as measured by spirometry, and further supported by appropriate secondary endpoints. However, in contrast to the Applicant's assertion, the efficacy data do not establish a clinically meaningful benefit in regard to the symptom of dyspnea.

C. Safety

The safety database submitted with this Application is sufficient to support approval. The program included adequate numbers of subjects exposed to the drug. The types of safety assessments used in the clinical studies was adequate, and was generally consistent with development programs for other inhalation drug products for a COPD indication. The safety profile established in the program is acceptable, given the efficacy that was established. Certain remaining safety considerations can be evaluated during Phase 4, as discussed above.

The numbers of patients exposed during development are discussed in Section B, above. In the Phase 3 studies, a total of 1152 patients were exposed for ≥200 days, and a total of 562 patients were exposed for ≥330 days. The safety monitoring in the Phase 3 studies included collection of adverse events, vital signs, physical examination, clinical laboratories, and ECGs. In addition, timed ECGs at doses higher than the proposed dose, and Holter monitor data are available from the Phase 2 experience.

The incidence of death was similar in the tiotropium and placebo groups. Two causes of death were reported in the tiotropium group but not in the comparator groups, myocardial infarction (4 deaths) and arrhythmia (1 death). One observation of potential significance is that, in the one-year, placebo-controlled studies, 5 of the 7 deaths in the tiotropium group were attributable to cardiac ischemia or arrhythmia, compared to only 1 of the 7 deaths in the placebo group. In the one-year, ipratropium controlled studies, 3 of the 9 deaths in the tiotropium group were due to myocardial infarction, compared with 0 of the 3 deaths in the ipratropium group.

Fewer patients in the tiotropium groups reported serious adverse events (SAEs), as compared with both the placebo and the active-control groups. The most common SAEs were COPD exacerbation and pneumonia, and neither was more common in the tiotropium group. None of the SAEs were considered by the investigator to be related to tiotropium. The incidence of discontinuation due to adverse event was lower in the tiotropium as compared to the placebo and the active-control groups. The only specific adverse event leading to discontinuation that was more frequent in the tiotropium group than placebo was dry mouth (3 events vs. 1 event in the one-year, placebo-controlled studies).

No significant safety signals were detected in regard to the vital signs, physical examinations, lab values, or ECGs.

The category of adverse events (AEs) which was most common in the tiotropium group was the Gastrointestinal category. Primarily, this was due to the increased occurrence of dry mouth among tiotropium patients (16% vs. 2.7% in the one-year, placebo-controlled studies). Other gastrointestinal AEs occurring more commonly in the tiotropium group in the one-year, placebo-controlled studies were: dyspepsia (5.8% vs. 4.6%), abdominal pain (4.7% vs. 3.0), constipation (3.5% vs. 2.4%), and vomiting (3.5% vs. 2.4%). In the category of Respiratory System AEs, upper respiratory tract infection (41.1% vs. 37.2%), epistaxis (3.6% vs. 1.9%), pharyngitis (8.9% vs. 7.3%), and sinusitis (11.3% vs. 9.4%) were more common in the tiotropium group in the one-year, placebo-controlled studies. Other AEs occurring more commonly in the tiotropium group in these studies were chest pain (6.9% vs. 4.6%), rash (4.2% vs. 2.2%), and urinary tract infection (7.3% vs. 5.1%). The adverse events dry mouth, constipation, and urinary tract infection showed evidence of an age interaction, being more common among older patients. The AE dry mouth also showed a gender interaction, with more women than men reporting dry mouth (23% vs. 13%). Other potentially significant events include urinary retention in 4 patients, all on tiotropium. These patients required placement of a Foley catheter and three were subsequently started on medication for benign prostatic hypertrophy. Events categorized as "micturation disorder" or "micturation frequency" occurred in 6 (1.1%) tiotropium patients and 0 (0%) placebo patients. These effects on the bladder confirm the preclinical findings suggesting anticholinergic relaxation of the bladder in rats. One patient, who was treated with tiotropium, was admitted to the hospital with a fecal impaction.

Adverse events in the category of "heart rate and rhythm disorders" were more common in the tiotropium group in the one-year, placebo-controlled studies (4.4% vs. 2.2%), as were SAEs in this category (1.3% vs. 0.5%). However, this signal was not seen in the ipratropium-controlled studies. Before- and on-treatment Holter data in 72 patients who participated in a Phase 2 study did not suggest a drug effect.

In summary, tiotropium was not associated with greater occurrences of death, SAE, or withdrawal due to adverse event. The most common adverse event with tiotropium was dry mouth. In addition, the AE profile suggested a systemic anticholinergic effect (dry mouth, constipation, urinary symptoms). It is possible that the effect on the urinary tract increases the risk of urinary tract infection. The safety data also raise the possibility that tiotropium may be associated with an increased risk of certain cardiac adverse effects.

