

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.

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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

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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

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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.

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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.

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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

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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.

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Introduction and Background

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

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“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

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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

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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.

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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

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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].

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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.

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- 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

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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:**

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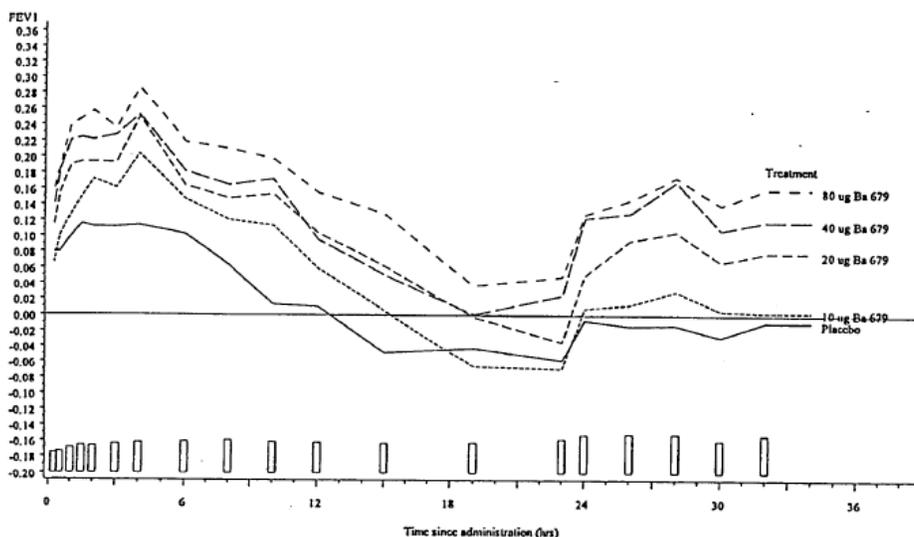
This is an unusual finding. However, interpretation is difficult in the absence of a placebo group.

- 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.

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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.

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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

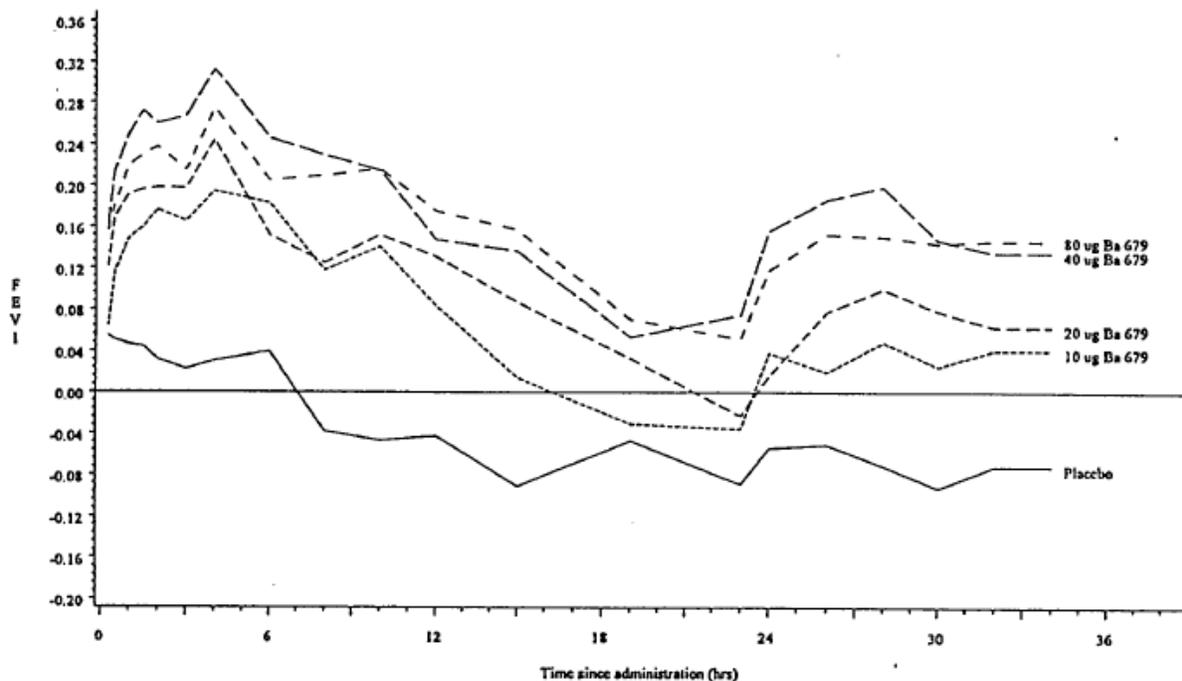
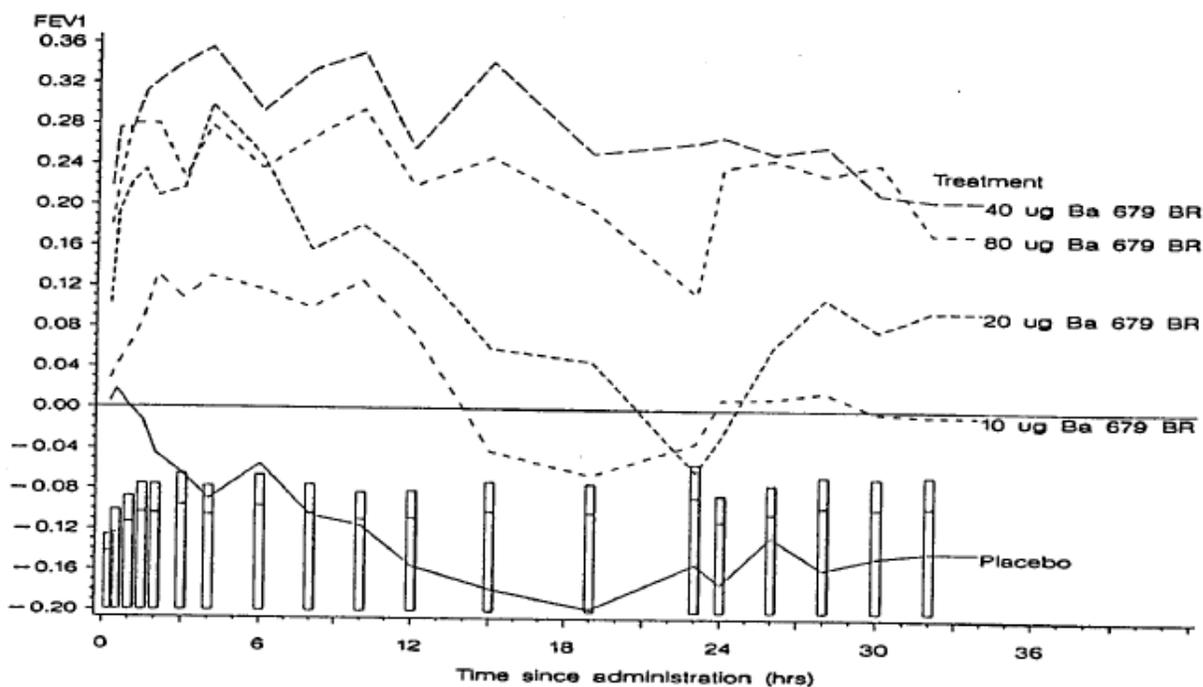


