]. One patient in the Respimat study (205.127) who was receiving tiotropium 2.5mcg developed worsening of hematuria that was considered unexpected and related to the study drug [iss.pdf/p206-7]. Of note, male rats developed proteinaceous material in the urinary bladder in the majority of preclinical studies [4/18/02 submission, iss.pdf/p272]. This was associated with a mild inflammatory response and diffuse hyperplasia of the bladder transitional epithelium, and prostatitis.

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

Asthma Studies

Among the four asthma studies (205.121, 205.201, 205.202, and 205.203), no deaths were reported and SAEs and AEs leading to discontinuation were few [iss.pdf/p208-9].

Healthy Volunteer Studies

The most common AEs in the single-dose studies were headache and taste perversion [iss.pdf/p209]. In the multiple-dose studies the most common AEs were dry mouth and taste perversion.

7. Adverse Events Related to the Pharmacologic Actions of the Drug

The Application included specific attention to adverse effects that might result from the anticholinergic effect of tiotropium. These include gastrointestinal effects (dry mouth, constipation, and dysphagia), cardiovascular effects (tachycardia), genitourinary effects (urinary retention, urinary tract infection), and ophthalmologic effects (glaucoma).

Dry Mouth

Dry mouth was consistently more common in tiotropium groups as compared with placebo and as compared with the active comparators, ipratropium and salmeterol. Dry mouth was more common in older patients and in women. The median onset of dry mouth, which was generally of mild or moderate intensity, was 15 to 35 days [iss.pdf/p211-3]. Severe dry mouth and discontinuation due to dry mouth were uncommon (three patients in each category in the one-year studies). In the one-year, placebo-controlled studies, tiotropium was also associated with increased frequency of certain adverse events that may be related to the drying effects of the drug. These include epistaxis (3.6% vs. 1.9%), pharyngitis (8.9% vs. 7.3%), sinusitis (11.3% vs. 9.4%), and moniliasis (3.6% vs. 2.4%) [iss.pdf/p212]. Among these, the frequency of pharyngitis, sinusitis, and moniliasis were greater in the tiotropium group (6.5%, 3.4%, and 2.8%, respectively) compared with the ipratropium group (2.8%, 2.2%, and 1.7%, respectively) in the one-year, ipratropium-controlled studies.

Constipation

In the one-year, placebo-controlled studies constipation was reported more frequently in the tiotropium group (3.5%) than in the placebo group (1.6%) [iss.pdf/p214]. One patient in the tiotropium group required hospitalization due to fecal impaction.

Dysphagia

Dysphagia was reported by three patients in the one-year studies. All three were in the tiotropium group [iss.pdf/p215]. Two of the patients underwent endoscopy as a result of the symptom.

Urinary Retention and Micturation Disorders

Urinary retention occurred in four patients (0.7%) receiving tiotropium in the one-year placebo-controlled studies [iss.pdf/216]. The four cases occurred between treatment days 18 and 174, in men between the ages of 69 and 77. All four required the placement of a Foley catheter and three were started on medication for BPH. Urinary retention also occurred in one patient receiving tiotropium in the six-month studies, but did not occur in any patients in the one-year,

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

ipratropium-controlled studies [iss.pdf/p216]. In addition, there were four reports of micturation disorders in the tiotropium group (in men aged 64 to 81 years) and none in the placebo group of the one-year, placebo-controlled studies, and one case of micturation disorder in each of the two treatment arms of the one-year, ipratropium-controlled studies.

Urinary Tract Infection

In the one-year, placebo-controlled studies, the incidence of urinary tract infection was greater in the tiotropium group (6.5% vs. 4.0%) [iss.pdf/p217]. In the one-year, ipratropium-controlled studies the incidence of UTI was not different between the tiotropium and the ipratropium groups. However, the incidence of cystitis was greater in the tiotropium group in those studies (2.5% vs. 0.0%). In the six-month studies the incidence of UTI was 1.2% in the tiotropium and 0.5% in the placebo group.

Cardiovascular Effects

The incidence of death due to cardiac events was not different in the tiotropium and placebo groups in the one-year studies (0.5% vs. 0.3%). However, there were subtle indications that tiotropium may be associated with increased frequency of adverse cardiac effects, specifically in the category of “heart rate and rhythm disorders.” (Note: Cardiac AEs are divided into three categories: “general,” “heart rate and rhythm disorders,” and “myo-, endo-, pericardial and valve disorders.”) In the one-year, placebo-controlled studies the incidence of “heart rate and rhythm disorders” was greater in the tiotropium group (4.4%, 24 patients) than in the placebo group (2.2%, 8 patients) (see table below) [iss.pdf/p231]. It should be noted that in the one-year ipratropium-controlled studies the incidence of “heart rate and rhythm disorders” was greater in the ipratropium group (5.0%) than in the tiotropium group (3.9%). The incidence of serious “heart rate and rhythm disorders” in the one-year, placebo-controlled studies was 1.3% in the tiotropium group and 0.5% in the placebo group [iss.pdf/p232]. This included two SAEs of supraventricular tachycardia, both of which occurred in patients on tiotropium. In the one-year studies, there were four discontinuations due to heart rate and rhythm disorders, all in the tiotropium group [iss.pdf/p234]. In the one-year, placebo-controlled studies, there were two deaths due to heart rate and rhythm disorders, both in the tiotropium group [iss.pdf/p233]. Although there was no difference between groups for “Myo-, Endo-, Pericardial and Valve Disorders” AEs in the one-year, placebo-controlled studies, there was a slightly greater incidence of SAEs in this category (2.0% vs. 1.3%) [iss.pdf/p232].

Cardiac Adverse Events, by WHO System Organ Class (1-year studies)							[iss.pdf/p231]	
	1-year, placebo-controlled studies				1-year, ipratropium-controlled studies			
	Tiotropium		Placebo		Tiotropium		Ipratropium	
	N	(%)	N	(%)	N	(%)	N	(%)
Total Treated	550	100	371	100	356	100	179	100
Cardiovascular Disorders, General	5	0.9	5	1.3	3	0.8	3	1.7
Cardiac Failure	5	0.9	4	1.1	1	0.3	1	0.6
Cardiac Failure, Right	0	0	0	0	2	0.6	0	0
Cardiomegaly	0	0	1	0.3	0	0	1	0.6
Cor Pulmonale	0	0	1	0.3	0	0	0	0
Heart Disorder	0	0	0	0	0	0	1	0.6
Heart Valve Disorder	0	0	0	0	1	0.3	0	0
Heart Rate and Rhythm Disorders	24	4.4	8	2.2	14	3.9	9	5.0

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

Cardiac Adverse Events, by WHO System Organ Class (1-year studies)								[iss.pdf/p231]	
		1-year, placebo-controlled studies				1-year, ipratropium-controlled studies			
		Tiotropium		Placebo		Tiotropium		Ipratropium	
		N	(%)	N	(%)	N	(%)	N	(%)
Total Treated		550	100	371	100	356	100	179	100
	Arrhythmia	4	0.7	1	0.3	0	0	1	0.6
	AV Block	0	0	0	0	1	0.3	1	0.6
	Bradycardia	1	0.2	1	0.3	0	0	0	0
	Bundle Branch Block	0	0	0	0	1	0.3	0	0
	Cardiac Arrest	1	0.2	0	0	0	0	0	0
	Extrasystoles	2	0.4	0	0	0	0	0	0
	Fibrillation Atrial	5	0.9	3	0.8	5	1.4	4	2.2
	Palpitation	4	0.7	2	0.5	3	0.8	3	1.7
	Sick Sinus Syndrome	1	0.2	0	0	0	0	0	0
	Tachycardia	4	0.7	1	0.3	4	1.1	0	0
	Tachycardia supraventricular	2	0.4	1	0.3	0	0	0	0
Myo-, Endo-, and Pericardial and Valve Dis		15	2.7	10	2.7	10	2.8	6	3.4
	Angina Pectoris	4	0.7	2	0.5	6	1.7	4	2.2
	Angina Pectoris Aggravated	2	0.4	0	0	1	0.3	1	0.6
	Cardiomyopathy	1	0.2	0	0	0	0	0	0
	Coronary Artery Disorder	4	0.7	4	1.1	0	0	0	0
	Heart Murmur	0	0	2	0.5	0	0	0	0
	Myocardial Infarction	3	0.5	2	0.5	3	0.8	1	0.6
	Thrombosis Coronary	1	0.2	0	0	0	0	0	0

In the one-year, placebo-controlled studies ECGs were done at baseline and every 90 days for the duration of the study. *Unfortunately, the protocol did not specify the timing of the ECGs in relation to study drug and that information was not captured on the case report forms [Submission date 7/16/02, page 5].* Therefore, it cannot be assumed that the ECGs were obtained at or near the expected Cmax. In these studies, there was no difference between groups in the incidence of ECG changes (1% vs. 1.8%). The Applicant states that there was no imbalance in regard to the type of ECG abnormalities noted. One patient in the one-year, ipratropium-controlled studies developed tachycardia 30 minutes after the first dose of tiotropium and discontinued the study.