The population studies in Phase 3 differs in some potentially significant ways from the population that would likely receive the drug if it is approved. The Phase 3 studies excluded patients with certain indications of active cardiac disease, such as recent myocardial infarction (1 year), recent hospitalization for heart failure (3 years), and cardiac arrhythmia requiring drug treatment. Given the likelihood that such patients would receive the drug once it is marketed, and the possible safety signal in terms of cardiac effects, it is reasonable to expect that the safety of tiotropium in such patients be explored in Phase 4 studies. Another potentially important difference between the Phase 3 population and the general COPD population is that patients with certain conditions that might be exacerbated by an anticholinergic drug (narrow angle glaucoma and prostatic hypertrophy/ bladder outlet obstruction) were excluded from the Phase 3 studies. It is also likely that patients with these conditions would receive the drug if it is approved. Therefore, it may be expected that the occurrence of systemic anticholinergic adverse events may be more common than was seen during the development program.

Because metabolism plays a relatively minor role in the elimination of the drug from the body, with a minor portion being metabolized by the cytochrome P450 system, it is not likely that systemic exposure to tiotropium will be significantly effected by drug-drug interactions. Poor CYP 2D6 metabolizers exhibit only 33% increase in exposure. Given that active renal secretion is involved in the excretion of tiotropium, it is theoretically possible that a drug that interfered with the relevant transporter could result in increased tiotropium exposure. However, co-administration of cimetidine, which is known to inhibit several transporters, resulted in only a 20% increase in exposure. Finally, because tiotropium does not inhibit CYP P450 enzymes, it is not expected to significantly alter exposures to other drugs that are metabolized by this system.

D. Dosing

The proposed dose of tiotropium bromide inhalation powder is one 18mcg capsule, once-daily. This is the dosing regimen that was utilized in Phase 3. The safety and efficacy conclusions from the Phase 3 studies are discussed above.

The proposed dosing interval has been sufficiently supported by the clinical efficacy data. In fact, the primary efficacy variable (trough FEV_1 response) was a reflection of end-of-dosing-interval efficacy and adequate efficacy was established.

The proposed dose was investigated in several Phase 2 studies. These studies are somewhat difficult to interpret because of several factors, including inadequate washout periods, differences in the formulations and delivery devices used, differences in the nominal doses studied (due to changes in labeling conventions), and, in one case, non-blinded dosing. Nonetheless, the studies generally demonstrated a dose-response in terms of efficacy and in terms of tolerability (dry mouth). Doses of approximately 36mcg were only modestly more effective than doses of approximately 18mcg, and were associated with a greater incidence of dry mouth.

In summary, the proposed dose of 18mcg QD is adequately supported by the Phase 2 and Phase 3 data.

E. Special Populations

Discussion regarding safety, efficacy, and pharmacokinetic characteristics among special populations are included in the section of this document entitled "Use in Special Populations."

Analyses of adverse event data for potential safety gender interactions revealed an increased occurrence of dry mouth in women. For instance, in the one-year, placebo-controlled studies, dry mouth occurred in 23% of the women and 13% of the men in the tiotropium group, and no such gender interaction was seen in the placebo group. In the 6-month studies, pharyngitis and sinusitis were also more common in women (7.7% and 7.7%) than in men (3.5% and 1.9%) in the tiotropium group. Additionally, the reported term "urinary retention" only occurred in men in the tiotropium group (1.1%).

The Applicant also analyzed the efficacy data for potential gender interaction. The acute FEV_1 response (peak and average over the period of post-dose spirometry) was slightly greater for men than for women. This observation may, all or in part, result from gender-based differences in lung volumes. In the six-month studies, the demonstrated effect on the TDI is based almost exclusively on the effect in men, as women showed no drug effect in analyses of mean TDI scores between treatment groups.

Finally, gender does not effect drug plasma concentrations or urinary excretion of tiotropium in patients with COPD [biosum.pdf/p22 and U99-3169.pdf/p149].

Safety and efficacy analyses aimed at detecting possible race interactions did not reveal evidence of such interactions. However, because very few patients in the Phase 3 studies were non-Caucasian, no firm conclusions can be drawn. There are limited data that suggest that no significant pharmacokinetic differences are present between African-American and Caucasian subjects. In one study African-American (n=9) and Caucasian (n=95) asthma patients excreted very similar amounts of tiotropium after once daily inhalations of 4.5, 9, 18, or 36mcg of tiotropium.

The applicant analyzed the adverse event data for potential age interactions. For that purpose, the patients were divided into three age groups: ≤60 years, 61-70 years, and ≥71 years. In those analyses, age interactions for the adverse events dry mouth, constipation, and urinary tract infection were identified.