FIGURE 5.1.1.3 - A: Increase in Adjusted Mean FEV₁ from Test-Day Baseline by Treatment on First Test Day Only



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- 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).

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- 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].

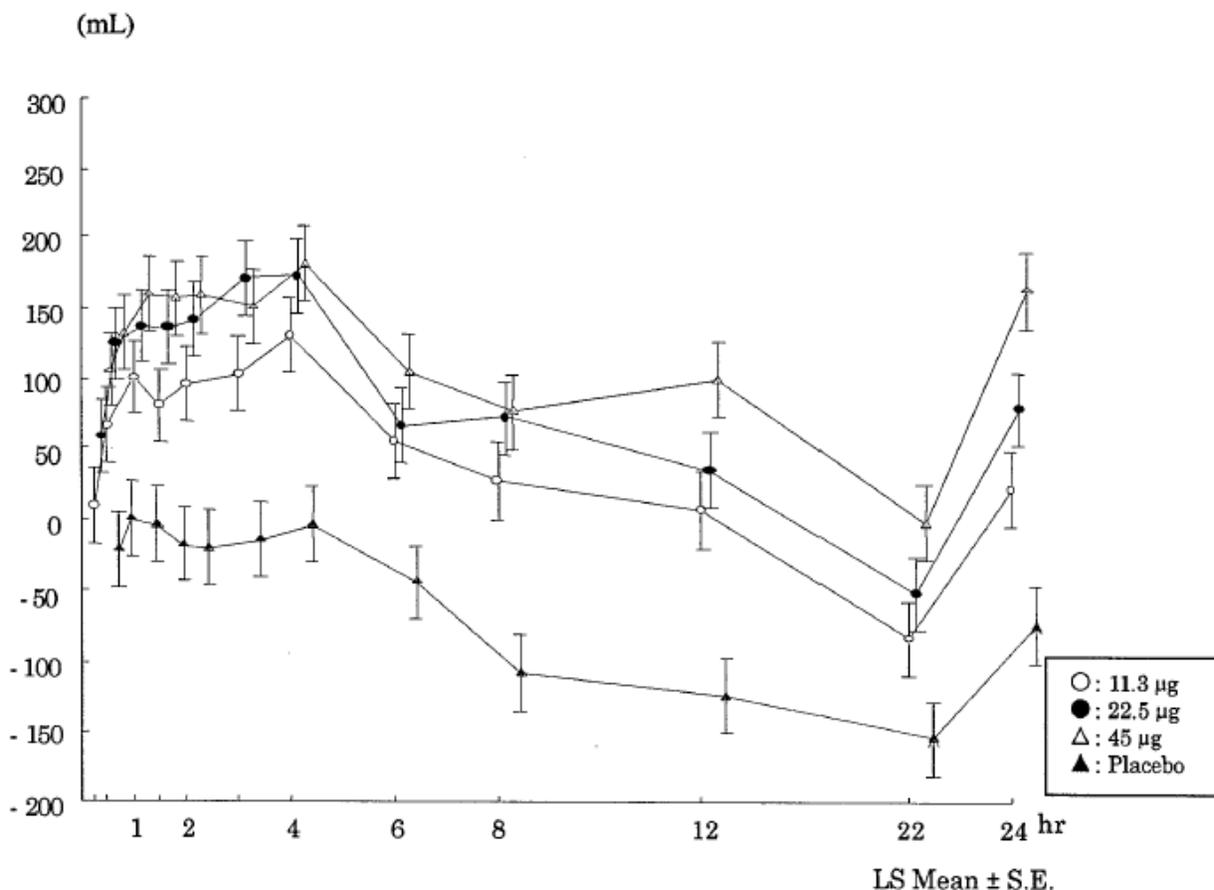


FIGURE 11.4.1.2: 3 Time Course of Changes in FEV_{1.0} (LS Mean)

- 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

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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

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- 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

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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)

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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)
	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.

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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.

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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

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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

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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.

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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

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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

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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.

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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

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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