In the six-month studies, ECGs were performed at baseline and at the completion of the study. The incidence of ECG changes was 1.7% in the tiotropium group and 0.8% in the placebo group. In the four-week, parallel-group, placebo-controlled, dose-ranging study (205.108) ECGs were performed at baseline and at one, three, and five hours after drug administration on Day 1 and Weeks 1, 2, and 4. No differences in the occurrence of ECG changes was noted between active and placebo groups [iss.pdf/p225]. Tachyarrhythmias were seen in three tiotropium patients (ventricular tachycardia in a patient receiving 4.5mcg, atrial fibrillation in a patient receiving 9mg, and sinus tachycardia in a patient receiving 18mcg) and in one patient in the placebo group (sinus tachycardia).

The ECG database is supported by timed ECGs (1, 3, and 5 hours post-dose) that were performed in the multiple-dose, dose-ranging study (205.108). In that placebo-controlled study, doses of 5.5mcg, 11.0mcg, 22.0mcg, and 44.0mcg were studied (33-35 patients per treatment

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

group). In addition to a baseline pre-dose ECG, timed ECGs (and 2-minute rhythm strips) were obtained after 8, 15, and 29 days of treatment [U96-3068.pdf/p111-14]. The ECGs and rhythm strips were centrally read by a cardiologist. There were no differences seen between placebo and active treatment in regard to ECG changes. Borderline QT interval was reported as intermittent in one placebo patient and transient in one tiotropium patient (22.0mcg). Specific QT or QTc interval data was not submitted.

Only one study included 24-hour Holter monitoring. This was the six-week, AM/PM dosing trial (205.123), in which there were three, double-blind treatment groups (tiotropium 18mcg AM dosing, tiotropium 18mcg PM dosing, and placebo, using the Handihaler device) [U00-0121.pdf]. The study was performed in the UK and the Netherlands, during the period May, 1997 to July, 1998 [U00-0121.pdf/p20]. Exclusion criteria were similar to other clinical studies. Patients with a history of significant disease other than COPD and patients with a recent history of heart failure or any cardiac arrhythmia requiring drug therapy were excluded. A total of 121 patients entered the trial (43 in the tiotropium PM dosing group, 38 in the tiotropium AM dosing group, and 40 patients in the placebo group). The mean age was 65.8 years, and 62% of the population was male. In this study, Holter monitoring was performed on two occasions. The baseline, 24-hour Holter monitor was placed on Day 0, and continued until Day 1, approximately 2 hours *after* the first dose of study medication [U00-0121.pdf/p44]. The second 24-Holter monitor was placed at Visit 4, at the end of the 6-week treatment period. The protocol does not specify when the monitor was placed in relation to study drug administration [U00-0121.pdf/p45]. The analysis of the Holter tapes was performed by a central facility (Hertford Medical, The Netherlands) [U00-0121.pdf/p41]. Data on supraventricular and ventricular ectopy, heart rate, and heart rate variability were collected and assessed [U00-0121.pdf/p101].

Reviewer's Comment: Interpretation of the comparisons of "baseline" and on-treatment Holter results is complicated by the fact that the first dose of study drug was given during the recording of the "baseline" Holter. *On-treatment Holter monitor results were available for 35 tiotropium PM patients, 37 tiotropium AM patients, and 31 placebo patients [U00-0121.pdf/p103]. No clear effect on the frequency of supraventricular or ventricular ectopy was observed. No episodes of atrial fibrillation or atrial flutter were observed, either at baseline or on treatment [U00-0121.pdf/p104]. One subject in the tiotropium PM group developed a four-fold increase in ventricular ectopy after medication [U00-0121.pdf/p104]. None of the treatment groups had a remarkable change in mean heart rate, minimum heart rate, or maximum heart rate. There were no episodes of AV block. The Applicant states that assessment of heart rate variability is a sensitive marker of anticholinergic effects on the heart. In general, an increase in variability is said to indicate an improvement in cardiac autonomic function. The Applicant states that tiotropium was associated with a minor decrease in heart rate variability [iss.pdf/p228].*

Ocular Events

The clinical studies did not suggest a drug-associated increase in the occurrence of glaucoma. In the one-year, placebo-controlled studies, glaucoma was reported in two patients receiving tiotropium and one patient receiving placebo [iss.pdf/p238]. In the one-year, ipratropium-controlled studies one case of glaucoma was reported in a patient receiving tiotropium. In the six-month studies, glaucoma was reported in one patient in the tiotropium group, one patient in

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

the salmeterol group, and two patients in the placebo group. In a study evaluating the safety following ocular administration of single increasing doses of a solution of tiotropium ranging from 0.02 to 0.40 mcg, tiotropium did not increase pupillometric pressure or affect pupillary diameter in healthy volunteers (Study 205.138).

D. Adequacy of Safety Testing

The safety assessments performed in the pivotal studies were generally satisfactory, with one exception. The cardiac safety database is limited and does not provide sufficient evidence of cardiac safety for this drug. There are several reasons to be concerned about possible cardiac effects of tiotropium. First, anticholinergic drugs, such as tiotropium, might be expected to have effects on cardiac rate and rhythm. Second, the drug is associated with detectable plasma concentrations, particularly with chronic use. Third, underlying cardiac disease is common in the proposed patient population. As with most clinical development programs, subjects with significant cardiac disease (e.g. myocardial infarction within 1 year, heart failure within three years, cardiac arrhythmia requiring drug therapy, and significant disease other than COPD), subjects with hypoxemia requiring daytime oxygen therapy, and subjects with a creatinine >2.0 mg/dL were excluded from participation in the Phase 3 clinical studies. Such patients, who will receive the drug if it is approved, may be at increased risk of adverse drug-related cardiac effects. Finally, because of the large volume of distribution and long elimination half-life, subjects who develop adverse drug effects will continue to be exposed for weeks after discontinuing the drug.

The cardiac safety database includes insufficient Holter monitor data. Holter monitors were performed in only one study (205.123). In that study, "baseline" Holters included a period of time on drug, complicating the interpretation of the comparison of baseline to on-treatment data. On-treatment Holters were only available for 37 patients treated with the proposed dose in the morning, 35 patients treated with the proposed dose in the evening, and 31 placebo patients. For comparison, the product label for Serevent Inhalation Aerosol (GlaxoSmithKline) indicates that Holter monitoring was performed on 284 COPD patients during five 24-hour periods

Although the ECG monitoring in the one-year, placebo-controlled studies was less than optimal because the on-treatment ECGs were not obtained at or near the expected C_{max} (and may have been obtained pre-dose), the ECG database is supported by the timed ECGs from the multiple-dose, dose-ranging study (205.108).

E. Four-Month Safety Update

The Four-Month Safety Update, dated April 18, 2002, was submitted electronically. *The references cited in this section of the Clinical Briefing Document refer to the April 18, 2002, submission.* The submission included an updated Integrated Summary of Safety including new safety data covering the period of December 14, 2000 to December 13, 2001, and Clinical Trial Reports for two studies (205.131 and 205.222). Study 205.131 is discussed briefly below. Study 205.222 was a study of the effect of concomitant cimetidine and ranitidine once daily on the single dose pharmacokinetics of tiotropium, performed in 18 subjects in Germany [iss.pdf/p93]. The updated ISS includes preliminary unblinded safety data from four studies [iss.pdf/p24]:

CLINICAL BRIEFING DOCUMENT

Integrated Review of Safety

- an exercise study with a treatment period of six-weeks (205.131) [iss.pdf/p28];
- a study evaluating changes in inspiratory capacity with a treatment period of four-weeks (205.218) [iss.pdf/p28];
- a study to evaluate the effect of a single dose of ipratropium after 19 days of tiotropium treatment in healthy volunteers aged 40-65 years(205.239) [iss.pdf/p30];
- and a placebo-only HandiHaler ease-of-use and learning retention study (205.220) [iss.pdf/p28].

However, the updated ISS safety database includes only 18 subjects not reported in the original ISS [iss.pdf/p109]. These are the 18 healthy volunteers who participated in the IV pharmacokinetic trial (single doses of 14.4 mcg). The preliminary safety data from the four unblinded studies listed above, are discussed separately [iss.pdf/p287-95]. Review of that discussion did not reveal any new potential safety concerns.

The submission also provides information on 4 previously unreported deaths, which occurred in Study 205.214, an ongoing study evaluating the effect of tiotropium on the severity and incidence of COPD exacerbations [iss.pdf/p277-9]. The causes of death were pulmonary embolism, monocytic leukemia, myocardial infarction, and intestinal obstruction (post-operative). The treatment assignment has not been unblinded.

IX. Appendix: Detailed Reviews of Individual Studies

One-Year Placebo-Controlled Studies:

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

a. Study Description

Design

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

Duration

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

Study Centers

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

Population

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

Materials

The study treatments were:

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

Each treatment was administered once daily, in the morning.