The efficacy data was also analyzed for age interaction, using the same three age categories. In the one-year placebo-controlled studies the mean average and mean peak responses were notably higher in the youngest age group, whereas the mean trough FEV_1 was slightly higher in the oldest age group. In the one-year, active-controlled studies, there was also evidence of an age interaction, with the younger patients showing a greater response in terms of mean average and peak FEV_1. This trend was not evident in the 6-month studies.

In regard to age effects on pharmacokinetic parameters, renal clearance of tiotropium is significantly lower in elderly patients (163 mL/min; mean age 74) compared with younger patients (326 mL/min; mean age 53). This decreased clearance is associated with increased systemic exposure, as indicated by an increase in the $AUC_{0\text{-}4\ hours}$ from 18.2 pg.h/mL to 26.1 pg.h/mL.

The effect of hepatic impairment was not studied because renal excretion dominated the elimination of tiotropium in healthy volunteers. Poor metabolizers of CYP 2D6 had 33% higher tiotropium plasma $AUC_{0\text{-}4\ hours}$, in comparison to extensive metabolizers [4/18/02 submission, iss.pdf/p269].

Patients with renal impairment demonstrate decreased renal tiotropium clearance and increased tiotropium plasma concentrations [biosum.pdf/p23]. The tiotropium plasma $AUC_{0\text{-}4\ hours}$ were 39%, 81%, and 94% higher in mild, moderate, and severe renal impaired patients compared to control subjects.

There are no clinical data to address the safety of this drug during pregnancy. No patients in the clinical program became pregnant during the studies. The COPD population is generally older, as suggested by the mean age of 60-65 years in the Phase 3 population. Nevertheless, some female patients with COPD may be of child-bearing potential. In addition, it is likely that, if approved, there would be significant off-label use in the younger, asthmatic population, which would certainly include women of childbearing potential. In preclinical studies there was no evidence of teratogenicity; however tiotropium was shown to be embryocidal and fetocidal. In addition, the preclinical experience suggests that tiotropium delays sexual maturation in rat pups exposed to the drug maternally. Inhalation doses of ≥7mcg/kg/day delayed sexual maturation by 1-3.5 days). The Agency Pharm/Tox team recommends that this drug be assigned pregnancy category C, based on the preclinical findings and absence of clinical data.

Clinical Review

I. 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. Spiriva 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 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 beta$_2$-adrenergic agonists (e.g. albuterol, pirbuterol, bitolterol, metaproterenol, and terbutaline), two long-acting beta$_2$-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, Spiriva would represent the first once-daily oral inhalation drug indicated for COPD. The proposal to include a claim that Spiriva is indicated for the treatment of dyspnea related to COPD would also be unique. Although the product label for theophylline products refer to symptoms of chronic lung disease, no other drug is approved specifically for the treatment of dyspnea 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 "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: FEV_1 and the Mahler Transition 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 was not marketed in any country [summary.pdf/p43]. Registration dossiers had been filed in [redacted], and approval had been obtained in two countries, The Netherlands and New Zealand. In Europe, the Mutual Recognition Procedure was being adopted, with Netherlands serving as the Reference Member Site.

According to the Briefing Document provided by the Applicant for the September 6, 2002, PADAC meeting, as of August 1, 2002, Spiriva® is being marketed in six countries (Denmark, Finland, Germany, Netherlands, Sweden, and Philippines). The launch date in all six countries was June, 2002 [Briefing Document, page 25].

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 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%).

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

CMC Aspects

The drug substance, tiotropium bromide, is a white to yellowish-white powder [summary.pdf/p45]. Tiotropium is a quaternary ammonium compound. The manufacturing, packaging, labeling, and control operations in the production of tiotropium drug substances are carried out by Boehringer Ingelheim's chemical manufacturing facility in Ingelheim, Germany. It is synthesized [redacted]

The drug product is a hard gelatin capsule containing a powder mixture of the drug substance and the inert carrier, lactose. The capsules are sealed in moisture-resistant aluminum foil blisters, which are referred to as [redacted] [summary.pdf/p58]. The tropical blister consists of three components, an aluminum based peelable lidding foil, a polyvinyl chloride forming film, and a [redacted] aluminum based bottom foil material. One blister card consists of two [redacted] joined along a perforated line.

The dose is delivered with the use of a reusable, hand-held, breath-actuated device called the HandiHaler. To administer a dose, the patient opens the HandiHaler, places a capsule into the capsule chamber, closes the mouthpiece, presses the button, then inhales through the mouthpiece [summary.pdf/p52]. Pressing the button causes two needles to pierce the capsule. Inhalation through the mouthpiece causes the pierced capsule to vibrate, aerosolizing the contents of the capsule. Although the capsule contains 18mcg of drug substance, with this device only [redacted] is actually delivered [FDA CMC 45-Day Review, Dr. Rogers].

