FDA PULMONARY-ALLERGY DRUGS
ADVISORY COMMITTEE MEETING – SEPTEMBER 6, 2002

Sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
NDA	SPIRIVA® (tiotropium bromide inhalation powder) 21-395
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The studies described in this report were performed in compliance with Good Clinical Practices and relevant Boehringer Ingelheim Standard Operating Procedures.

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ABBREVIATIONS

Ae_{0-4h}		Urinary excretion of unchanged substance over 4 hours after administration
Ae_{0-24h}		Urinary excretion of unchanged substance over 24 hours after administration
ANCOVA	-	Analysis of covariance
AUC	-	Area under the curve
AUC_{0-4h}		Area under the drug plasma concentrations time curve over 4 hours after administration
Avg	-	Average
BDI	-	Baseline Dyspnea Index
BI	-	Boehringer Ingelheim
BID	-	Twice daily
BIPI	-	Boehringer Ingelheim Pharmaceuticals, Inc.
BI-WHO-ARTL	-	Boehringer Ingelheim - World Health Organization - Adverse Reaction Terminology List
CL_{CR}		Creatinine clearance
CNS	-	Central Nervous System
COPD	-	Chronic Obstructive Pulmonary Disease
CRF	-	Case report form
dL	-	Deciliter
ECCS	-	European Community for Coal and Steel
ECG	-	Electrocardiogram
ED	-	Electronic data
E_{max}		Maximum effect
EVENT DUR	-	Event duration
FDA	-	Food and Drug Administration
FEV_1	-	Forced expiratory volume in one second
FVC	-	Forced vital capacity
FO2	-	Inhalator Ingelheim device
GCP	-	Good clinical practice
GM	-	Gram
g/L	-	Gram per liter
HPLC-MS/MS		High performance liquid chromatography with tandem mass spectrometric detection
Inh	-	Inhalation
IB	-	Ipratropium bromide
IRB	-	Institutional Review Board
ISE	-	Integrated Summary of Efficacy
ISS	-	Integrated Summary of Safety
ITT	-	Intent-to-Treat
IV	-	Intravenous
L	-	Liter
LDH	-	Lactate dehydrogenase
LFDCF	-	Least favorable data carried forward
LOCF	-	Last observation carried forward

ABBREVIATIONS continued

LVCF	-	Last visit data carried forward
MCC	-	Mucociliary clearance
mcg	-	Microgram
µg	-	Microgram
mg	-	Milligram
mL	-	Milliliter
N.A.	-	Not applicable
PBO	-	Placebo
PDMAP	-	Project data management and analysis plan
PEFR	-	Peak expiratory flow rate
PFT	-	Pulmonary function test
PI	-	Penetration index
PRN	-	As occasion requires
QID	-	Four times daily
QoL	-	Quality of life
REM	-	Rapid eye movement
RFI	-	Request for information
SAE	-	Serious adverse event
SaO_2	-	Oxygen saturation
SE	-	Standard error
SGOT	-	Serum glutamic oxaloacetic transaminase
SGPT	-	Serum glutamic pyruvic transaminase
SGRQ	-	St. George's Respiratory Questionnaire
SOC	-	System organ class
Std Dev	-	Standard deviation
TBC	-	Tracheobronchial clearance
TBR	-	Tracheobronchial retention
TDI	-	Transition Dyspnea Index
TDI FS	-	Transition Dyspnea Index Focal Scores
TDMAP	-	Trial data management and analysis plan
TEST DRUG REL	-	Test drug relationship to adverse event
TRT DUR	-	Duration of study treatment at onset of adverse event
TRT REQ	-	Treatment required for adverse event

EXECUTIVE SUMMARY

The development program established the safety and efficacy of SPIRIVA® (tiotropium), a long-acting inhaled antimuscarinic bronchodilator, in the maintenance treatment of bronchospasm and dyspnea associated with Chronic Obstructive Pulmonary Disease (COPD). The program, which was developed in consultation with FDA, consisted of six pivotal long-term studies and several special studies.

PROPOSED INDICATION AND DOSE

The data presented in this briefing document will demonstrate that inhalation of SPIRIVA® (tiotropium) has an acceptable benefit-risk profile to support the following indication:

- 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.
- The proposed dosage for adults is 18-mcg tiotropium once daily, inhaled from SPIRIVA® capsules using the HandiHaler device.

RATIONALE FOR TIOTROPIUM IN THE MANAGEMENT OF COPD

COPD affects tens of millions of Americans and is a serious health problem in the U.S.: in 1994 it was estimated that 16 million patients have been diagnosed with some form of COPD, and as many as 16 million more are undiagnosed (Petty, 1997). COPD was the fourth leading cause of death in the U.S. in 1998 (National Center for Health Statistics, 1998), and is estimated to become the primary cause of death by 2010.

Although, COPD is a disease state characterized by airflow limitation that is not fully reversible (GOLD) there is a significant reversible component to the airflow limitation as measured by spirometry in most patients. Bronchodilator therapy, including anticholinergic therapy, is recommended as the first-line maintenance therapy for COPD (ATS). Dyspnea is the reason most patients seek medical attention and is a major cause of disability and anxiety associated with the disease (GOLD). By improving both airflow and the most common symptom of COPD, dyspnea, tiotropium provides clinically significant benefits to the patient. The results of the studies in the clinical program confirm that tiotropium provides both bronchodilation and improvements in dyspnea when administered once daily in patients with COPD.

SPIRIVA® CLINICAL PROGRAM

The SPIRIVA clinical core program consisted of six pivotal studies ranging from 6-months to 1-year in duration. The long duration of these studies allowed for a thorough characterization of tiotropium in this chronic disease process. The demographics of all six pivotal studies were similar. The population of patients enrolled in these studies was predominately male, with a mean age of 65 years and with a smoking history of at least 10 pack/years. The mean baseline FEV_1 ranged from 1.0-1.2 L, consistent with moderate to severe disease. Patients with a history of asthma were excluded, as were patients determined to have a serious disease other than COPD.

In all six pivotal studies, serial spirometry on test days was evaluated in support of bronchodilator efficacy and the Transition Dyspnea Index (TDI) was used to evaluate dyspnea. Further support for dyspnea was provided through correlation with secondary endpoints such as quality of life instruments, symptom scores, other questionnaires, and rescue medication use. The studies are described below:

- **Studies 205.114/117 (#114) and 205.115/128 (#115):** Two 1-year, placebo-controlled replicate studies, treating a total of 518 COPD patients with tiotropium and 328 with placebo.
- **Studies 205.122a/126a (#122a) and 205.122b/126b (#122b):** Two 1-year, ipratropium-controlled replicate studies, treating a total of 329 patients with tiotropium and 161 patients with ipratropium.
- **Studies 205.130 (#130) and 205.137(#137):** Two 6-month, placebo- and salmeterol-controlled replicate studies, with a total of 386 patients treated with tiotropium, 388 patients treated with salmeterol, and 362 patients treated with placebo.

PRIMARY CLINICAL ENDPOINTS

The primary spirometry endpoint in the 1-year studies was FEV_1 trough (measured immediately before the morning dose of study medication) after 12 weeks of therapy. This endpoint was chosen as the primary endpoint because it establishes the 24-hour duration of action of once a day tiotropium administration.

The Transition Dyspnea Index Focal Score was pre-specified as a co-primary endpoint with trough FEV_1 in comparison to placebo in the 6-month studies. The TDI focal score of ≥1 was pre-specified as clinically meaningful improvement from baseline and the analysis of the

percentage of patients under active treatment compared to placebo reaching this target was pre-specified as the primary analysis.

Bronchodilation

Traditionally, the bronchodilator efficacy of COPD therapy is assessed through the measurement of the forced expiratory volume in one second (FEV_1). As COPD is characterized by airway obstruction that is partially reversible, expected improvements in FEV_1 are more modest than those seen with asthma. In the tiotropium clinical program the primary efficacy measurement for bronchodilation was FEV_1 trough at 92 days in the 1-year studies, and 169 days in the 6-month studies. FEV_1 trough was defined as the average of two measurements just prior to morning dose.

In four, 1-year, pivotal studies, the FEV_1 trough responses were significantly superior following tiotropium administration when compared to placebo or ipratropium. The magnitude of the responses was comparable between replicate studies. The mean FEV_1 trough was 0.14 L over placebo ($p<0.0001$) in each of the two studies and 0.13-0.14 L over ipratropium ($p<0.0001$).

In the two 6-month studies, the mean FEV_1 trough response for tiotropium ranged from 0.12-0.13 L over placebo. The differences between the tiotropium and placebo treatment groups were statistically significant ($p<0.01$).