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

CLINICAL BRIEFING DOCUMENT

Appendix
Study 205.114/205.117

Objective

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

Inclusion Criteria

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

Exclusion Criteria

Notable exclusion criteria were:

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

Conduct

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

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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

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

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

- Morning and evening PEFr: performed by the subject twice daily during the study period. The AirWatch™ Monitoring System was used to record the measurements electronically. Morning measurements were performed immediately upon arising after the subject had “cleared out” mucus. Evening measurements were performed at bedtime. (Note: The original protocol indicated that “peak flow *and* FEV₁ measurements will be recorded *three times daily* by the patient throughout the 54-week evaluation period including the two-week baseline period and one-year treatment period.” [U99-3169.pdf/p306]. This was subsequently changed in Amendment 1 to two times daily. The reference to FEV₁ was not removed [U99-3169.pdf/p353]. In response to a request for information, the Applicant stated that, although the FEV₁ data was captured using the AirWatch Monitor, a decision was made prior to the initiation of the trial to not analyze the home FEV₁ data because of concerns regarding its reliability [Submission 7/16/02, page 4]).
- COPD symptoms (wheezing, shortness of breath, coughing, and tightness of chest): These scores are based upon *the Investigator's assessment* of the patient's condition *during the week just prior* to the contact [U99-3169.pdf/p306]. They were recorded on case report forms (CRFs) at the end of baseline period, at the end of the first week of therapy, and every 3 weeks for the next 12 weeks. During the remaining 36 weeks of treatment the COPD symptom evaluations were made at 3-week intervals, either during clinic visits or during telephone contacts midway between visits.
- Physician (or designee) global evaluation: at the end of the baseline period, at the end of the first week of therapy, and every 3 weeks for the next 12 weeks. During the remaining 36 weeks of treatment the physician global evaluations were made at 6-week intervals. The evaluations were made prior to pulmonary function testing, and reflected the physician's opinion of the overall clinical condition. The evaluation was to be based on the need for concomitant medication, number and severity of exacerbations since the last visit, severity of cough, ability to exercise, amount of wheezing, etc. The scores could range from 1 (poor) to 8 (excellent).
- Rescue albuterol use recorded daily by the patient.
- St. George's Hospital Respiratory Questionnaire (SGRQ), SF-36, and the Mahler BDI/TDI: administered at the end of the baseline period, after 7, 13, 25, 37, and 49 weeks of treatment.

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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

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

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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

The following tables outline the study procedures.

Study Procedures, First 13 Weeks: 205.114/205.117								[U99-3169.pdf/p68-9]
Trial Period:	Screen	Treatment Period (First 13 Weeks)						
Visit #:	1	2	3	4	5	6	7	
Weeks on Therapy:		0	1	4	7	10	13	
Day:	-14	1	8	29	50	71	92	
Physical Examination	X						X	
Vital Signs (seated)	X	X	X		X		X	
Laboratory Tests (fasting)	X						X	
12-lead ECG	X						X	
Theophylline level ¹								
Dispense Drugs		X	X	X	X	X	X	
Investigational Drugs		X	X		X		X	
PFTs (FEV ₁ and FVC)	X	X ²	X ²		X ²		X ²	
Quality of Life		X			X		X	
Energy/Fatigue Questionnaire		X	X	X	X	X	X	
Pharmacoeconomic Data		X	X	X	X	X	X	
Review of PEFR Records		X	X	X	X	X	X	
Global Evaluations		X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	
Concomitant Therapy	X	X	X	X	X	X	X	
PK samples ³				X	X	X	X	

¹Theophylline levels on all patients at Visit 1 and only on patients taking theophylline at subsequent test day visits

²Two baseline tests and tests at 30, 60, 120, and 180 minutes post drug administration

³Ten sites were designated to perform PK sampling

Study Procedures, Weeks 13-52: 205.114/205.117													[U99-3169.pdf/p68-9]
Trial Period:	Treatment Period (Week 13 through Week 52)												**
Visit #:		8		9		10		11		12		13	14
Telephone Calls	7.1		8.1		9.1		10.1		11.1		12.1		
Weeks on Therapy:	16	19	22	25	28	31	34	37	40	43	46	49	+3
Physical Examination													X
Vital Signs (seated)				X				X				X	
Laboratory Tests (fasting)				X				X				X	
12-lead ECG				X				X				X	
Theophylline level ¹				X				X				X	
Dispense Drugs		X		X		X		X		X			
Investigational Drugs				X				X				X	
PFTs (FEV ₁ and FVC)				X ²				X ²				X ²	
Quality of Life				X				X				X	X
Energy/Fatigue Questionnaire		X		X		X		X		X		X	X
Pharmacoeconomic Data	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of PEFR Records		X		X		X		X		X		X	X
Global Evaluations		X		X		X		X		X		X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X

¹Theophylline levels on all patients at Visit 1 and only on patients taking theophylline at subsequent test day visits

²Two baseline tests and tests at 30, 60, 120, and 180 minutes post drug administration

**Post-treatment period

Concomitant Therapy

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

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

Data Analysis

A sample size was primarily based on safety considerations (“i.e. to expose an adequate number of patients to tiotropium”). A sample size of 400 patients (240 in the tiotropium group and 160 in the placebo group) was expected to provide a power of 90% to detect a difference in mean FEV₁ response of 0.056 liters between tiotropium and placebo, using a 5% level of significance and a two tailed t-test [U99-3169.pdf/p59-60]. **Reviewer’s Note: Although a total of 400 patients were expected to provide 90% power, a total of 470 patients were randomized. This will not be an issue provided that the effect size demonstrated is felt to be clinically significant.** The Applicant utilized a 3:2 randomization scheme in order to achieve the desired number of subjects for long-term exposure.

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

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

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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

The final rules for handling missing data were determined at a blinded report planning meeting held prior to un-blinding of the treatment codes for the interim analysis. Linear interpolation between two adjacent measurements was used to estimate random, middle and missing spirometry measurements. For values at the end of the serial spirometry that were missing because rescue medication was taken, the minimum observed FEV₁ value on that test day (even if it was the pre-dose value) was used as the estimate. The last available value was used as the estimate for data that were missing for reasons unrelated to the subject's response to treatment.

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

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

The primary efficacy variable was the "trough FEV₁ response," which was defined as the change from baseline in the mean of the two FEV₁ values at the end of the dosing interval (approximately 23 and 24 hours post drug administration) [U99-3169.pdf/p315]. The baseline FEV₁ was calculated as the mean of the two FEV₁ values measured in the morning of the randomization visit, prior to administration of study medication. The primary efficacy endpoint was the trough FEV₁ response at the end of the first 13 weeks of treatment [U99-3169.pdf/p53]. *Note: The original protocol defined the primary efficacy variable, but not the specific endpoint [U99-3169.pdf/315]. The primary efficacy endpoint (i.e. Week 13) was declared in a protocol amendment [U99-3169.pdf/p55 and p352].*

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

- Average and peak FEV₁ response for the first 3 hours post-treatment on each test day.
- Trough, average, and peak FVC response on each test day.
- Individual FEV₁ and FVC measurements at each time point.
- Weekly mean of PEFr measured by the patient at home twice daily
- Physician's global evaluation
- COPD symptom scores (wheezing, shortness of breath, coughing, and tightness of chest).
- Amount of albuterol therapy used during the treatment period
- Number of nocturnal awakenings during the first 13 weeks
- Number and length of COPD exacerbations and of hospitalizations for respiratory disease during the treatment period.

CLINICAL BRIEFING DOCUMENT

Appendix

Study 205.114/205.117

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

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

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

b. Patient Disposition

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

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

Patient Disposition and Reasons for Withdrawal, Study 205.114/205117		[U99-3169.pdf/p83]	
	Tiotropium N (%)	Placebo N (%)	
Entered/Randomized	279	191	
Completed the Trial	235 (84.2)	139 (72.8)	
Discontinued For:			
Adverse Event Total	23 (8.2)	26 (13.6)	
Unexpected Worsening of Disease Under Study	12 (4.3)	12 (6.3)	
Unexpected Worsening of Other Pre-existing Disease	1 (0.4)	2 (1.0)	
Other Adverse Event	10 (3.6)	12 (6.3)	
Lack of Efficacy	7 (2.5)	13 (6.8)	
Administrative	14 (5.0)	12 (6.3)	
Non-compliant with Protocol	0 (0)	0 (0)	
Lost to Follow-up	3 (1.1)	4 (2.1)	
Consent Withdrawn	11 (3.9)	1 (0.5)	
Other	0 (0)	1 (0.5)	

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

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

Demographics and Baseline Characteristics, Study 205.114/205.117		[U99-3169.pdf/p85-6]		
		Tiotropium	Placebo	Total
Total Treated		279	191	470
Sex	Male	186 (66.7)	121 (63.4)	307 (65.3)
Race	Caucasian	264 (94.6)	168 (88.0)	432 (91.9)
	Negroid	15 (5.4)	21 (11.0)	36 (7.7)
	Mongoloid	0 (0.0)	2 (1.0)	2 (0.4)
	Australoid	0 (0.0)	0 (0.0)	0 (0.0)
Age	Mean	64.95	65.51	65.18
	Range	40 – 85	39 – 81	39 - 85
Smoking History (pack years)	Mean	64.54	60.51	62.90
	Range	11 – 240	10 – 160	10 - 240
Duration of COPD (years)	Mean	9.28	8.57	8.99
	Range	0.1 – 50	0.3 – 40	0.1 - 50
Screening FEV ₁ (L)	Mean	1.04	1.00	1.02
	Range	0.37 – 3.03	0.30 – 2.63	0.30 – 3.03
FEV ₁ /FVC x 100	Mean	46.2	46.18	46.19

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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

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

c. Efficacy Review

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

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

Primary Endpoint

The primary efficacy endpoint was the trough FEV₁ response at the end of the first 13 weeks of treatment. The trough FEV₁ response was defined as the change from baseline in the mean of the two FEV₁ values at the end of the dosing interval (approximately 23 and 24 hours post drug administration) [U99-3169.pdf/p315]. The baseline FEV₁ was calculated as the mean of the two FEV₁ values measured in the morning of the randomization visit, prior to administration of study medication.