The final capsules formulation was used in all Phase 3 studies. The final design of the HandiHaler was used in all Phase 3 studies [summary.pdf/p60]. However, it is important to note that the formulation changed between Phase 2 and Phase 3. The Phase 3 formulation contained a [redacted] lactose [FDA CMC IND EOP2 Review, Dr. Rogers]. This change resulted in a significant decrease in particle size. A decrease in particle size may result in more drug delivery to the lung. Thus, the 18mcg dose used in Phase 2 likely delivered less drug to the lung as compared to the 18mcg dose used in Phase 3.

The Agency CMC review is currently ongoing. However, preliminary findings include the identification of a possibly significant stability issue [FDA CMC 45-day Review]. [redacted] These changes, [redacted], would be expected to significantly effect the clinical performance of the drug.

Animal Pharmacology and Toxicology

The preclinical evaluation of tiotropium included *in vitro* receptor binding studies, *in vivo* pharmacology and pharmacokinetic studies, and acute and chronic toxicology studies. The *in vitro* binding studies suggested preferential occupation of the muscarininc M_3-receptors over the M_1 and M_2-receptors (Kd=9pM vs. Kd=151 and 32pM) [summary.pdf/p63]. The dissociation from the M_3-receptor is slower than for M_1 or M_2 (half-life 27hrs compared with 11 and 4 hours). Affinity for the histamine H-1 receptor was noted, although it was approximately 3 orders of magnitude lower than at M_3-receptors [summary.pdf/p66]. *In vivo* pharmacodynamic studies performed using intravenous administration in rabbits, and inhalation administration in rats, guinea pigs, and dogs demonstrated that tiotropium provided protection against bronchospasm induced by intravenous or inhaled acetylcholine [summary.pdf/p64]. Systemic administration of tiotropium induced anticholinergic effects (inhibition of salivation, lacrimation, gastric secretion, increase in heart rate, mydriasis, and antimiosis) in animals. Studies using pharmacologically active doses of inhaled tiotropium in guinea pigs and dogs did not reveal effects on heart rate or contractility [summary.pdf/p65].

Single- and multiple dose toxicology studies were performed primarily in the rat and dog. In acute inhalation toxicity studies, the approximate LD_{50} (ALD_{50}) values were >6.5mg/kg in mice, >21mg/kg in rats and dogs [summary.pdf/p73,and DPADP Pharm/Tox Review]. In acute toxicity studies using oral gavage and bolus IV injection in mice and rats, the ALD_{50} was in the range of 1217- >5000mg/kg and 15.5 – 21.5 mg/kg, respectively [summary.pdf/p74]. Adverse effects noted in the acute toxicity studies were reduced food consumption, stagnation or reduction in body weight gain, dyspnea, ocular changes (e.g. mydriasis), constipation, tachycardia, hunched posture, lateral or ventral recumbancy, convulsions and tremor.

Multiple-dose toxicology studies primarily utilized an aqueous aerosol formulation for inhalation studies. These studies, which were performed in rats and dogs for periods of up to 12 months, were supplemented by 13-week bridging studies using a lactose-powder formulation for inhalation. Additionally, oral and IV multiple dose studies were performed. Adverse effects interpreted as anticholinergic pharmacologic effects were increase in heart rate, mydriasis, dry oral and nasal mucosa (resulting in decreased food consumption and decreased body weight gain), decrease in lacrimal secretion, and coprostasis [summary.pdf/p82].

There were three additional species-specific adverse effects of the drug seen in the toxicology studies. These were: proteinaceous deposits in the urinary bladder in male rats, lenticular cataracts in rats, and keratoconjunctivitis sicca in dogs. The bladder findings in the male rats were observed at doses as low as 13mcg/kg. The Applicant postulates that this finding is a result of anticholinergic relaxation of the detrusor muscle, leading to reflux of secretions from the accessory reproductive gland in the urinary bladder. Because there is no such mechanism in humans the Applicant considers the finding to be rodent-specific. However, a systemic anticholinergic effect on bladder contractility would be expected in humans. In several rat inhalation studies, dose-related discrete disciform cataracts on the anterior lens pole were observed. Histopathologically, these were characterized by mild focal proliferation of the subcapsular lens epithelium, forming epithelial plaques. Because these were not seen in oral or IV studies, the Applicant postulates that they were the result of prolonged topical exposure of the eyes during nose-only inhalation [summary.pdf/p83]. Finally, a dose-dependent finding of keratoconjunctivitis sicca (KCS) in multiple-dose toxicology studies in dogs using inhalation, oral and IV routes of administration [summary.pdf/p88-92]. The Applicant postulates that finding, injury and inflammation involving the corneal and conjunctival epithelium, was due to an decreased tear production related to an exaggerated anticholinergic effect in the dog.