Supporting evidence for the bronchodilator efficacy in all of these studies is provided by secondary endpoints, including: trough FEV_1 response at other timepoints, peak and average FEV_1 response at all time points and FVC and peak expiratory flow rate. These endpoints demonstrate consistent improvement in the tiotropium treatment groups, and show significantly superior efficacy compared to placebo and ipratropium.

There was no evidence of tachyphylaxis or a rebound effect following 1-year treatment.

- Patients treated with tiotropium achieved a statistically significant, and clinically relevant, and consistent improvement in bronchodilation in all six pivotal Phase 3 Studies.

Relief of Dyspnea (Shortness of Breath)

Dyspnea was measured by the Transition Dsypnea Index (TDI), a validated instrument that has shown both internal and external consistency. As discussed above, the TDI was pre-specified as the co-primary endpoint with FEV_1 trough measured at Day 169 in the 6-month pivotal studies. An improvement in TDI focal score of one unit or more from

baseline was pre-specified as clinically meaningful, and the primary analysis compared the percent of responders with an improvement of one or more in TDI focal score between tiotropium and placebo.

In each of the two, 6-month placebo- and salmeterol- controlled studies, the percentage of patients demonstrating a clinically meaningful response ranged from 42% to 43% in the tiotropium treatment groups, compared to 28% to 30% in the placebo treatment groups. This difference was statistically significant in each study. For tiotropium, the mean change in TDI focal score over placebo exceeded the minimal clinically important difference (MCID) of one unit in each of the two studies, and achieved statistical significance in each. Other time points showed similar trends, with the superiority of tiotropium over placebo increasing with time.

The consistency of this beneficial effect on dyspnea, is supported by the four 1-year studies, in which the TDI focal score, measured as a secondary endpoint, demonstrated that tiotropium was significantly superior to either placebo or ipratropium in relieving dyspnea consistently over the 1-year treatment period. However, a clinically meaningful difference of one unit for mean differences was not achieved. A retrospective analysis on the percent of patients achieving a clinically-meaningful change was significantly superior for tiotropium versus both placebo and ipratropium at all time points in a combined analysis of the replicate studies, except percent responders at Day 92 in the ipratropium-controlled studies (p=0.056).

The relief of dyspnea was further supported by a reduction in the need for rescue beta-agonist therapy in the pivotal clinical studies.

- In the two pivotal, 6-month, Phase 3 studies, patients treated with tiotropium demonstrated a statistically significant and clinically meaningful improvement in dyspnea as compared to those treated with placebo, as measured by the Transition Dyspnea Index (TDI).

- In the four, 1-year pivotal studies, similar benefits of tiotropium in treating dyspnea were observed. However, measurement of dyspnea in these studies was not pre-specified as a primary endpoint.

- Dyspnea response was supported by related measures in that those who were considered responders (as defined by a TDI Focal Score of greater to or equal to one unit) used less albuterol, had improved health status and experienced fewer exacerbations.

SUMMARY OF SAFETY

The consolidated safety database consists of >1700 patients receiving tiotropium by inhalation of the powder capsule formulation, including 1308 patients from the six pivotal Phase 3 studies who inhaled the recommended 18 mcg daily dose.

The rate of adverse events was comparable across treatment groups. The most common effect differing from placebo was dry mouth. It was predominately mild and occurred in 14-16% of the tiotropium patients, as compared with 4% of placebo treated patients. Overall, only 0.3% of patients discontinued due to dry mouth. Other possible antimuscarinic adverse events included upper respiratory symptoms, constipation, increased heart rate, and urinary retention. These events were usually infrequent and rarely serious.

A lower percentage of patients suffered adverse events leading to discontinuation of treatment in the tiotropium-treated patients (8.9%), than in the placebo-treated (14.8%), ipratropium-treated (12.3%), or salmeterol-treated (14.8%) patients. In the 1-year studies, a lower percentage of patients suffered serious adverse events of any kind in the tiotropium-treated patients (17.2%), than in the placebo-treated (21.0%) or the ipratropium-treated (25.7%) patients. In the 6-month studies, a lower percent of patients from the tiotropium-treated group (9.2%) suffered any serious adverse event, than in the placebo-treated (13.8%) or the salmeterol-treated (12.3%) groups. The lower rate of discontinuations and serious adverse events in the tiotropium groups were mainly due to a decrease in COPD exacerbations in the tiotropium groups.

The profiles of serious and fatal adverse events were consistent with the demographics of patients within the clinical studies. Fatal events in the tiotropium treatment groups (1.3%) were comparable to control groups in these studies (placebo 1.7%; ipratropium 1.7% and salmeterol 1.5%).

Laboratory results, ECG's, vital signs, and physical examinations indicate no imbalance of clinically important abnormal findings.

- The safety profile consistent with antimuscarinic pharmacology and ipratropium experience.
- The most common adverse event is dry mouth.
- There was no indication of increased risk of any life-threatening event or death from any cause.

BENEFIT / RISK DISCUSSION

In summary, tiotropium provides clinically important benefits for the treatment of COPD, both in terms of bronchodilation and dyspnea. These important benefits are associated with adverse effects similar to those seen with currently available treatments for COPD. Therefore, tiotropium exhibits a favorable risk-benefit ratio.

FDA regulations (21 CFR 201.57(c) iii) allow labeling of relief of symptoms associated with a disease in the Indications and Usage section of product labeling. As previously noted, dyspnea is the reason most patients seek medical attention and it is a major cause of disability and anxiety associated with the disease. The importance of this information to the prescribing physician warrants its inclusion in the Indication section of the labeling.

In conclusion, the favorable clinical profile and benefit-risk ratio for tiotropium, as well as the importance of dyspnea as the key symptom of COPD, support the proposed Indication statement.

1. INTRODUCTION

1.1 PURPOSE AND CONTENT OF THE BRIEFING DOCUMENT

The U.S. Food and Drug Administration (FDA) Division of Pulmonary and Allergy Drug Products has called for an Advisory Committee to meet on September 6th, 2002 to consider the benefit/risk of SPIRIVA® (tiotropium bromide) 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 dosage for adults is 18 mcg tiotropium cation once daily inhaled from SPIRIVA® capsules using the HandiHaler® device.

This briefing document has been compiled by Boehringer Ingelheim Pharmaceuticals, Inc. to serve as a review document for the Advisory Committee members. Included are relevant clinical pharmacology, clinical efficacy and clinical safety data for SPIRIVA®.

1.2 RATIONALE SUPPORTING THE USE OF SPIRIVA® IN THE TREATMENT OF COPD

1.2.1 Burden of Disease

COPD affects tens of millions of Americans and is a serious health problem in the U.S. In 1994 it was estimated that 16 million patients have been diagnosed with some form of COPD and as many as 16 million more are undiagnosed (Petty, 1997). COPD was the fourth leading cause of death in the U.S. in 1998 (National Center for Health Statistics, 1998). COPD accounted for an estimated 668,362 hospitalizations for which COPD was the first listed discharge diagnosis in 1998 (National Center for Health Statistics, 1998 (2)). COPD accounts for 13.2 million office visits to doctors in 1997 (National Center for Health Statistics, 1999). COPD costs the U.S. economy an estimated 31.9 billion dollar a year (American Lung Association, 2000).

Although COPD symptoms are chronic rather then episodic, the severity of symptoms may vary during the year. During their worst 3-month period of the year, 79% of patients reported dyspnea (shortness of breath) at least a few days a week and 58% had dyspnea everyday (Confronting COPD in America Survey, American Lung Association , 2001). Seventy-six percent had coughed at least a few days a week, 53% had coughed every day. Seventy-two percent had brought up phlegm at least a few days a week and 48% every day. Forty-nine percent had been awakened at night by coughing, wheezing or dyspnea at least a few days a

week and 23% every night. There was a striking impact of dyspnea on every day activities. Twenty-eight percent had difficulty breathing even when sitting or lying still. Thirty-two percent got dyspnea when talking and 44% got dyspnea when washing or dressing. Seventy-two percent feel breathless when walking up one flight of stairs, demonstrating the level of inactivity imposed on these patients and the importance of reported dyspnea as leading symptom. A majority of COPD patients said that the condition limits what they can do limits to normal physical exertion 70%, household chores 56%, social activities 53%, and sleeping 50%. Thirty-four percent said COPD keeps them from working.

The disease burden of COPD can also be seen in the demand for urgent or emergency medical care. Among persons 45 and older with COPD, 14% were hospitalized over night in the past year for their condition, 19% had emergency room visits and 26% had other emergency visits in the past year (American Lung Association, 2001).