Tiotropium was statistically superior to placebo on the primary endpoint (p=0.0001) [U99-3169.pdf/p96]. The mean trough FEV₁ response at Week 13 (test day 92) was 0.11 liters in the tiotropium group (N=268), and –0.03 liters in the placebo group (N=174).

CLINICAL BRIEFING DOCUMENT

Appendix
Study 205.114/205.117

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 FEV₁ response for the first 3 hours post-treatment, the trough, average, and peak FVC response, and the individual FEV₁ and FVC measurements at each time point, on each test day.

In regard to FEV₁, tiotropium was statistically significantly superior to placebo for the trough, average, and peak FEV₁ responses on all test days. The FEV₁ data, provided in the table below, raise an interesting observation regarding the pharmacodynamic time course of tiotropium. The treatment effect (defined here as the difference between the mean responses for active and placebo groups) was lower on Day 1 than on subsequent test days, suggesting that multiple dosing is required to achieve “steady state.” For instance, both the average and peak responses were lower on Day 1 than on other test days. The “average” and “peak” responses decreased subsequent to Day 8 in both the tiotropium and the placebo groups. Thus the effect size (active minus placebo) remained relatively constant from Day 8, onward.

Mean FEV ₁ Trough, Average, and Peak Responses (Liters) (Study 205.114/205.117, ITT data set)					[U99-3169.pdf/p96]
Response	Test Day	Tiotropium (N=268)	Placebo (N=174)	Difference	P-value
Trough	Baseline	1.01	1.01		
	8	0.12	-0.00	0.12	0.0001
	50	0.11	-0.00	0.11	0.0001
	92	0.11	-0.03	0.14	0.0001
	176	0.11	-0.04	0.15	0.0001
	260	0.11	-0.04	0.15	0.0001
	344	0.11	-0.05	0.16	0.0001
Average	1	0.16	0.02	0.14	0.0001
	8	0.22	0.02	0.20	0.0001
	50	0.20	0.01	0.19	0.0001
	92	0.20	-0.02	0.22	0.0001
	176	0.19	-0.02	0.21	0.0001
	260	0.19	-0.01	0.20	0.0001
	344	0.19	-0.03	0.21	0.0001
Peak	1	0.24	0.08	0.15	0.0001
	8	0.28	0.08	0.21	0.0001
	50	0.27	0.08	0.19	0.0001
	92	0.26	0.05	0.21	0.0001
	176	0.26	0.04	0.22	0.0001
	260	0.25	0.06	0.20	0.0001
	344	0.26	0.04	0.22	0.0001

In addition, each individual FEV₁ measurement on each test day (excluding the pre-dose measurements on test day 1) was statistically superior to placebo.

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

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

point after the first dose at which the mean FEV₁ reaches a clinically significant threshold. In the product labels for two related products (Atrovent Inhalation Aerosol, and Combivent Inhalation Aerosol), this threshold is defined as an improvement of 15%. More recently, in keeping with American Thoracic Society standards, the threshold has been defined as 12% and at least 200ml. This newer threshold was used in the label for Serevent DISKUS for the COPD indication, which was approved in March, 2002. The table below would suggest that, despite the mean peak response reported in the table above, the mean FEV₁ did not reach this newer threshold at any time point on test Day 1 (using either of two definitions of Baseline: the -5 minute value, or the mean of the -1 hour and -5 minutes values).

Mean FEV ₁ (Liters) On Test Day 1, Tiotropium Treatment Group (Study 205.114/205.117, ITT data set, N=268)			
[derived from data found at: U99-3169.pdf/p93]			
Time Point	Mean FEV ₁	Change from Baseline (Liters) (Baseline defined as the -5 minute value)	Change from Baseline (Liters) (Baseline defined as the mean of - 1 hour and -5 minute values)
-1 hour	1.00		
-5 minutes	1.02		
30 minutes	1.14	0.12	0.13
1 hour	1.17	0.15	0.16
2 hours	1.19	0.17	0.18
3 hours	1.20	0.18	0.19

This apparent discrepancy between the mean peak FEV₁ and the mean FEV₁ might indicate that the time to peak FEV₁ may differ among individual patients, such that the mean for the entire group never reached 200ml at any single post-dose time point. To investigate this issue further, the Applicant was asked to provide data regarding the percentage of patients who reached their peak FEV₁ at each time point. On test day 1, the percentage of patients who reached their peak FEV₁ gradually increased at each timepoint, with the greatest percentage at 3 hours [Submission date 7/16/02, page 8]. Data for the remaining test days indicated that at all of the four timepoints, <30% of the patients exhibited their peak FEV₁. Thus, there is no single timepoint at which the majority of patients reached their peak FEV₁. The description of the pharmacodynamic features in the product label should capture this.

Percentage of Patients Who Reached Their Peak FEV ₁ at Each Timepoint (Test Day 1; Study 205.114/205.117)		
[Submission dated 7/16/02; page 8]		
Timepoint	Tiotropium (N=279)	Placebo (N=191)
30 minutes	14.7%	26.2%
1 hour	20.4%	25.1%
2 hours	29.7%	26.7%
3 hours	35.1%	22.0%

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

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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

Mean FVC Trough, Average, and Peak Responses (Liters) (Study 205.114/205.117, ITT data set)					[U99-3169.pdf/p103]
Response	Test Day	Tiotropium (N=268)	Placebo (N=174)	Difference	P-value
Trough	Baseline	2.21	2.21		
	8	0.27	0.00	0.27	0.0001
	50	0.27	0.01	0.26	0.0001
	92	0.24	-0.04	0.28	0.0001
	176	0.27	-0.04	0.31	0.0001
	260	0.26	-0.04	0.30	0.0001
	344	0.25	-0.03	0.29	0.0001
Average	1	0.39	0.07	0.31	0.0001
	8	0.50	0.10	0.40	0.0001
	50	0.47	0.05	0.42	0.0001
	92	0.42	0.02	0.40	0.0001
	176	0.45	0.02	0.42	0.0001
	260	0.43	0.04	0.39	0.0001
	344	0.41	0.01	0.40	0.0001
Peak	1	0.56	0.21	0.35	0.0001
	8	0.67	0.25	0.42	0.0001
	50	0.64	0.20	0.45	0.0001
	92	0.59	0.18	0.40	0.0001
	176	0.61	0.16	0.45	0.0001
	260	0.57	0.18	0.39	0.0001
	344	0.57	0.15	0.42	0.0001

In addition, each individual FEV₁ measurement on each test day (excluding the pre-dose measurements on test day 1) was statistically superior to placebo.

Peak Expiratory Flow Rate (PEFR) Endpoints

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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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

¹Common 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**

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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 FEV₁ of 1.17mL, and a mean predicted creatinine clearance of 78.5mL/min [U99-3169g.pdf/p631].

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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	C5min	C2h	C-5min	C5min	C2h
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

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

The Applicant also states that plasma drug concentrations and urinary excretion did not differ between patients with FEV₁<0.8L and patients with FEV₁>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 FEV₁ response after 13 weeks of treatment. The 13-week trough FEV₁ (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 FEV₁ responses. Two points should be made regarding the spirometry pharmacodynamics. First, the Day 1 mean post-dose FEV₁ in the tiotropium group did not reach the threshold customarily used to indicate a significant bronchodilator response ($\geq 12\%$ and $\geq 200\text{ml}$ improvement) at any of the serial spirometry time points. However, the mean peak FEV₁ response (without subtracting placebo) on Day 1 and on all subsequent test days was $>200\text{ml}$. 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 FEV₁ 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
<ul style="list-style-type: none"> ▪ Physician's Global Evaluation (all test days) ▪ Mahler TDI Focal Score (all test days)^a ▪ COPD symptom^b: Shortness of Breath (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 	<ul style="list-style-type: none"> ▪ Energy Fatigue Questionnaire ▪ COPD symptom^b: Cough ▪ COPD symptom^b: Tightness in Chest ▪ COPD Exacerbations (all analyses)
<p>^aEffect size surpassed the Applicant's proposed threshold for minimal clinically important change on the final test day only. ^bAssessed by the Investigator ^cEffect size did not reach the accepted threshold for minimal clinically important change.</p>	

CLINICAL BRIEFING DOCUMENT

Appendix Study 205.114/205.117

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].

CLINICAL BRIEFING DOCUMENT

Appendix

Study 205.114/205.117

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).

CLINICAL BRIEFING DOCUMENT

Appendix:
Study 205.115/205.128

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 study 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)	

CLINICAL BRIEFING DOCUMENT

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

CLINICAL BRIEFING DOCUMENT

Appendix:

Study 205.115/205.128

(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 FEV₁ response at the end of the first 13 weeks of treatment. The trough FEV₁ response was defined as the change from baseline in the mean of the two FEV₁ values at the end of the dosing interval (approximately 23 and 24 hours post drug administration). The baseline FEV₁ was calculated as the mean of the two FEV₁ 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 FEV₁ 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 FEV₁ response for the first 3 hours post-treatment, the trough, average, and peak FVC response, and the individual FEV₁ and FVC measurements at each time point, on each test day.