Reproductive toxicology studies showed no evidence of teratogenic effect [summary.pdf/p92]. However, a Segment I study in rats showed fetal resorption associated with inhalation of doses ≥7mcg/kg [DPADP Pharm/Tox Review]. Other studies showed post-implantation loss and litter loss along with maternal toxicity at inhalation doses of ≥7 mcg/kg/day in rats and 50 mcg/kg/day in rabbits. No such effects were seen at 0.8 mcg/kg/day. Tiotropium also delayed sexual maturation in rat pups exposed to the drug maternally. Inhalation carcinogenicity studies did not suggest a neoplastic or carcinogenic potential [summary.pdf/p100].

III. 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 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 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

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

IV. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

1. *Summary*

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Human Pharmacokinetics and Pharmacodynamics

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.

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

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 can 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 Sponsor 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 Sponsor 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 has a very long elimination half-life (5-6 days) (Study #205.105, Report #U99-1315). Thus, washout periods of 25-30 days were required in PK studies [biosum.pdf/p17]. 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 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]. 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]. Experiments in rats demonstrated that tiotropium crosses the placenta and is excreted in the milk of lactating rats [biosum.pdf/p19].

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 secreted into the GI tract, and another part is non-enzymatically cleaved to alcohol and acid; however, mass balance studies were not performed. 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 Sponsor 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 $AUC_{0\text{-}4h}$ 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 $AUC_{0\text{-}4h}$ values were 18.2pg.h/mL in the younger group and 26.1pg.h/mL in the older group.

- Patients with renal impairment demonstrate lower renal clearance and higher plasma concentrations. Tiotropium plasma concentrations ($AUC_{0\text{-}4h}$) 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 Sponsor states that such studies were not performed because renal excretion dominated the elimination of tiotropium in healthy volunteers.
- The Sponsor 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 absorption. 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 Sponsor 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 Sponsor 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 $AUC_{0\text{-}4h}$ 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 exposure: 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 Medical Officer Review 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 Netherlands 11/91-4/92	Dose-ranging Open label XO	10mcg 20mcg 40mcg	RESPIMAT	Single Dose	6 (2F/ 4M)	COPD	FEV_1

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
		80mcg 160mcg					
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

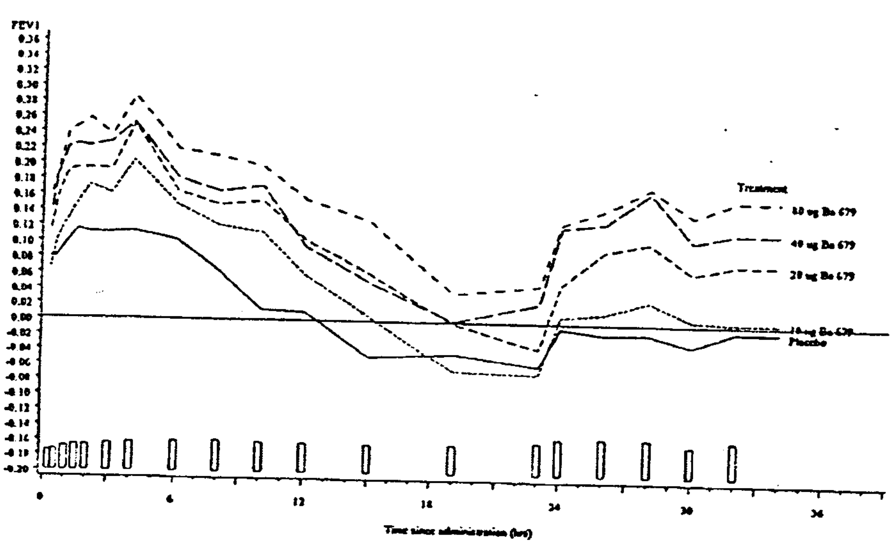
Summaries of the COPD Dose-Ranging Studies

- 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 FEV_1 ≥15% above baseline). For inclusion into the study, patients were required to demonstrate reversible airway obstruction, defined as a >15% improvement in FEV_1 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 FEV_1, the time to peak FEV_1, and the area under the 24-hour FEV_1 curve (divided by 24).
  - The mean peak FEV_1 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 FEV_1 change from baseline, which ranged from 110 to 148 minutes, did not show dose-ordering [U92-0750.pdf/p43]. The FEV_1 $AUC_{0-24h}/24$ 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 FEV_1 curves demonstrate an interesting finding. In all dose groups,, the FEV_1 declined gradually to a nadir at 23 hours. However, in all dose groups the 24-hour FEV_1 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: 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 FEV_1 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 FEV_1 30 minutes after inhalation of ipratropium bromide. The primary efficacy variable was FEV_1, focusing on peak response, and average FEV_1 over a various time periods (8, 12, 24, and 32 hours).
  - The baseline FEV_1 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 FEV_1 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.