1.2.2 Definition, Current Management and Therapeutic Need in COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD, U.S. National Heart, Lung and Blood Institute and World Health Organization supported) has published a global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (Pauwels et al, 2001). GOLD defines COPD as a "disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases." The American Thoracic Society (ATS) defines COPD similarly: "A disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperactivity, and may be partially reversible" (Celli et al, 1995). More than two thirds of COPD patients report that they suffer from dyspnea and dyspnea is the most prominent complaint motivating a patient to seek medical care. The ATS defines dyspnea as sensations experienced by individuals who complain of unpleasant or uncomfortable respiratory sensations (Consensus Statement, ATS 1999). Emphysema, primarily a histological definition, and chronic bronchitis are complex pathophysiological conditions and frequently co-exist in the same patient. There is appreciable overlap in the clinical use of the terms COPD, chronic bronchitis and emphysema.

The basic components of the NHLB / WHO workshop recommendations for a global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (GOLD, Pauwels et al, 2001) are:

- assess and monitor disease,
- reduce risk factors,
- manage stable COPD, and
- manage exacerbations.

The overall approach to managing stable COPD is characterized by a stepwise increase in treatment, depending on the severity of the disease. Bronchodilators are the mainstay of symptomatic management of COPD and represent the only class of drugs with FDA approval for the treatment of COPD. They are given on an as needed basis or on a regular basis to prevent or reduce symptoms. Inhaled anticholinergics and $ß_2$-agonists are well-established principles; however, limitations as to convenience and effectiveness may limit compliance and contribute to under-utilization, leading to sub-optimal control of the disease. A recent survey (Confronting COPD in America, American Lung Association, 2001) suggests that, in addition to the disease burden of COPD, patients also perceive that their current medications present a "treatment burden"; 31% feel their medication schedule makes it difficult to lead an active life; 62% say that taking multiple medicines is inconvenient; and 57% say they would be better about taking medicine if it were more convenient. Nine out of 10 patients say they want a medication that allows normal activity levels. Existing therapies, the short acting bronchodilator $ß_2$-agonists, ipratropium, theophyllines, and even long-acting $ß_2$-agonists with their twice-a-day regimens leave appreciable room for improvement of pharmacotherapy.

1.2.3 Scientific Rationale for the Development of SPIRIVA®

A causal therapy of COPD other than smoking cessation or avoidance of noxious environmental factors does not exist. A basal anti-inflammatory therapy has not been identified and the use of oral or inhaled corticosteroids is controversial (Pauwels et al, 2001, Mc Evoy and Niewoehner 2000, Niewoehner, 2001).

Parasympathetic pathways mediated by acetylcholine are the major constrictor pathways in human airways. Anticholinergic bronchodilator response increases with increasing severity of disease (Gross et al, 1989).

Bronchodilators relax airway smooth muscle. Two classes of inhaled drugs are currently utilized, beta-agonists and anticholinergics. Beta-agonists act as functional antagonists to bronchoconstrictive mediators, whereas anticholinergics are specific antagonists to

acetylcholine-mediated airway tone and constrictive stimuli. This may explain why beta-agonists are regularly more effective in the treatment of bronchospasm in asthma, whereas anticholinergics are at least as effective, or more effective, than $beta_2$-agonists in COPD (Corne and Anthonisen, 2002).

Efferent cholinergic fibers originate in the nucleus ambiguous and dorsal motor nucleus of the brain stem. Cholinergic fibers travel along the trachea, main bronchi and airways with the vagus nerve to parasympathetic ganglia located in the airway wall down to the level of the small bronchi. Vagal stimulation results in release of acetylcholine from cholinergic nerve terminals and activation of muscarinic cholinergic receptors on smooth muscle and mucus gland cells inducing basal airway tone, cholinergic bronchoconstriction and mucus secretion in the airways (Gross and Skorodin, 1984). Five subtypes of muscarinic receptors (M_1 to M_5) have been identified, but only M_1 to M_3 have importance in human airways. M_1 receptors are found in autonomic ganglia and facilitate ganglionic transmission. M_1-receptors are also found in glands to stimulate secretion and in alveolar walls with unknown function. M_2 receptors are found prejunctionally on post-ganglionic nerve terminals and, on activation, inhibit further release of acetylcholine, so function as regulating autoreceptors. From animal experiments, it may be concluded to be advantageous not to block M_2 receptors. M_3 receptors are located at the airway smooth muscle and submucosal glands mediating bronchoconstriction and mucus secretion (Barnes, 1993; Zaagsma et al, 1997). Vagally transmitted bronchoconstriction can result from reflexes mediated by irritant receptors in the airways, responding to dust, smoke, chemicals, or pharmacologic agents like histamine, prostaglandins, and bradykinin (Barnes, 1993 (b)). Cholinergic agonists like methacholine may directly induce bronchospasm. In theory, agents that are selective receptor antagonists for M_1 and M_3 would be preferable, because any pharmacologically induced paradoxical reaction could not occur and junctional acetylcholine concentrations might not be increased, resulting in higher potency, or even higher efficacy (maximum effectiveness) of the agent.

The preclinical profile of tiotropium is described in Section 8. Briefly, tiotropium is a N-quaternary ammonium compound with low gastrointestinal bioavailability, in this respect similar to ipratropium. Pharmacological studies profile tiotropium as a specific, highly potent, competitive (reversible) muscarinic antagonist, demonstrating very slow dissociation from especially M_3-muscarinic receptors. The slow dissociation from muscarinic receptors is thought to be responsible for its long duration of action and very stable pharmacological effects demonstrated in several in-vitro and in-vivo models (Disse, 1993/P93-0539).

The aforementioned physiological and pathophysiological considerations and the qualities of tiotropium, profile this drug as an ideal antimuscarinic for inhaled administration in COPD.

1.2.4 Clinical Rationale for the Development of SPIRIVA®

The importance of dyspnea as a key symptom for patients with COPD was outlined in Section 1.2.1. Dyspnea associated with airflow limitation is a key clinical symptom even more prominent then chronic cough and phlegm production. Dyspnea impacts patient's activities of daily living from their ability to work and to perform household chores to participation in social activities. Dyspnea is the major symptom for which COPD patients seek medical care.

Although patients with COPD are often considered to have relatively fixed obstruction, there is a significant reversible component in most patients to airflow limitation as measured by spirometry. In 1986 Anthonisen et al described that 68% of patients demonstrated an increase of FEV_1 >15% in a large study of 985 patients with COPD. While smoking cessation is a primary goal of therapy for those patients who still smoke, pharmacotherapy to alleviate airway obstruction and dyspnea with beneficial sequelae like reduction of exacerbations and improvement in health status is the only established remedy at present.

No medication has shown potential to modify disease progression in COPD. For these reasons bronchodilator therapy is an important component of care. American (Celli, 1995/P95-4381), European (Siafakas, 1995/P95-3225), and international treatment guidelines (GOLD, Pauwels et al, 2001) all place bronchodilators as the foundation of their stepwise treatment algorithms. They are the only agents currently approved by the FDA for COPD treatment in the U.S.

Inhaled anticholinergic drugs such as ipratropium bromide and oxitropium bromide have had some three decades of use and have emerged as safe and effective agents in treating patients with COPD (Gross,1998/P89-0446; Feruson,1993/P93-0916; Disse, 2001). With their minimal gastrointestinal bioavailability, side effects have been limited, thus making anticholinergics established maintenance therapy in a disease associated with many comorbidities. The primary limitation of these agents is the need for frequent (i.e., four times daily) dosing and consequently appreciable variability from peak effect to trough before the next dose. With limited compliance, a patient may contribute to increased variability of airflow and a suboptimal level of disease control.

Tolerance to anticholinergics has not been described with ipratropium, oxitropium, or tiotropium. In fact, a meta-analysis comprising a large number of patients with COPD after 3-months of treatment showed an increased baseline and sustained daily response in contrast to a slight loss of response with short acting beta-agonist therapy (Rennard et al, 1996). Whereas the tertiary compound atropine, by systemic or inhaled route, has been shown to slow mucociliary clearance, this was not the case with N-quaternary anticholinergics, ipratropium or oxitropium (Disse, 2001).

Bronchodilator therapy should be as effective, long-lasting, stable and convenient as achievable, and the reasons above suggest that an improved approach would be a once-daily anticholinergic for COPD.

The pharmacological profile of tiotropium translates into prolonged and stable anticholinergic bronchodilation in patients with COPD. The duration of action for tiotropium supports once-a-day administration with a stable 24-hour profile of efficacy compared to q.i.d. administration for ipratropium. Significant and clinically meaningful relief of dyspnea was shown with several appropriate instruments for tiotropium. Reductions in exacerbations of COPD and improvements in measures of health status support the view that treatment with tiotropium provides significant benefit for patients.