In regard to FEV₁, tiotropium was statistically significantly superior to placebo for the trough, average, and peak FEV₁ responses on all test days [U99-3170-01.pdf/p73]. The FEV₁ 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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.115/205.128

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 FEV₁ 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 FEV₁ 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 FEV₁ barely reached this newer threshold on test Day 1. Using the mean of the –1hour and –5minute values as the “baseline”, the mean FEV₁ reached 200ml greater than baseline at 3 hours post-dose. However, using the –5 minute value alone as the baseline, the mean FEV₁ never reached 200ml greater than baseline. It is noted that the FEV₁ 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

CLINICAL BRIEFING DOCUMENT

Appendix:
Study 205.115/205.128

The apparent discrepancy in the FEV₁ response reported as the mean peak FEV₁ versus the mean FEV₁ (see tables above) might indicate that the time to peak FEV₁ 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 FEV₁ at each time point. On test day 1, the percentage of patients who reached their peak FEV₁ 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 FEV₁. Thus, there is no single timepoint at which the majority of patients reached their peak FEV₁. 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)		
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)					
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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.115/205.128

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

[†]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."

CLINICAL BRIEFING DOCUMENT

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

CLINICAL BRIEFING DOCUMENT

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 week* compared to patients in the placebo group [U99-3170-01.pdf/p91-4].

Nocturnal Awakenings

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

COPD Exacerbations

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

Health-Related Quality of Life

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

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

Mean Baseline SGRQ Scores (Study 205.115/205.128, ITT data set) [U99-3170-01.pdf/p95]						
Score	Tiotropium			Placebo		
	N	Mean	(SE)	N	Mean	(SE)
Symptoms	252	58.43	(1.31)	154	57.89	(1.73)
Activities	251	63.45	(1.23)	153	61.35	(1.52)

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.115/205.128

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

¹Common 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

CLINICAL BRIEFING DOCUMENT

Appendix:

Study 205.115/205.128

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

Analysis of “Rebound”

Following the end of the treatment period, patients were followed for an additional 3 weeks. During this period patients recorded 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 FEV₁ was approximately 1 liter, or 45% of the predicted normal value.

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

CLINICAL BRIEFING DOCUMENT

Appendix:

Study 205.115/205.128

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

Efficacy was also supported by statistically significant improvements in numerous secondary spirometry variables including trough, mean, and peak FVC responses during the 3-hour serial spirometry on all test days. Statistically significant improvements were also demonstrated for the weekly mean morning and evening 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
<ul style="list-style-type: none"> ▪ Physician's Global Evaluation (all test days) ▪ Mahler TDI Focal Score (all test days)^a ▪ COPD symptom^b: Shortness of Breath (15/17 test days) ▪ COPD symptom^b: Wheeze (9/17 test days) ▪ Total SGRQ score (all test days)^c ▪ SGRQ "Impacts" domain score (all test days) 	<ul style="list-style-type: none"> ▪ Energy Fatigue Questionnaire ▪ COPD symptom^b: Cough ▪ COPD symptom^b: Tightness in Chest ▪ COPD Exacerbations (all analyses) ▪ Nocturnal Awakenings
<p>^aEffect size surpassed the Applicant's proposed threshold for minimal clinically important change at 9 and 12 months only.</p> <p>^bAssessed by the Investigator</p> <p>^cEffect size did surpassed the accepted threshold for minimal clinically important change at 6 and 12 months only.</p>	

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

d. Safety Review

The safety findings from this study, along with the safety data from the other placebo-controlled studies, will be reviewed in depth in the Integrated Review of Safety section of this 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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.115/205.128

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

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

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

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

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

-

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.130

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

Objectives

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

Inclusion Criteria

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

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

Exclusion Criteria

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

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.130

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

Conduct

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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.130

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

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

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

The table below summarizes the study procedures.

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

¹Theophylline levels on all patients at Visit 1 and only on patients taking theophylline at subsequent test day visits

²Prior to drug administration and 30, 60 minutes, 2, 3, 4, 6, 8, 10, 12 hours post dose

Concomitant Medications

Albuterol inhalation aerosol was provided for as-needed use.

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.130

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

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

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

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

Data Analysis

Efficacy Endpoints

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

The protocol amendment changed the primary efficacy endpoints to the trough FEV₁ response, AND the focal score from the Mahler 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 FEV₁ 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 FEV₁ response on each test day
- Trough, average and peak FVC measured at the same times as FEV₁ on each test day
- Individual FEV₁ and FVC measurements at each time point

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.130

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

Statistical Model

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

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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.130

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

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

Missing Data

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

Sample Size

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

b. Patient Disposition

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.130

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

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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.130

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

c. Efficacy Review

Data Sets Analyzed

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

For the analysis of spirometry data, all randomized patients with baseline (pre-treatment on test day 1 [Visit 2]) and trough FEV₁ on test-day 15 (Visit 3) after 2 weeks of randomized treatment were included in the ITT data set. Additionally, the Applicant states that the protocol amendment specified that analysis of the “per-protocol” population for the co-primary endpoint of trough FEV₁ response on Day 169 would exclude subjects who deviated from the protocol in such a manner as to potentially obscure the trough FEV₁ 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 FEV₁ response and the TDI focal score, both evaluated on test-day 169 (Week 24) of randomized treatment. These were analyzed in a step-wise fashion. The primary comparison was tiotropium versus placebo. The numbers of patients included in the analyses of these two endpoints are provided in the table above.

CLINICAL BRIEFING DOCUMENT

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

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

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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix:
Study 205.130

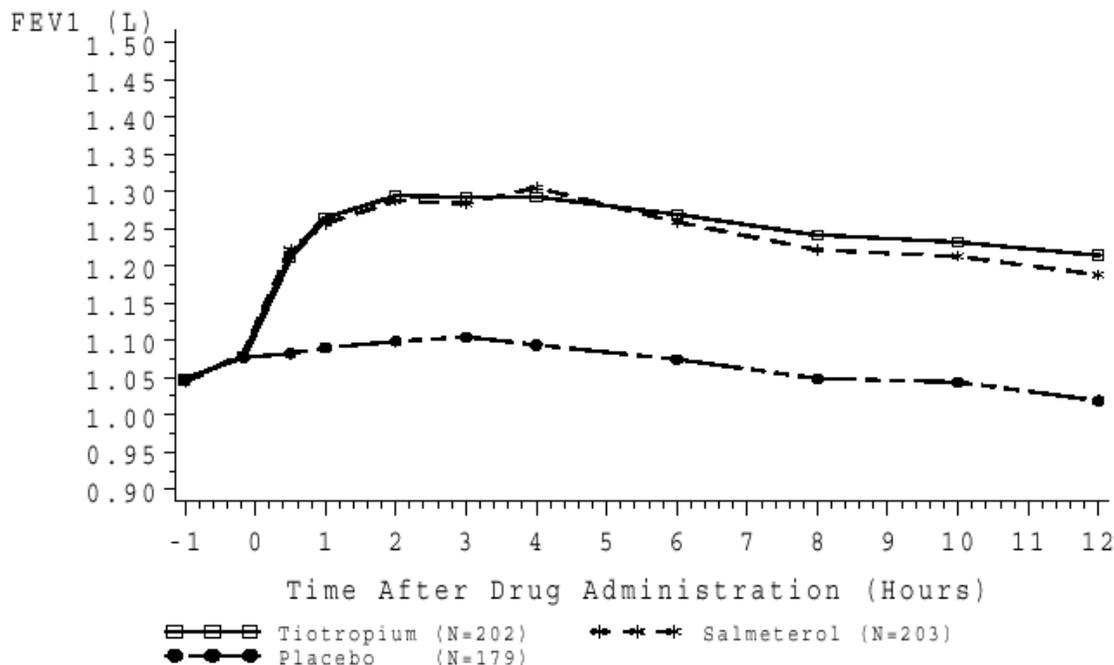
group. The adequacy of the justifications of both the definition of clinical response (i.e. ≥ 1 unit) and the significance of the observed effect size are be discussed in the Integrated Review of Efficacy section of this Clinical Briefing Document.

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 FEV₁ 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 FEV₁ for tiotropium and salmeterol were not statistically different on the first day of treatment. However, the FEV₁ 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 FEV₁ at Day 1 and Week 24.