Figure 5.1.1.1 - A: Increase in Adjusted Mean* FEV_1 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 FEV_1 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.

FIGURE 5.1.1.3 - A: Increase in Adjusted Mean FEV_1 from Test-Day Baseline by Treatment on First Test Day Only

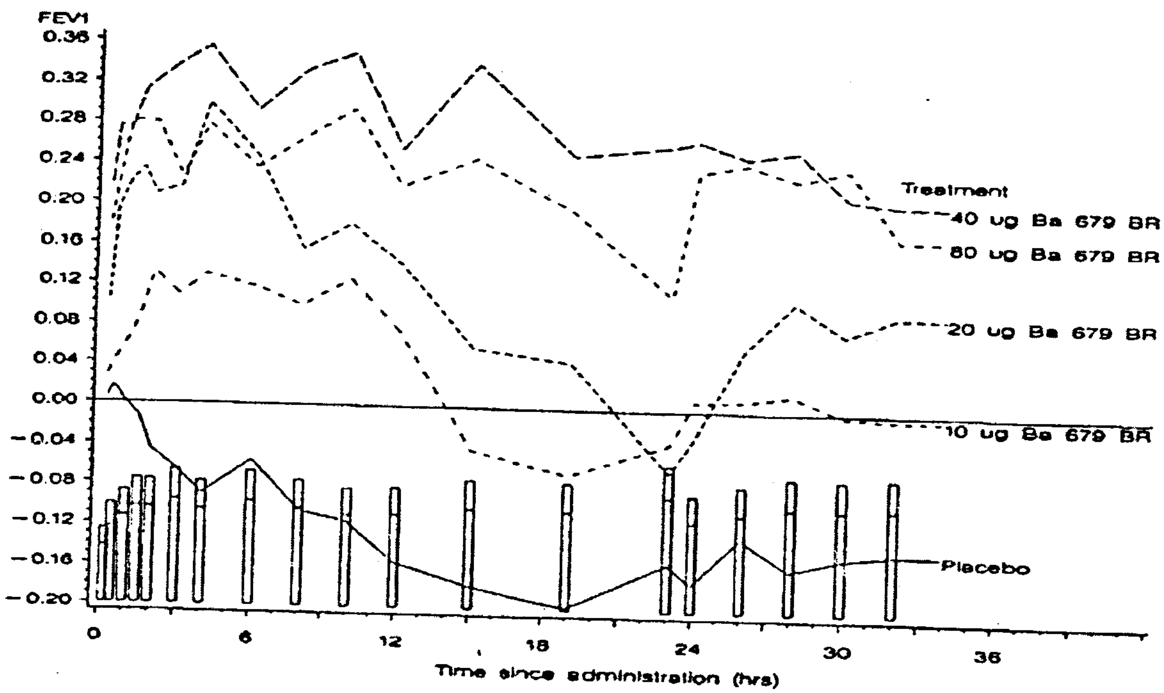
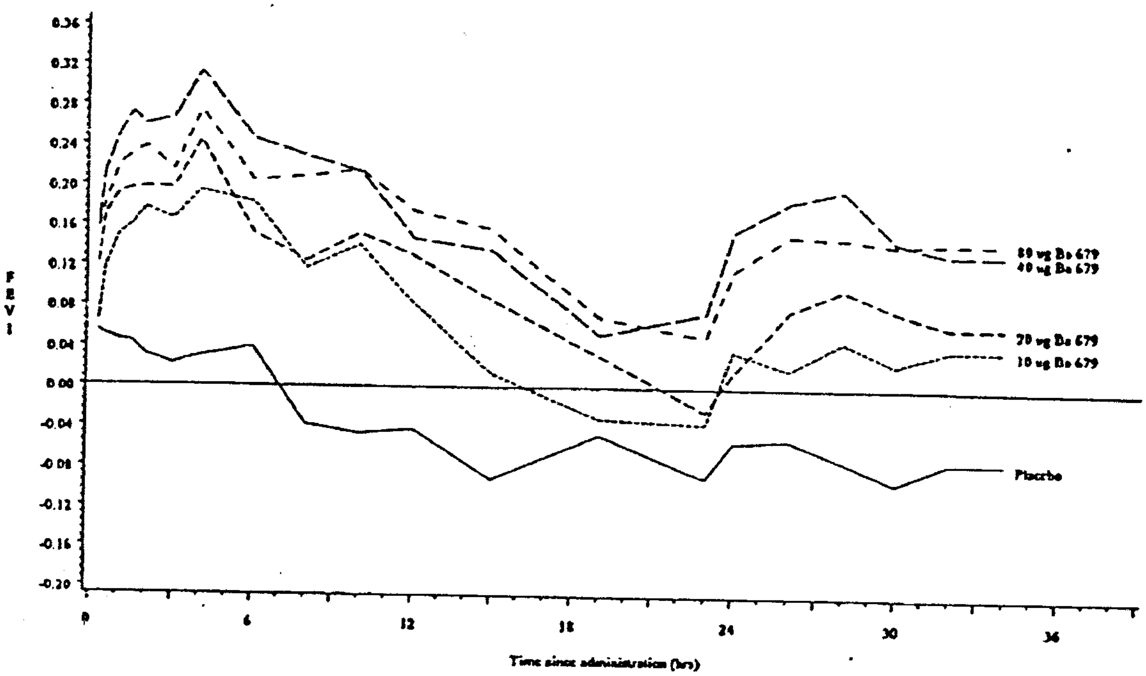