Inhaled medications compare favorably to available systemic medications, i.e., theophyllines, but have more prominent side effects concerning gastrointestinal, central nervous system and cardiovascular reactions. With inhaled medications, many patients have difficulties using metered-dose inhalation aerosols correctly. This leads to reduced efficacy and contributes to non- compliance, especially if several daily inhalations are required. The HandiHaler® device, a dry powder inhaler for tiotropium, simplifies treatment for these patients since it does not require coordination of inspiration with actuation.

For these reasons, the preclinical and clinical profile of tiotropium offers significant and clinically meaningful benefit to patients with COPD. Approval of this medication in the U.S. will appreciably augment the armamentarium of physicians and help to overcome some of the limitations of currently available therapy. Availability of SPIRIVA® in a breath-actuated, easy-to-use delivery device simplifies COPD management, leading to improved control of COPD for many patients.

1.3 OVERVIEW OF SPIRIVA® CLINICAL DEVELOPMENT

The clinical development of tiotropium focused on treatment of patients with COPD. Phase 2 studies in asthma did not demonstrate efficacy, and for this reason Phase 3 studies have not been initiated. Safety data from the studies in asthma are included in the tiotropium safety database. As of the cut-off date of December 13, 2000, 31 clinical studies have been completed; 30 using single and multiple-dose administration of tiotropium at doses ranging from 0.02-288 mcg expressed as the cation, and one study using only placebo inhalation powder capsules.

Several formulations and devices were used in the clinical program. All Phase 3 pivotal studies were conducted using the final capsule formulation and the HandiHaler® inhalation device intended for marketing.

Eleven human pharmacology studies have been performed which include nine with healthy male volunteers, one with COPD patients and one with renally impaired patients and healthy volunteers.

Three Phase 2 single-dose studies and one Phase 2 multiple-dose, dose-ranging study (4 weeks) have been conducted in COPD patients.

The primary support for efficacy of tiotropium 18 mcg inhalation powder once-a-day is provided by six Phase 3 studies in patients with COPD, four 1-year (#114 and #115, placebo-controlled, conducted in the United States; #122A and #122B, ipratropium controlled, conducted in Belgium and The Netherlands) and two 6-month (#130 and #137, placebo- and salmeterol- controlled, conducted worldwide).

Five special studies served to provide special safety and efficacy information. These include a 6-week study comparing morning (a.m.) to evening (p.m.) tiotropium dosing with placebo and a mucociliary clearance study. Onset of steady state was evaluated and conducted as a subgroup in one center from Study #122A. A separate report was written on this subset of data. One study assessed the appropriateness of the inhalation device HandiHaler® for COPD patients who can generate only low inspiratory flow rates.

The clinical program included 4,124 subjects, including 224 healthy volunteers: 3,411 COPD patients, 471 asthma patients and 18 renally impaired patients. Of these subjects, 57 healthy volunteers, 1,723 COPD patients and 337 asthma patients (total of 2,117 subjects) were exposed to tiotropium by inhalation of the powder capsule formulation. There were 1,701 subjects exposed to the 18 mcg dose. Of this number, 47.6% were exposed to the drug for

more than 200 days and 33.6% for more than 330 days. Additional information regarding dose, extent of exposure and disposition is provided in Section 4.

1.4 OVERVIEW OF THE DEVICE: HANDIHALER® AND THE DRY POWDER FORMULATION

SPIRIVA® is administered by the HandiHaler®, a powder inhaler device consisting of molded plastic. It is a high resistance, breath-actuated, hand-held device. Individual medication-filled capsules are inserted by the patient into this device. The capsule is pierced by the patient by depressing a side button. Evacuation of the powder is achieved by the inspiratory flow generated by the patient. The patient's inspiratory flow vibrates the capsule and allows for dispersion of the powder into the airstream. In vitro studies have shown that there is evacuation of powder at flow rates as low as 20 L/min and studies in COPD patients have demonstrated that patients with a wide range of disease severity are able to generate the necessary flow rate (#132). The HandiHaler® is robust and easy to use. As a breath-actuated device it does not require special co-ordination of inhalation and actuation. These characteristics make the HandiHaler® an ideal delivery device for treatment of COPD patients, many of whom have difficulty coordinating the actuation-inhalation process. The drug-device combination system appears to be robust and an acceptable device for long-term use.

The capsules holding drug substance consist of a gelatin enclosure of 5.5 mg lactose carrier as diluent for the medication. In earlier studies the drug doses were expressed in terms of the salt/hydrate, i.e., tiotropium bromide monohydrate (22.5 mcg). In order to conform to more recent nomenclature, this was changed from the start of Phase 3 to drug doses expressed as the mass of the active entity in the molecule, i.e., tiotropium cation (18 mcg).

1.5 REGULATORY

1.5.1 Proposed Indication and Dosage and Administration

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.

The recommended dosage of SPIRIVA® is inhalation of the contents of one capsule, once daily, with the HandiHaler inhalation device.

1.5.2 Overview of Significant FDA Interactions During the Clinical Development of SPIRIVA®

The NDA was submitted on December 13, 2001 and accepted for filing on February 11, 2002. The initial IND submission was made on November 23, 1994. Clinical questions on the proposed Phase 2 dose-range study were raised during the IND review and in the IND acknowledgement letter. The overall study design and scope of the proposed dose-ranging study was considered acceptable following submission of complete responses to the clinical questions that arose during IND review.

An End-of-Phase 2 meeting was held on December 20, 1996. The purpose of this meeting was to reach agreement on the overall Phase 3 clinical development program. The dose selection of 18 mcg tiotropium was found acceptable and the overall study designs for the Phase 3 pivotal studies were agreed to, following BI implementation of specific FDA recommendations. Protocol amendments incorporating these recommendations were submitted to the IND. The key recommendations are summarized below:

- Trough FEV_1 at 13-weeks should be the primary endpoint in the pivotal studies.
- Real-time diary-records for patient assessment of pulmonary function should be provided to supplement the retrospective assessment done at study visits.
- In order to pursue a label claim of no significant difference between p.m. and a.m. dosing, the protocol of Study #123 should be amended from three to 6-weeks duration.
- In order to better assess cardiac effects occurring during oxygen desaturation with sleep in patients receiving p.m. dosing, BI should perform holter monitoring at baseline and for a full 24 hours post dose in one of the centers where Study #123 will be conducted.
- In order to demonstrate that patients with poor pulmonary function can generate adequate peak flow through the device, BI should conduct a small study in a subset of these patients.

A Pre-NDA clinical meeting was held on May 12, 1999. The primary objective of this meeting was to agree on the overall presentation of data from the pivotal studies in the NDA in support of tiotropium as an anticholinergic bronchodilator for use in patients with chronic obstructive pulmonary disease (COPD). Key issues are summarized below:

- The overall analysis plans for the efficacy and safety data from the two 1-year, placebo-controlled and the two 1-year, ipratropium-controlled studies were acceptable.

- Although the 1-year report is being submitted in the NDA, it was confirmed that trough FEV_1 at 13-weeks would still be the primary endpoint.

- A liver insufficiency study and specific drug interaction studies were not considered necessary on the basis of tiotropium's low bioavailability, renal excretion >70% and metabolism which is a minor pathway in tiotropium's excretion.

A Type B clinical meeting was held on July 24, 2000, related to BI's intention to secure an indication for tiotropium for relief of dyspnea, in addition to bronchodilation. Consistent with the Division's recommendations, protocol amendments for Studies #130 and #137 were submitted to the IND. Key protocol amendment changes and agency agreements relevant to the evaluation of dyspnea, are summarized below.

- FEV_1 trough response and TDI focal score were included as co-primary endpoints, spirometric comparisons to salmeterol were changed to a secondary endpoint.

- Superiority of tiotropium over placebo was to be established in trough FEV_1 response prior to comparing TDI focal scores between tiotropium and placebo.

- Sample size issues were amended to include a pre-definition of clinically meaningful difference for the responder analysis.

- Separate analysis for dyspnea were to be conducted for each study.

- The analysis was to include all patients in an Intent to Treat evaluation.

- BI chose to define subjects who demonstrated an increase of one unit or greater change in TDI as responders, BI needs to justify the clinical significance of this cut-off. In addition, the clinical significance of any difference demonstrated in the percentages of responders in each group needs to be justified. Validation data need to be provided for these definitions of minimal meaningful changes.