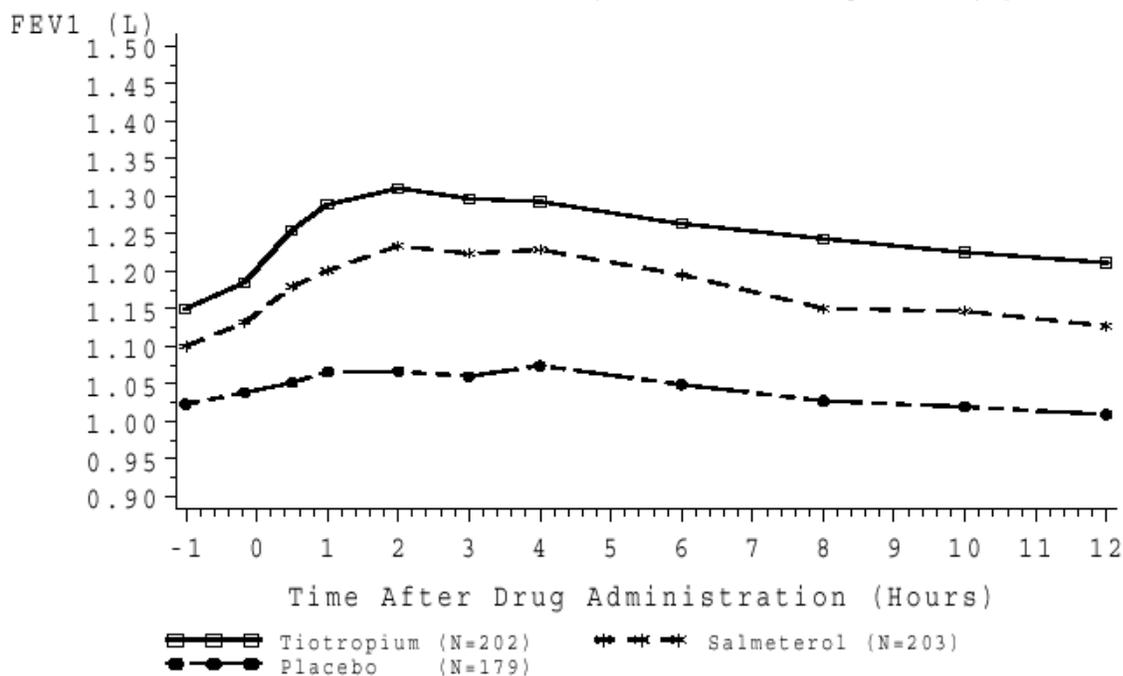
Mean FEV₁, Day 1 (ITT data set, Study 205.130) [U01-1236-1.pdf/p82]



CLINICAL BRIEFING DOCUMENT

Appendix:
Study 205.130

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



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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.130

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

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

Subjects measured their PEFr twice daily and recorded the values in their diaries. The mean morning PEFr 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 PEFr 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%).

CLINICAL BRIEFING DOCUMENT

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.130

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

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

COPD Exacerbations and Hospitalizations

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

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

Other Secondary Endpoints

CLINICAL BRIEFING DOCUMENT

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 at least some post-treatment data. The TDI focal score decreased by 0.82 in the tiotropium group from the end of treatment period to the end of the washout period. Interestingly, the TDI focal score in the placebo group increased by 0.31 during this period. The mean weekly AM PEFR in the tiotropium group decreased from 29.74 L/min above baseline at the end of the treatment period to 20.41 L/min above baseline during the third week of the washout period [U01-1236-1.pdf/p165]. In keeping with the TDI data from the washout period, the mean weekly PEFR in the placebo group actually improved during the washout period (from 8.42 L/min greater than baseline at the end of the treatment period to 18.4 L/min during the last week of the washout period) [U01-1236-1.pdf/p166]. PM PEFR values followed a similar pattern during the washout period. These data, and the remainder of the washout period data do not suggest a “rebound” effect related to discontinuation of tiotropium [U01-1236-1.pdf/p167-73]. The failure of the PEFR to return to baseline values in the tiotropium group may indicate continued effect of the drug. Alternatively, patients may not have been at their true baseline at the time of enrollment.

Pharmacokinetic Data

This study did not include pharmacokinetic assessments.

Reviewer’s Comments on Efficacy

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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.130

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

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

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

d. Safety Review

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

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

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

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

CLINICAL BRIEFING DOCUMENT

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 \geq 3%) adverse events occurring more frequently in the tiotropium group as compared to the placebo group were: upper respiratory tract infection (20.1% vs. 15.9%), mouth dry (10.0% vs. 3.5%), influenza-like symptoms (9.6% vs. 4.5%), headache (8.6% vs. 5.5%), coughing (5.7% vs. 3.5%), pharyngitis (5.3% vs. 4.5%), accident household (4.8% vs. 2.5%), chest pain (4.3% vs. 4.0%), sinusitis (3.8% vs. 2.5%), dyspepsia (3.3% vs. 1.5%), and nausea (3.3% vs. 3.0%) [U01-1236-1.pdf/p182].

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

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

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

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

a. Study Description

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

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

b. Patient Disposition

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

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.137

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 FEV₁ 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,

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.137

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

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

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

Primary Endpoint

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

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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix:
Study 205.137

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

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

Secondary Endpoints

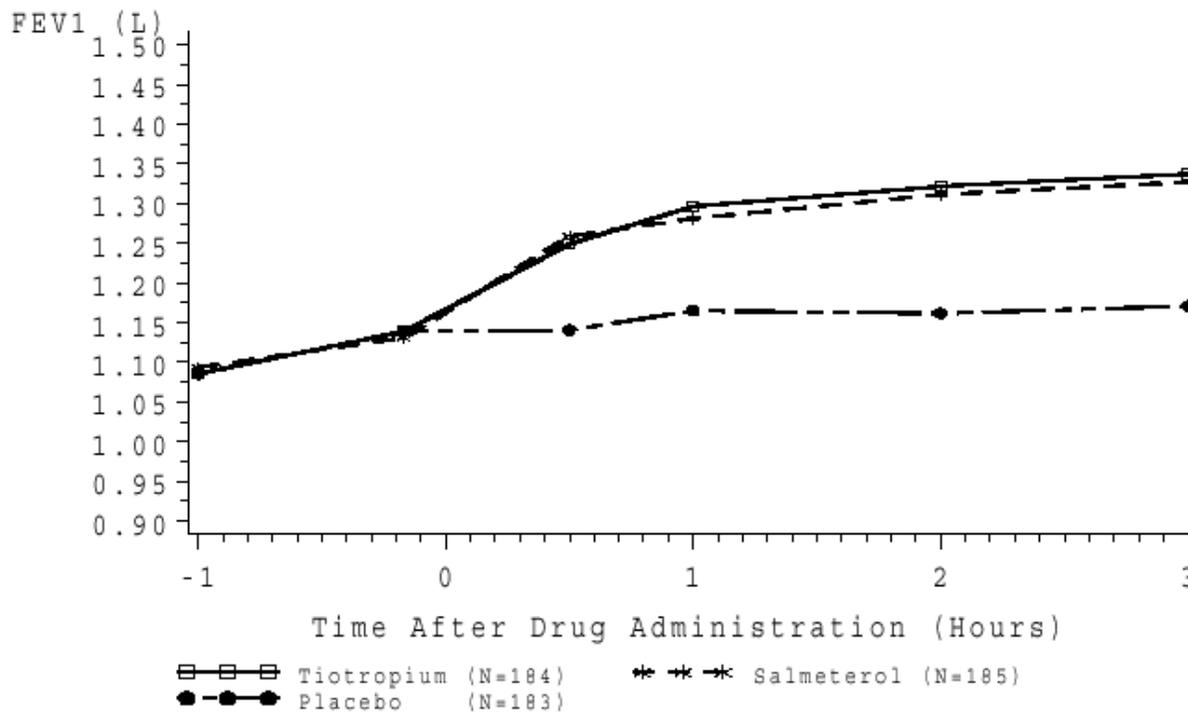
Pulmonary Function Endpoints

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

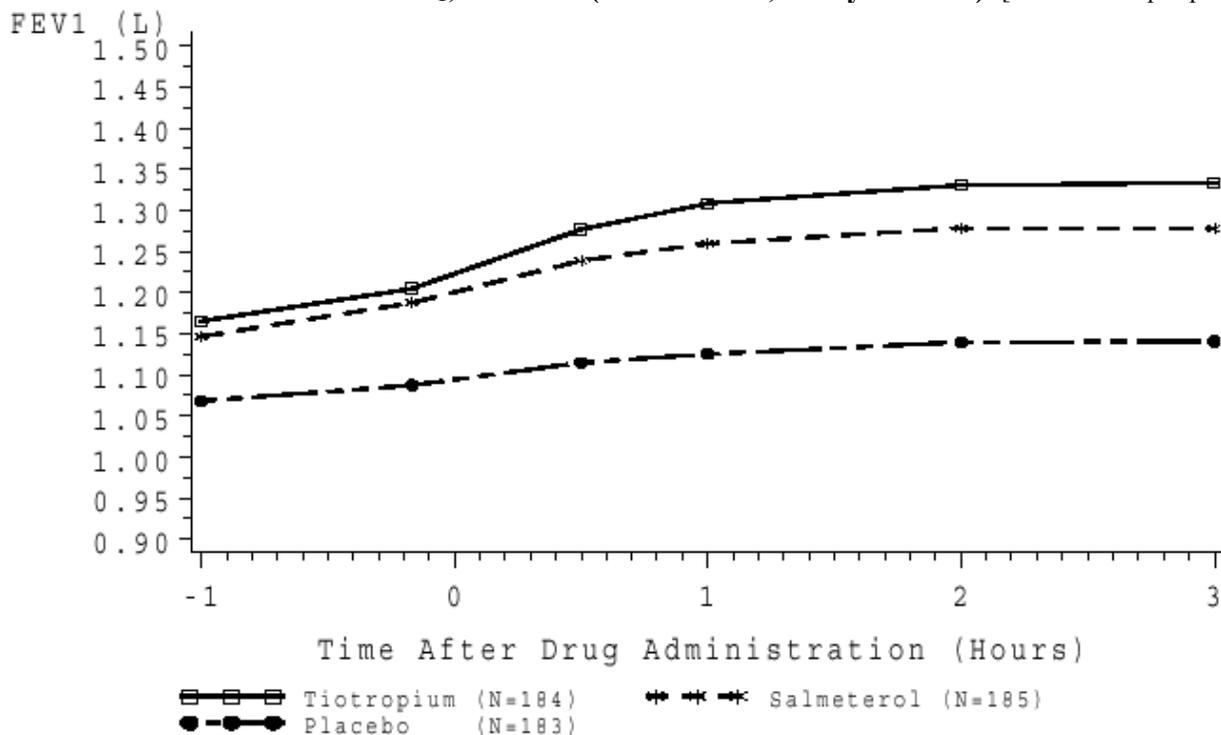
CLINICAL BRIEFING DOCUMENT

Appendix:
Study 205.137

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



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



CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.137

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

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

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

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

Subjects measured their PEFr twice daily and recorded the values in their diaries. The mean morning PEFr 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 ($p < 0.01$) [U01-1231-1.pdf/p125-6]. The difference between tiotropium and placebo ranged from 14.9 L/min (during Week 1) and 21 L/min. The difference between tiotropium and salmeterol was not statistically significant at any treatment week.