Figure 5.1.1.2 - A: Increase in Adjusted Mean * FEV_1 From Test-Day Baseline, Excluding Test Days Which Follow Ba 679 BR 20 μg, 40 μg or 80 μg - Intent-To-Treat Data Set



- The serial FEV_1 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 FEV_1 at 1 hour after inhalation of an anticholinergic agent (Tersigan® Aerozol). The

primary endpoint was the peak FEV_1. Secondary endpoints included FEV_1 $AUC_{0\text{-}24h}$, time to peak FEV_1, time to response (defined as an increase in FEV_1 of ≥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 FEV_1 was significantly higher in all active treatment groups, as compared with placebo. A dose response effect was demonstrated for peak FEV_1 and FEV_1 $AUC_{0\text{-}24hours}$. Although the incremental improvement in peak FEV_1 between the 22.5mcg dose and the 45mcg dose was minimal, the increment in FEV_1 $AUC_{0\text{-}24hours}$ 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).
- The serial FEV_1 curves in other single-dose dose-ranging studies indicated a rise in the FEV_1 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, figure below suggests that the effect was greater in the active treatment groups, suggesting an element of drug effect [U00-0156.pdf/p74].

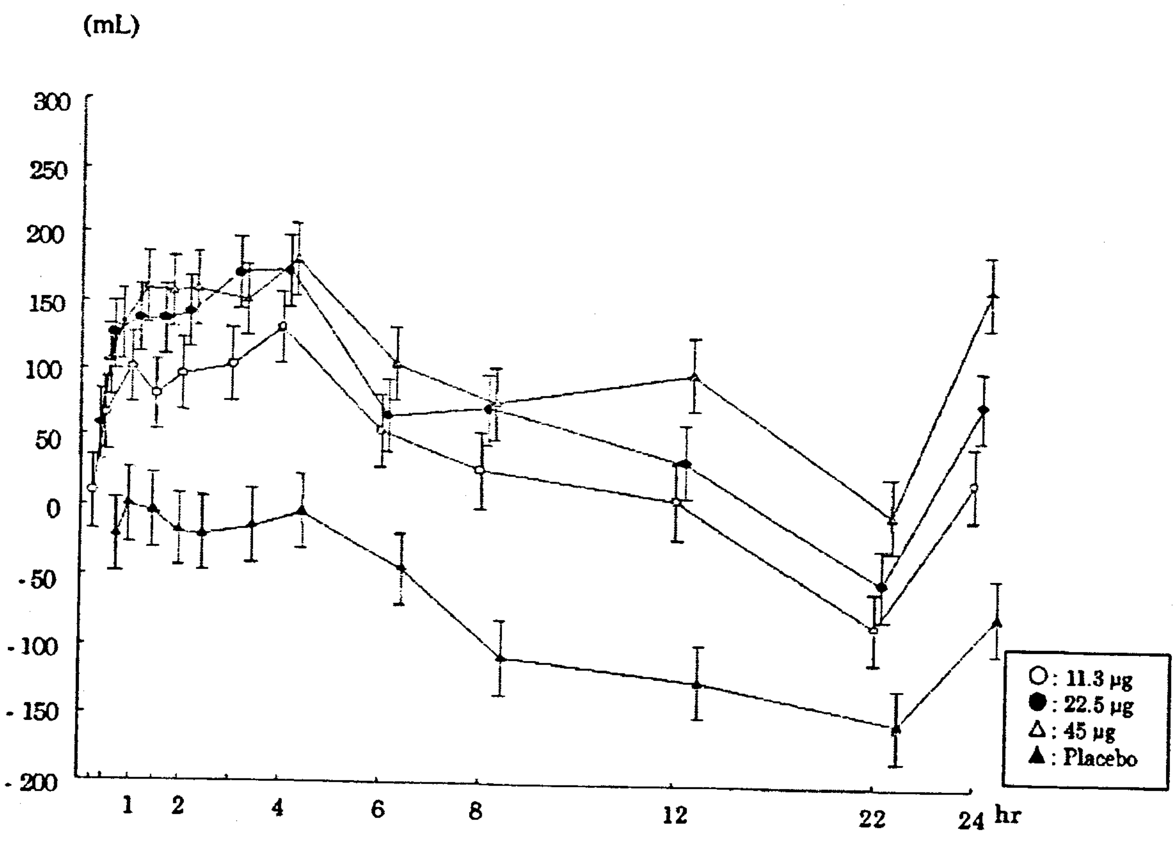


FIGURE 11.4.1.2: 3 Time Course of Changes in $FEV_{1.0}$ (LS Mean)

- 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 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 FEV_1, "with emphasis on the last four hours of the dosing interval" [U96-3068.pdf/p32]. Secondary endpoints included FEV_1 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 FEV_1 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 FEV_1 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 FEV_1 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, intraformulaiton double-blind, parallel group study." (Report #U00-0077)
  - This was a multicenter, randomized, double-blind, placebo-controlled, multiple-dose, parallel group study performed in 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 FEV_1,at Day 23, "with emphasis on the last two hours of the dosing interval" [U00-0077.pdf/p47]. Secondary endpoints included FEV_1 during the first four hours post-dose.

- Trough FEV_1 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 FEV_1 was consistently higher in the 18mcg HandiHaler group than in the other treatment groups. Interestingly, the placebo response was consistently greater in the — . 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 — 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 ≥40mcg, 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 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 29.7days, 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 (Pupilary 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 0.4µg, 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 FEV_1 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)
	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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IV. 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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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	1year (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

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 were postmarketing data available in the submission because, as of the date of the submission, the drug had not been marketed in any country [summary.pdf/p43]. Of note, according to the Briefing Document prepared by the Applicant for the September 6, 2002, PADAC meeting, as of August 1, 2002, the drug is being marketed in six countries (Denmark, Finland, Germany, Netherlands, Sweden, and Philippines). The launch date in all six countries was June, 2002 [Applicant's Briefing Document, page 25].