- To check for consistency of effects, BI will need to show that these changes in TDI are correlated to clinical improvements in the patients, as well as provide data on responder and mean values for dyspnea at all test days.

- Superiority of tiotropium with regard to dyspnea must be supported by other clinical data in the studies.

1.5.3 Non U.S. Marketing History

As of August 1, 2002, SPIRIVA® is being marketed in six countries. Provided below in TABLE 1.5.3:1 is a listing of countries, and their respective launch dates.

TABLE 1.5.3:1 Country Launch Dates as of August 1, 2002

Country	**Launch Date**
Denmark	June 2002
Finland	June 2002
Germany	June 2002
Netherlands	June 2002
Sweden	June 2002
Philippines	June 2002

As of August 1, 2002, SPIRIVA® has not been withdrawn from the market or rejected by any regulatory authority for safety issues.

2. CLINICAL PHARMACOLOGY AND BIOAVAILABLITY

2.1 PROGRAM OBJECTIVES

The clinical pharmacology program was designed to investigate the tolerability of tiotropium in healthy subjects, the onset of action and spirometric dose-response relationship in COPD patients as well as the pharmacokinetics in healthy subjects and COPD patients. A total of 21 clinical studies were performed with respect to clinical pharmacology. Pharmacokinetics have been examined in 600 subjects in 15 clinical studies (142 healthy males in Phase 1 and 434 patients in later Phases, including 166 females). Eighteen subjects with mild to severe renal impairment were studied in comparison to six healthy male subjects.

A recent study (report included in the four-month safety update), investigated the effect of a block of renal cation secretion by cimetidine (6 subjects) and ranitidine (12 subjects) on tiotropium pharmacokinetics.

2.2 PHARMACODYNAMICS

Pharmacologic studies profile tiotropium as a specific, highly potent, competitive (reversible) muscarinic antagonist at all subtypes of muscarinic receptors M_1 to M_5, demonstrating very slow dissociation especially from M_3 receptors. Single-dose studies in mild asthma (#121) as well as single-dose studies in COPD patients (#119, #120) revealed clinically significant bronchodilation measured as FEV_1 response and approximate dose ordering. The duration of action exceeded 24 hours.

The multiple-dose, dose-ranging study was conducted over a period of 4 weeks in order to assure evaluation at steady state (#108). This was a parallel group study evaluating 4.5, 9, 18, and 36µg tiotropium dry powder (via FO2 device, a precursor device to HandiHaler® with identical properties) relative to placebo in 169 COPD patients. The inclusion/exclusion criteria were identical to the 1-year studies (see Section 3.2). The primary endpoint was the trough FEV_1, and the reasoning for this choice of endpoint to support 24-hour efficacy is outlined in Section 3.3. Trough was defined as the lung function measurement prior to the daily dose.

Trough and peak FEV_1 values were significantly superior following all doses of tiotropium relative to placebo starting at the first week and maintained through the 4 weeks of observations. Approximate dose ordering was numerically evident; however, the dose-response curve was quite flat in the dose-range investigated. An E_{max} model fitted to the

steady-state trough FEV_1 values (all measurements from week two to four) allowed estimation of an E_{max} value of 0.138 L (95% CI: 0.075-0.201). In this presentation of the data 9 mcg tiotropium provided 75% of the maximum effect, 18 mcg: 86%, and 36 mcg: 92% of the maximum effect. The evaluation supports the choice of 18 mcg for Phase 3 because it reaches near 90% of maximum efficacy, while doubling of the dose (36 μg) achieves only a minimal further increase in efficacy. PEFR response was superior for all doses of tiotropium relative to placebo. Following cessation of therapy, PEFR responses gradually returned to baseline over the 3-week post-treatment observation period, indicating that there was no rebound.

Pharmacokinetic steady state was reached in approximately three to four weeks, with plasma concentrations showing two to three-fold accumulation versus first dose. The onset and steady state of the pharmacodynamic effect was evaluated by spirometric measurements by one center in Phase 3 study #122A as detailed in Section 5.4.1. The onset of a clinically and statistically significant increase in trough FEV_1 response occurred within 24 hours after the first dose of tiotropium. Pharmacodynamic steady state was achieved within 1 week of treatment and the majority of the effect was seen within the first 3 days of therapy.

2.3 PHARMACOKINETICS AND METABOLISM

Tiotropium is a sparingly water soluble ester between the N-quaternary alcohol N-methylscopin (also the main metabolite) and dithienylglycolic acid. The bromide monohydrate is the salt form used. The doses and concentrations always refer to the cation, tiotropium. The bioanalytical assay (HPLC-MS/MS) typically had a limit of quantification of 5 pg/mL, which allowed the quantification of the renal excretion of tiotropium and its plasma concentrations for 2 to 4 hours after doses of 18 mcg by dry powder inhalation. Trough concentrations following multiple doses of 18 mcg once daily were mostly below the limit of quantification, but they could be inferred from 36 mcg doses and are expected in the range of 2-4 pg/mL. Many basic pharmacokinetic data were therefore obtained with higher doses than the 18 mcg proposed as the therapeutic dose.

Absorption: As an N-quaternary drug, tiotropium is poorly absorbed after administration of an oral solution and its bioavailability is negligible (2-3%). Thus, most of the 19.5% absolute bioavailability observed after dry powder inhalation is due to absorption from the lung. Peak plasma concentrations were regularly observed in the first collected blood samples (5 minutes after inhalation) and ranged between 15 and 20 pg/mL in COPD patients in steady state after 4 weeks. The urinary excretion half-life indicates an expected steady state to be reached after about four weeks of therapy. This was confirmed by unchanged plasma concentrations and

urinary excretion values from 4 weeks onwards. However, high intra- and inter-individual variability with inhalation precludes differentiation between pharmacokinetic data obtained after 2 weeks and 4 weeks.

Tiotropium plasma concentrations decline rapidly in a multicompartmental manner and fall below the limit of quantification 2 to 4 hours after inhalation of 18 mcg. They showed no relevant deviation from dose-proportionality and thus pharmacokinetic data obtained with higher doses can be extrapolated to doses of 18 mcg.

Distribution: Tiotropium has a high volume of distribution of 32 L/kg, which indicates extensive binding to tissue. Plasma protein binding is rather low at 72% and does not influence the pharmacokinetics of tiotropium.

Metabolism: Tiotropium is mainly excreted unchanged in urine (73.6 % after an intravenous dose). The ester is cleaved nonenzymatically, although there may be some protective effect of tissue protein binding. Total metabolism has only a minor contribution to the clearance of tiotropium (~20% after an intravenous dose; ~30% after inhalation). In vitro experiments with liver microsomes confirmed the close similarity of the qualitative metabolic pattern in rat and man; however, the extent of metabolism was much higher in the rat. The dithienyl moiety is initially oxidized by cytochrome P450 and then conjugated with glutathione. The enzymatic metabolism can be inhibited by the CYP 2D6 inhibitor quinidine (major) and also by the CYP 3A inhibitors ketoconazole and gestodene; thus CYP 2D6 and CYP 3A4 are involved in tiotropium metabolism. The contribution of CYP 2D6 was recently confirmed in a clinical study after intravenous infusion (study #222). In this study, four poor metabolizers of CYP 2D6 had a 33% higher urinary excretion compared to extensive CYP 2D6 metabolizers. Tiotropium itself did not inhibit CYP 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A, even in high supratherapeutic concentrations. Thus a relevant influence of tiotropium on the metabolism of other drugs, or of other drugs on tiotropium, is not expected.

Elimination: Urinary excretion of unchanged substance accounted for 73.6 % of an intravenous tiotropium dose. The renal clearance (669 mL/min) exceeded the creatinine clearance (118 mL/min), indicating secretion of tiotropium by a renal cation transporter. Tiotropium plasma concentrations declined in a multicompartmental manner (four compartment model) and the terminal elimination half-life of urinary excretion was 5 to 7 days. This long half-life may be due to back diffusion from peripheral tissues. The total clearance was 880 mL/min after intravenous infusion.

2.4 SPECIAL POPULATIONS

Elderly: There was no relevant increase in tiotropium plasma concentrations in COPD patients >70 years despite a decrease in renal excretion from 1.97% of dose to 1.42 % of dose (Ae_{0-4h}). This was confirmed by data from the 1-year study (#114).

Renal insufficiency: As expected, tiotropium plasma concentrations (AUC_{0-4h}) rose by 39%, 81% and 94% in patients with mild (CL_{CR} 50-80 mL/min), moderate (CL_{CR} 30-50 mL/min) and severe renal insufficiency (CL_{CR} <30 mL/min). The doubling of tiotropium plasma concentrations was confirmed by data from the 1-year, placebo-controlled study (#114).