The mean evening PEFr 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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.137

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

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

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

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

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

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

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

CLINICAL BRIEFING DOCUMENT

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 for coughing on test days 113 only. Tiotropium was statistically superior to placebo for *wheezing* and *tightness of chest* on test day 15 only. Salmeterol was statistically superior to placebo for wheezing on test day 15 only, and was not statistically superior to placebo for tightness of chest on any test day. The effect sizes for tiotropium were 0.17 for Wheezing, 0.17 – 0.24 for Shortness of Breath, and 0.16 – 0.19 for coughing, and 0.14 for Tightness of Chest [U01-1231-1.pdf/p156-8]. The only statistically significant comparison between tiotropium and salmeterol was the Day 15 coughing score, which favored tiotropium.

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

COPD Exacerbations and Hospitalizations

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.137

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

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

Other Secondary Endpoints

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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.137

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

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

Analysis of Washout Period

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

Pharmacokinetic Data

This study did not include assessments of pharmacokinetic parameters.

Reviewer’s Comments on Efficacy

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.137

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

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

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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.137

whether a change in the TDI score of 1 unit is demonstrated to be clinically meaningful. In addition, the significance of the observed effect size must be considered.

d. Safety Review

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

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

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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix:

Study 205.137

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.

CLINICAL BRIEFING DOCUMENT

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

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

²between 8AM and 10AM

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

Objectives

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

CLINICAL BRIEFING DOCUMENT

Appendix:
Study 205.122A/205.126A

Efficacy Variables

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

Secondary efficacy endpoints were:

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

Safety Variables

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

Inclusion Criteria

Notable inclusion criteria were:

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

CLINICAL BRIEFING DOCUMENT

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 \geq 400 per microliter (males) or \geq 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

CLINICAL BRIEFING DOCUMENT

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

¹Theophylline levels on all patients at Visit 1 and only on patients taking theophylline at subsequent test day visits

²prn albuterol MDI

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

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

¹Theophylline levels only on patients taking theophylline

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

**3-week post-treatment period

Concomitant Medications

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

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

CLINICAL BRIEFING DOCUMENT

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 \leq the equivalent of 10 mg of prednisone QD or 20 mg of prednisone QOD); inhaled corticosteroids; theophylline preparations; mucolytic agents not containing bronchodilators; concomitant prescription or over-the-counter medications for treatment of other conditions unless specifically disallowed.

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

Data Analysis

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

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

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

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

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

CLINICAL BRIEFING DOCUMENT

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 FEV₁ response of 0.075 liters at 5% significance level with approximately 90% power using a two-tailed t-test.

b. Patient Disposition

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

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

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

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

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

CLINICAL BRIEFING DOCUMENT

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

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

Secondary Endpoints

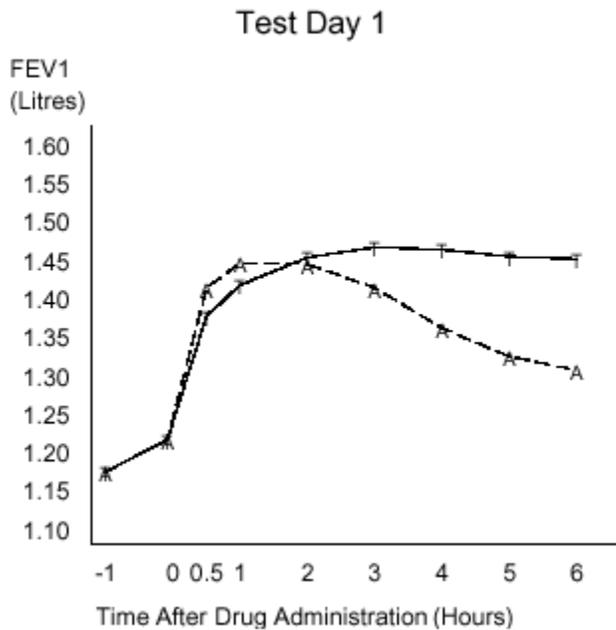
Pulmonary Function Endpoints

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

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

CLINICAL BRIEFING DOCUMENT

Appendix:
Study 205.122A/205.126A



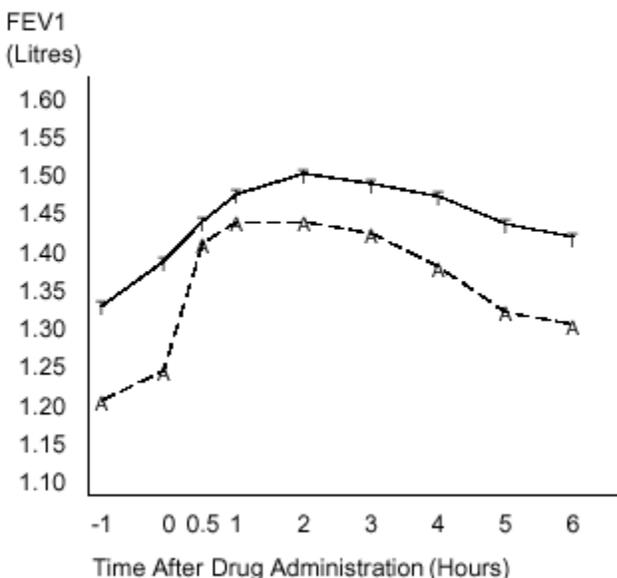
[T= tiotropium A=ipratropium Source: U00-3113.pdf/p66]

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

CLINICAL BRIEFING DOCUMENT

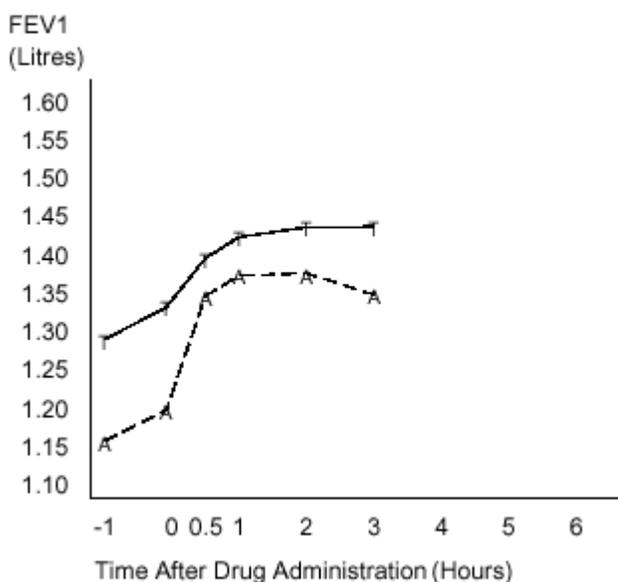
Appendix:
Study 205.122A/205.126A

Test Day 92



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

Test Day 364



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

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

CLINICAL BRIEFING DOCUMENT

Appendix:

Study 205.122A/205.126A

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).

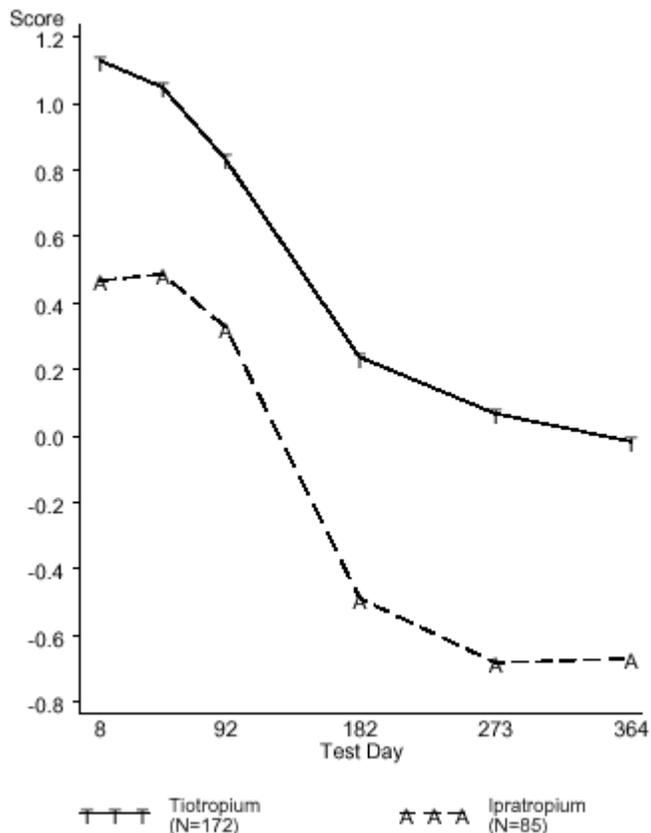
Patient Reported Outcomes

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.