C. Literature Review

A literature review was not performed.

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V. 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 Medical Officer Review. Safety data from the individual studies were also reviewed but are not reported in detail within the reviews of the individual studies. Rather, the safety review is included in the Integrated Review of Safety. Individual pharmacokinetic and pharmacodynamic studies were reviewed primarily for evidence to support the proposed dose and dosing interval. Finally, the Applicant submitted, along with the required 4-month Safety Update, a study report for an additional supportive clinical study (Study 205.131). This study, which was a six-week placebo-controlled study involving serial exercise testing in patients with COPD, was reviewed, with a focus on the primary efficacy endpoint and the efficacy endpoints related to subjective dyspnea (See Appendix).

B. Overview of Materials Consulted in Review

This Medical Officer Review 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 (DSI) 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. The centers were: 1) Dr. [redacted] Center #33, Study 205.130); and 2) Dr. [redacted] Center #36, Study 205.130). As a result of the audit, DSI concluded that the 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 (Dr. [redacted]. At the second study site, which enrolled 13 patients into Study 205.130, one potentially important protocol violation was noted (Dr. [redacted] 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 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, that 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 ([redacted] The Applicant states that because [redacted] , 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.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The evidence derived from the six pivotal clinical trials establishes the efficacy of tiotropium as a bronchodilator in patients with COPD. A probably clinically meaningful bronchodilator effect is maintained throughout the proposed dosing period. The data regarding the effect of this drug on the symptom of dyspnea in this patient population is not convincing enough to merit the proposed dyspnea indication, which would be unique among drugs for COPD, nor should it be included elsewhere in the product label.

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.

The Applicant proposes to include data regarding [redacted], in the product label. In keeping with prior precedent, this will not be allowed.

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	Netherlands and Belgium	1year (52 weeks)	R, DB, PG Active comparator	247	Trough FEV_1 response at 13 weeks

Pivotal Clinical Studies							
Study Number (Report #)	Study Type	Treatment Groups	Location	Duration	Design	Number of Subjects	Primary Endpoint
		– Placebo capsule QD + Ipratropium MDI 40mcg QID					(mean of values at 23 and 24 hours)
205.130 (U01-1236)	Safety/ Efficacy	– Tiotropium 18mcg capsule QD + Placebo MDI BID – Placebo capsule QD +SalmeterolMDI 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

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 (FEV_1). 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 FEV_1 and an index of subjective dyspnea, the Mahler Transition 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 Medical Officer Review. In these studies, a total of 921 patients with COPD were, following a 2-week baseline period,