Liver insufficiency: The pharmacokinetics of tiotropium in patients with liver insufficiency were not studied, because of the minor contribution of metabolism to tiotropium clearance.

2.5 INTERACTIONS

Relevant interactions due to inhibition or induction of tiotropium metabolism are not expected due to the minor contribution of metabolism to the tiotropium clearance. Vice versa, tiotropium did not inhibit CYP 450 isoenzymes. The blockade of the main clearance pathway, the secretion into urine by cation transporters, was studied in a recent clinical interaction study with supratherapeutic doses of cimetidine (400 mg t.i.d) and maximum doses of ranitidine (300 mg once daily) (#222). The clinically relevant dose of ranitidine had no effect, and cimetidine increased tiotropium plasma concentrations by only 20%.

2.6 CLINICAL PHARMACOLOGY CONCLUSIONS

The clinical pharmacology of tiotropium was investigated in 22 clinical studies comprising healthy subjects and patients with COPD (including one study in asthma). The study population also included subjects with renal insufficiency. Tiotropium was administered as intravenous infusion, as oral solution, and primarily by oral inhalation. Further studies describe specific topics such as the effect of administration to the eyes and the onset of pharmacodynamic steady state.

- Tiotropium demonstrated bronchodilation measured by FEV_1 following single and multiple dosing in COPD patients. An approximate dose-dependent acute bronchodilator response was consistently demonstrated and the duration of action exceeded 24 hours. With multiple dosing the dose-response curve became very flat with no significant distinction between doses, allowing selection of 18 mcg as the dose to be investigated in Phase 3.

- The majority of the steady-state pharmacodynamic effect was achieved within a few days of treatment and pharmacodynamic steady state was reached within 1 week of dosing. There was significant and clinically meaningful bronchodilation at the end of the dosing interval, i.e., 24 hours after administration of the drug.

- Tiotropium did not produce any effect on routinely measured safety and tolerability parameters, such as vital signs, ECG or clinical laboratory values.

- Decreased salivary secretion was observed following multiple daily dosing in healthy volunteers, representing the most sensitive extra-pulmonary anticholinergic effect. Pupil diameter was not affected. Consistent with this, dry mouth was reported as an adverse event following multiple, once-daily dosing in both healthy subjects and patients. The reduced salivary secretion, as well as reported dry mouth, appeared to be dose-related.

- The absolute bioavailability of tiotropium after dry powder oral inhalation is 19.5%, but as low as 2-3% after oral administration. It is estimated that a minimum of 17% of an inhaled tiotropium dose is deposited in the lungs.

- The first collected blood samples five minutes after inhalation of 18 mcg tiotropium regularly show the highest tiotropium plasma concentrations (between 15 and 20 pg/mL) at steady state following multiple once-daily administration.

- The drug is extensively bound to tissue and shows a volume of distribution of 32 L/kg. Plasma protein binding is 72%.

- Tiotropium is mainly eliminated by renal excretion (73.6 % of the dose as parent compound) with its renal clearance exceeding the creatinine clearance. A certain proportion of drug is degraded by non-enzymatic ester cleavage and by enzymatic metabolism (~20 %) via CYP 2D6 and CYP3A with subsequent glutathione conjugation.

- The terminal elimination half-life is between 5 and 7 days; total clearance is 880 mL/min.

- The major portion of pharmacokinetic steady-state concentrations in plasma is achieved within 14 days of once-daily inhalation of 18 mcg tiotropium. Steady state is achieved within 4 weeks with a two to threefold accumulation of tiotropium plasma concentrations versus first dose.

- Steady-state trough plasma concentrations after inhalation of 18 mcg tiotropium are regularly below or in the range of the limit of quantification (~2-4 pg/mL). There are

much higher concentrations in lung tissue after inhalation, which allows effective receptor occupation in the target tissue.

- As expected for mainly renally eliminated drugs, there was an increase in drug plasma concentrations in patients with moderate to severe renal dysfunction as well as, a slight increase in patients at advanced age.
- An interaction study with a blocker of renal cation secretion by supratherapeutic cimetidine doses (400 mg t.i.d.) revealed not more than a 20% increase of the tiotropium AUC following i.v. administration. Maximum clinically used doses of ranitidine had no effect.
- Drug-drug interactions by tiotropium are not expected due to the low dose and concentrations of tiotropium, its proven absence of cytochrome P450 interaction, and the low contribution of enzymatic metabolism to the clearance of tiotropium.

3. DESIGN OF PIVOTAL STUDIES

3.1 INTRODUCTION AND OVERVIEW OF STUDIES

The designs of the six pivotal clinical Phase 3 studies in patients with COPD are summarized below.

Study	Objective	Treatment Duration (weeks)	Randomised Patients
#114	long-term efficacy and safety vs. placebo	49	470
#115	Same as #114	49	451
#122A	long-term efficacy and safety versus Atrovent (ipratropium) MDI	52	288
#122B	Same as #122A	52	247
#130	long-term efficacy and safety vs. placebo and Serevent (salmeterol) MDI	24	623
#137	Same as #130	24	584

The four 1-year studies randomized a total of 1,456 COPD patients. The two 6-month studies randomized an additional 1,207 patients.

3.2 PROTOCOL AND DESIGN OVERVIEW OF THE SIX PIVOTAL PHASE 3 STUDIES

The purpose of the six long-term, multi-center, randomized, double-blind, (double-dummy in ipratropium-controlled and placebo- and salmeterol-controlled studies), parallel group studies was to evaluate the long-term safety and efficacy of the 18 mcg tiotropium powder capsules orally inhaled once daily via the HandiHaler® in patients with COPD. All six studies used similar protocols and inclusion and exclusion criteria.

The two placebo-controlled studies (#114, #115) used an identical protocol. Study #114 included additional pharmacokinetic assessments. These studies were conducted in the U.S. More patients received tiotropium since a 3:2 randomization was used.

The two ipratropium-controlled studies (#122A, #122B) used an identical protocol and were conducted in The Netherlands and Belgium. Atrovent 40 mcg (2 puffs of 20 mcg each) by

inhalation aerosol taken four times daily was used as the active control. More patients received tiotropium since a 2:1 randomization was employed.

The two placebo- and salmeterol-controlled 50 mcg, 6-month studies (#130, #137) used similar protocols, the only difference being the duration of pulmonary function testing on clinic visit days (twelve hours post drug administration in #130, 3 hours in #137). These studies were conducted in 18 countries. Randomization was on a 1:1:1 basis.

All COPD long-term studies were based on a core protocol with inclusion and exclusion criteria that aimed to recruit a homogenous population of COPD patients who were relatively stable with, on an average, moderately severe airway obstruction. The criteria included forced expiratory volume in 1 second (FEV_1) ≤65% of predicted normal (≤60 % in the 6-month studies) and FEV_1 ≤70% of FVC. The predicted normal FEV_1 was based on the Morris equation for the 1-year placebo-controlled studies and the European Community for Coal and Steel (ECCS) equation for the ipratropium-controlled and the placebo- and salmeterol-controlled studies. Patients were required to be 40 years of age or older and have a smoking history of more than 10 pack-years. Patients with a history of asthma, allergic rhinitis or atopy, or with a total blood eosinophil count above 600/ mm^3 (≥400/mm^3 (males) or ≥320/mm^3 (females) in the ipratropium-controlled studies) were excluded. Also excluded were patients with significant disease other than COPD. A significant disease was defined as a disease which in the opinion of the investigator may either put the patient at risk because of participation in the study, or a disease which may influence the results of the study or the patient's ability to participate in the study. Specifically excluded were patients with symptomatic prostatic hypertrophy or bladder neck obstruction, narrow angle glaucoma, heart failure leading to hospitalization within the past 3 years, myocardial infarction within the past year or with cardiac arrhythmia requiring drug treatment.

Following an initial screening and a 2 week baseline period, patients were randomized into the double-blind portion of each study. Pulmonary function testing was conducted at baseline and after 1, 7, 13, 25, 37 and 49 weeks of therapy in the 1-year placebo-controlled studies, 1, 7, 13, 26, 39 and 52 weeks of therapy in the ipratropium-controlled studies, and 2, 8, 16 and 24 weeks in the placebo- and salmeterol-controlled studies. The testing occurred at 1-hour prior to and just prior to drug administration and at 30, 60, 120 and 180 minutes post-dosing. Additional hourly testing was conducted for up to 6-hours post-dosing in the ipratropium-controlled studies for the first 13 weeks and for 12 hours in Study #130 (placebo-/salmeterol-controlled). Patients returned for a final clinic Visit 21 days after discontinuation of study drug. The patients continued to record peak expiratory flow rate

(PEFR) measurements and concomitant therapy use during the 21 day, post-study drug interval.