CLINICAL BRIEFING DOCUMENT

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

CLINICAL BRIEFING DOCUMENT

Appendix:

Study 205.122A/205.126A

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

CLINICAL BRIEFING DOCUMENT

Appendix:

Study 205.122A/205.126A

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

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

Pharmacokinetic Data

Pharmacokinetic data were not collected in this study.

Reviewer’s Comments on Efficacy

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

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

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

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.122A/205.126A

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

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

d. Safety Review

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

The safety data from this study, combined with the data from Study 205.122B/205.126B, will be discussed in detail in the Integrated Review of Safety section of this document. The following is a brief summary of the salient safety findings of this study.

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

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

CLINICAL BRIEFING DOCUMENT

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 \geq 3%) adverse events occurring more frequently in the tiotropium group as compared to the placebo group were: upper respiratory tract infection (49.2% vs. 37.1%), mouth dry (17.8% vs. 11.3%), back pain (5.8% vs. 4.1%), pharyngitis (5.8% vs. 0.0%), chest pain (4.7% vs. 0.0%), urinary tract infection (4.2% vs. 3.1%), fatigue (3.1% vs. 1.0%), eczema (3.1% vs. 1.0%), and skin disorder (3.1% vs. 0.0%), [U00-3113.pdf/p120-1].

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

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

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

CLINICAL BRIEFING DOCUMENT

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%)	

CLINICAL BRIEFING DOCUMENT

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 FEV₁ was 1.23 liters (40.5% of predicted) at the screening visit [U00-3114.pdf/p55]. The table below summarizes the baseline and demographic features of the study subjects.

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

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

c. Efficacy Review

Primary Endpoint

The primary efficacy variable was the trough FEV₁ response, defined as the mean change from baseline at the end of the dosing interval for tiotropium (i.e. approximately 23 to 25 hours post tiotropium administration). As discussed elsewhere, ipratropium, based on its known pharmacodynamics, would not be expected to be effective at this timepoint. Baseline FEV₁ (Visit 2) and trough FEV₁ (subsequent visits) were calculated as the mean of two pre-treatment

CLINICAL BRIEFING DOCUMENT

Appendix:

Study 205.122B/205.126B

FEV₁ readings measured in the morning, prior to administration of study medication. *The protocol did not state which specific treatment visit would serve as the primary efficacy endpoint.*

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

Secondary Endpoints

Pulmonary Function Endpoints

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

Following the first dose of study medication there was no statistically significant difference between groups for the mean FEV₁ until Hour 4. [U00-3114.pdf/p63] On that day, the mean FEV₁ in the tiotropium group was statistically superior to ipratropium at hours 4, 5, and 6 ($p \leq 0.0024$; 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 FEV₁ data following the first dose.

CLINICAL BRIEFING DOCUMENT

Appendix:
Study 205.122B/205.126B

Test Day 1

4.pdf/p61]

FEV1
(Litres)
1.60
1.55
1.50

(minutes and -5 minutes) values were
, with effect sizes of 0.09 to 0.20 liters
serial FEV₁ values on test day 92 (Week

Test Day 92

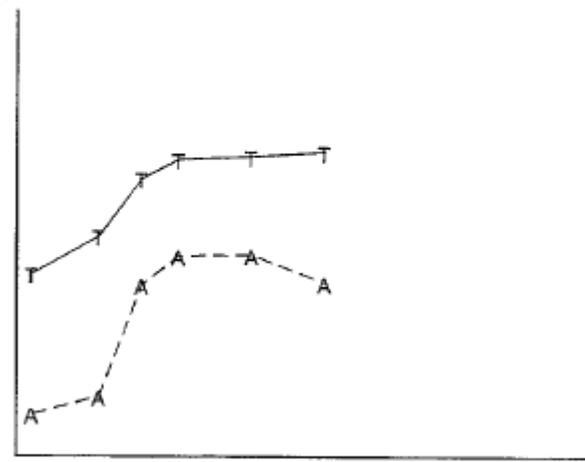
p61]

Test Day 364

p62]

FEV1
(Litres)

1.60
1.55
1.50
1.45
1.40
1.35
1.30
1.25
1.20
1.15
1.10



Time After Drug Administration (Hours)

CLINICAL BRIEFING DOCUMENT

Appendix: Study 205.122B/205.126B

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

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

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

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

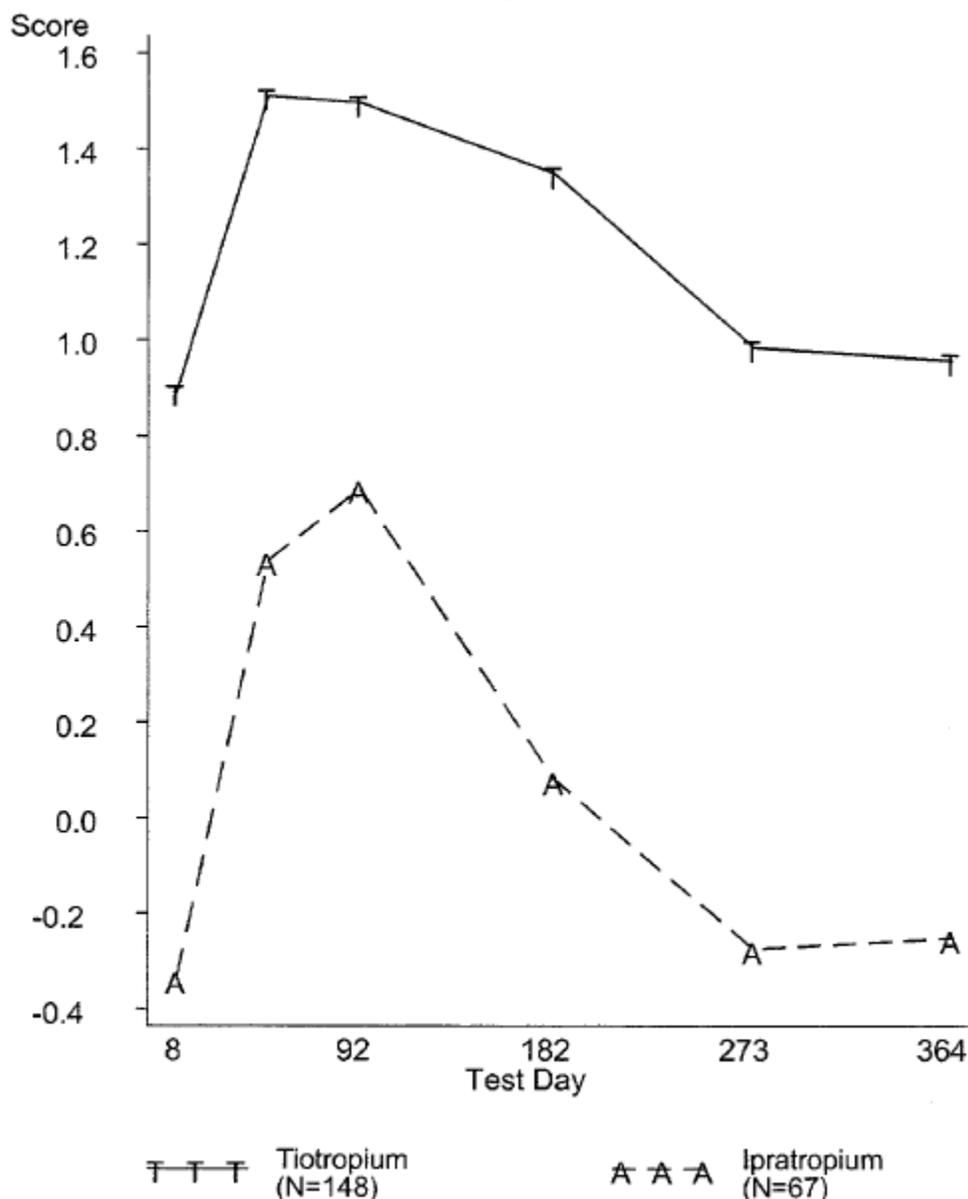
CLINICAL BRIEFING DOCUMENT

Appendix:
Study 205.122B/205.126B

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

CLINICAL BRIEFING DOCUMENT

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.

CLINICAL BRIEFING DOCUMENT

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

CLINICAL BRIEFING DOCUMENT

Appendix:

Study 205.122B/205.126B

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

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

Pharmacokinetic Data

Pharmacokinetic data were not collected in this study.

Reviewer’s Comments on Efficacy

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

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

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

CLINICAL BRIEFING DOCUMENT

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 FEV₁ in the tiotropium group was statistically superior to ipratropium with treatment differences ranging from 0.09 to 0.12 liters). On the remaining dosing days, tiotropium was statistically superior to ipratropium for mean FEV₁ at all timepoints (excepting 30 minutes and 1 hour on test days 8 and 50). Bronchodilator efficacy was also supported by morning and evening PEFr data throughout the treatment period (except Week 1 for morning PEFr). However, the use of rescue albuterol medication was not statistically different between the two groups.

Patient reported outcome assessments provided varying results. In regard to the symptom of dyspnea, the mean TDI focal score in the tiotropium group was statistically superior to ipratropium on all test days. However, the effect reached the 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)

CLINICAL BRIEFING DOCUMENT

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

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

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

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