3.3 EFFICACY MEASURES, PRIMARY AND SECONDARY ENDPOINTS IN THE PIVOTAL STUDIES

3.3.1 FEV_1 Trough, Peak and Average as Well as Other Spirometry Endpoints

FEV_1 was chosen as the primary efficacy measure due to its wide acceptance as a reproducible and objective indicator of disease severity and prognosis in COPD (Fletcher and Peto, 1977; ATS 1991; Crapo 1981; Kanner 1996).

To establish the 24-hour duration of the bronchodilator efficacy of tiotropium, the trough FEV_1 response after 13 weeks of treatment was chosen as the primary endpoint in the 1-year studies and as co-primary endpoint in the 6-month studies at the end of the dosing period. Trough FEV_1 was defined as the mean of the two FEV_1 readings at the end of the dosing interval, at approximately 23 to 24 hour post-drug administration for tiotropium. Trough FEV_1 response was defined as change from baseline in trough FEV_1. Baseline FEV_1 was calculated as the mean of the two FEV_1 readings measured in the morning of the randomization visit prior to the first administration of study medication. Trough FEV_1-response reflects the remaining and stable bronchodilator drug activity at the end of the dosing interval.

The secondary FEV_1 endpoints included other timepoints for trough FEV_1 measurement, as well as peak and average response post administration of drug or comparator. Peak indicates maximum activity of drug action, but is superimposed with the rise to maximum of circadian variability. Average reflects the measurement period mean. Similar endpoints were also evaluated for the forced vital capacity (FVC). FEV_1 and FVC were assessed during clinic visits, whereas morning and evening peak expiratory flow rates (PEFR) were measured by patients at home and were computed as weekly means to compare across treatment groups.

3.3.2 Dyspnea, Baseline/Transition Dyspnea Index (BDI/TDI) and Validation

The Instrument

As outlined in Section 1, dyspnea is the key symptom of COPD and is most often why patients with COPD seek medical attention. The baseline dyspnea index/transition dyspnea index (BDI/TDI, Mahler et al, 1984) was used to assess the effect of treatment on relief of dyspnea. The BDI was developed to rate the severity of dyspnea at a single state and the TDI to denote changes from that baseline. The scores in both indices depend on ratings for three different categories: functional impairment, magnitude of task, and magnitude of effort. The BDI was administered at study baseline. Dyspnea was rated in five grades from 0 (severe) to 4 (unimpaired) for each category and added to form a BDI focal score (range 0 to 12). The drug treatment period defined the transition period and changes in dyspnea from baseline recorded as TDI at each subsequent visit. The changes were rated by seven grades, ranging from –3 to +3 where negative numbers indicated deterioration, 0 was no change, and positive numbers indicated improvement. The ratings for the three categories were added to form the TDI focal score (-9 to +9).

Validity of Instrument

The BDI and TDI have been validated over the course of its development and as validity has been confirmed with the tiotropium database. For example, inter-rater reliability has been documented along with construct validity by Eiken et. al. (1995). Additionally, concurrent validity of the BDI was demonstrated by Mahler and Well (1998) with their correlations to the Medical Research Council (MRC) questionnaire and the Oxygen Cost Diagram.

The construct and concurrent validity of the BDI and TDI have been confirmed with the tiotropium development database FIGURE 3.3.2:1 shows the association of TDI focal score with the change at the end of one year in other respiratory outcome measures such as SGRQ (St. George's Respiratory Questionnaire) domains, FEV1 response, dyspnea rating based on patients daily records (Dyspnea Diary) and physician global evaluation (PGE). The construct validity was demonstrated by significant correlations ($p<0.05$) between BDI and other baseline measures and between TDI and changes in other measures at the end of 1-year (TABLE 3.3.2:1). Concurrent validity in the tiotropium database was observed by the significant correlation between BDI/TDI and other dyspnea measures such as the dyspnea diary responses (TABLE 3.3.2:2).

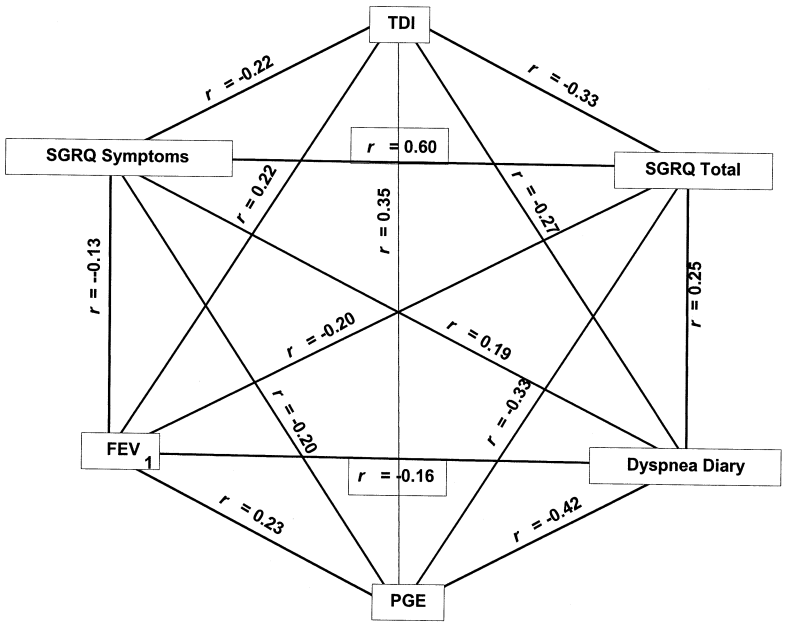


FIGURE 3.3.2:1 The Association of TDI Focal Score with changes in other Respiratory Outcome Measures over the 1-Year Placebo-Controlled Study (Studies #114 and #115), Treatment Groups Combined

TABLE 3.3.2:1 Construct Validity of BDI/TDI in Tiotropium Database

	FEV_1	**SGRQ**	**PGE**
BDI (cross-sectional)	r = 0.26 p<0.05	r = -0.65 p<0.05	r = 0.43 p<0.05
TDI (longitudinal)	r = 0.22 p<0.05	r = -0.33 p<0.05	r = 0.35 p<0.05

Data Source: Studies #114 and #115. Treatment groups combined.

TABLE 3.3.2:2 Concurrent Validity of BDI/TDI in Tiotropium Database

	Dyspnea Diary	**SGRQ Symptom**	**SGRQ Activity**
BDI (cross-sectional)	r = -0.50 p<0.05	r = -0.33 p<0.05	r = -0.66 p<0.05
TDI (longitudinal)	r = -0.27 p<0.05	r = -0.22 p<0.05	r = -0.27 p<0.05

Data Source: Studies #114 and #115. Treatment groups combined.

An improvement by one unit or more in TDI focal score is considered clinically relevant because it describes a perceivable improvement in at least one of the three components of the TDI, functional impairment, magnitude of task or magnitude of effort (Mahler et al, 1999, Witek & Mahler, 2002). For example, an improvement of "+1" in the functional impairment domain of the TDI describes a patient who is "*Able to return to work at reduced pace or has resumed some customary activities with more vigor than previously due to improvement in shortness of breath.*" The meaningfulness of a TDI response was supported by related measures. For example, when the entire trial cohort was categorized by those improving breathlessness (TDI focal score at end of study ≥+1 unit) vs. patients not achieving this level of improvement, those improving were found to use significantly less albuterol (FIGURE 3.3.2:2), have improved health status (TABLE 3.3.2:3) and have fewer exacerbations (TABLE 3.3.2:4).

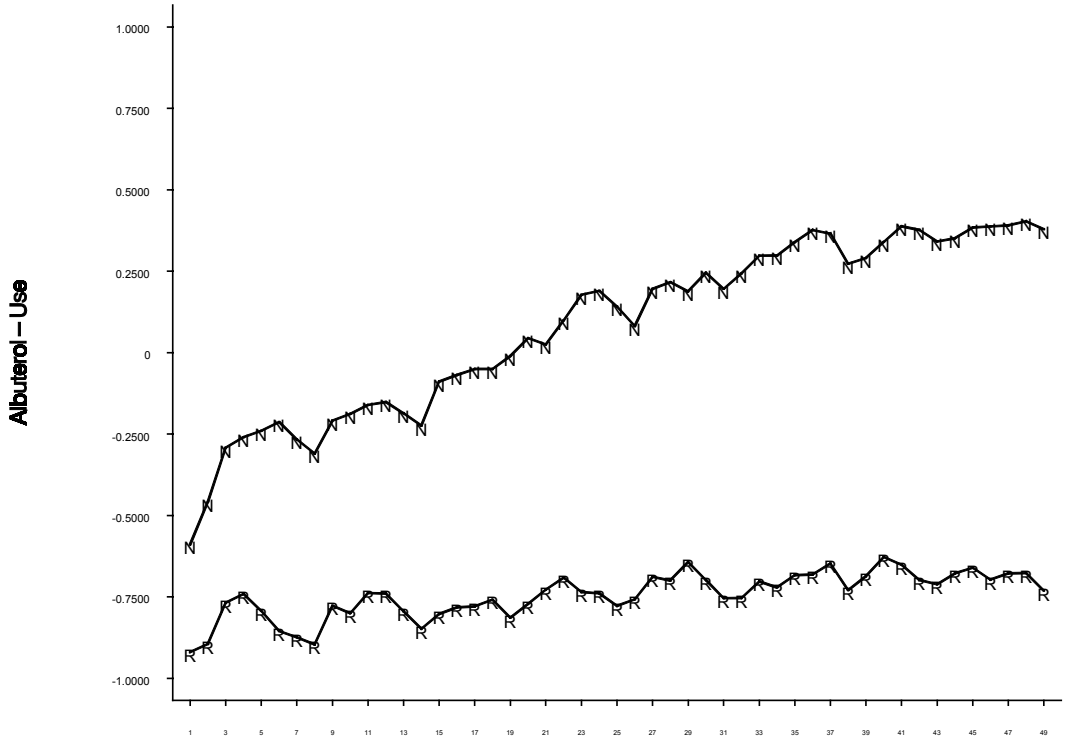


FIGURE 3.3:2:2 Mean Change in Albuterol Use Compared to Baseline in the Placebo-Controlled Trial Cohort. Those showing improved breathlessness on the TDI (R) used significantly less supplemental albuterol than those not improving (N). Albuterol use is expressed in changes in doses based on weekly averages.

TABLE 3.3.2:3 SGRQ Total Score in Subjects Improving vs. Not Improving Breathlessness Based on TDI.

SGRQ total score at last visit	***N***	**Mean ± SE**
All Patients with Improved Breathlessness[1]	323	-6.52 ± 0.67*
All Patients with No Change or Worsening Breathlessness[2]	501	0.74 ± 0.50

*P <0.05 for difference in 1 and 2 N includes both tiotropium and placebo patients.
[1] = TDI focal score ≥1 at the end of the study
[2] = TDI focal score <1 at the end of the study
(from: Witek and Mahler, J Clin Epidemiol 2002, in press)

TABLE 3.3.2:4 Exacerbation Rate in Subjects Improving vs. Not Improving Breathlessness Based on TDI.

Exacerbations (% Patients with at least one event)	***N***	**%**
All Patients with Improved Breathlessness[1]	326	34*
All Patients with No Change or Worsening Breathlessness[2]	506	44

* P <0.01 for difference in 1 and 2.
[1] = TDI focal score ≥1 at the end of the study
[2] = TDI focal score <1 at the end of the study
(from: Witek and Mahler, J Clin Epidemiol 2002, in press)

Improvements or worsenings of score can be expressed as either proportion of patients achieving meaningful changes (i.e., at least one unit) or as mean changes. When expressed as proportions, it becomes clear what the data mean clinically, as it is described explicitly how many patients have achieved that specific treatment goal.

Tiotropium Evaluation

Dyspnea was assessed as a secondary endpoint by TDI focal score in the 1 year studies. This was supported by investigators' assessment of patients' COPD symptom scores, number of nighttime awakenings' scores recorded in patient daily records (for first 13 weeks only in

1-year, placebo-controlled studies), use of concomitant respiratory medications, daily albuterol use, energy-fatigue questionnaires (only in 1-year studies) and physician's global evaluations (measured only in placebo-controlled studies).

Consistently positive results for relief from dyspnea in the 1 year studies led Boehringer Ingelheim to reconsider the focus of evaluations in the still ongoing 6-month studies. After discussion with the FDA on July 24, 2000 with regard to supporting a dyspnea indication, Boehringer Ingelheim agreed to include dyspnea as a co-primary endpoint to trough FEV_1 in the two independent 6-months studies to ensure that all regulatory requirements for an indication "treatment of dyspnea associated with COPD" would be met. Specifically, the percentage of patients with an improvement of one unit or more in TDI focal score from baseline (percent of responders) in comparison between tiotropium and placebo at the end of the dosing interval was defined as the co-primary endpoint. Improvement in TDI focal score of one unit or more was considered a priori as clinically meaningful as outlined above. In addition, the mean improvement in TDI focal score versus placebo was to be recorded to support the endpoint defined above. Data in support of the improvements in dyspnea were observed in several secondary endpoints including general COPD symptom score assessment, supplemental albuterol use, and physician's global evaluation.

3.3.3 Secondary Endpoints

Health status

Disease-specific health related quality of life (HRQoL) was assessed with the St. George's Respiratory Questionnaire (SGRQ), with the impact domain being the primary analysis in the 1-year studies and the total score in the 6-month studies. A change from baseline by four units was defined by the author as a clinically meaningful change. The 36 Item Short-Form Health Survey (SF-36) instrument was utilized for a generic quality of life assessment.

COPD Exacerbations

A COPD exacerbation was defined as a complex of respiratory symptoms reported as adverse events with a duration of three or more days. In the 1-year studies evaluation of exacerbations including pneumonia (all exacerbation related endpoints) was of an exploratory nature, whereas it was prespecified as a secondary endpoint for pooled analysis in the two 6-month studies. Several ways to evaluate exacerbations were prespecified to compare across treatment groups: the number of patients with at least one COPD exacerbation, time to first

exacerbation, number of COPD exacerbations and exacerbation days per number of patient days of treatment exposure.

Peak Expiratory Flow

Subjects measured morning and evening peak expiratory flow rate (PEFR) with a hand-held electronic or mechanical peak flow meter and recorded the L/min electronically or on their personal diary card. The weekly means were evaluated.

Rescue medication use

All subjects were given albuterol MDIs for use as needed during the study. Subjects recorded the number of doses (1-year, placebo-controlled studies) or inhalations (ipratropium-controlled and placebo- and salmeterol-controlled studies) of albuterol over the previous 24-hours on their personal diary cards.

Nighttime Awakenings Requiring Albuterol

Subjects also recorded the number of nighttime awakenings due to symptoms requiring the use of albuterol that they experienced during the previous night on their personal diary card in the first thirteen weeks of the 1-year studies.

3.4 SAFETY CRITERIA

For analysis of safety, each set of replicate studies was always analyzed as a package. Adverse events were reported at each visit in response to the question "How have you felt since your last visit?" The event, date of onset, end date, intensity of the event, treatment required for the event, the investigator's assessment of whether the event was possibly related to the study drug, action taken with the study drug and outcome of the event were recorded on the CRF. The terms used by the investigators to report adverse events were classified using BI-WHO-ARTL in order to group related terms, allowing a true occurrence rate to be obtained. The respiratory system was additionally divided into upper and lower respiratory system disorders by preferred term as determined by the clinical monitor.

Fluctuations in the patient's COPD symptoms (wheezing, shortness of breath, coughing and tightness of the chest) were tracked separately by the patient on a daily basis. At each visit throughout the study, after reviewing the patient's condition and requirement for rescue albuterol since the previous visit, the severity of these symptoms was summarized on the CRF. Any worsening of these symptoms was recorded as an adverse event only if additional

medication was required, the study drug was discontinued, it met the requirements for a serious event, or the patient showed clear deterioration from baseline.

Laboratory tests were performed on all patients at baseline and at 3-month intervals throughout the treatment period. The tests, including hematology, clinical chemistries, and urinalysis, were performed by a central laboratory. A twelve-lead ECG was performed at the same intervals as the laboratory tests. Any significant abnormalities at baseline were recorded on the medical history form and any new or worsening conditions during the study were recorded as adverse events.

Vital signs were measured at the screening visit and on test days at the same intervals as, and just prior to, the pulmonary function testing. In the 6-month studies laboratory testing, ECGs and physical examinations were conducted at baseline and at the final visit only.

3.5 STATISTICAL METHODS

The two placebo-controlled, 1-year studies used an identical protocol. Data from these two studies were analyzed separately, but also pooled and analyzed as one combined study. Similarly, the two identical ipratropium-controlled 1-year studies were analyzed separately and pooled as one combined study. Analysis of covariance with baseline as a covariate was used as statistical model. The intention-to-treat principle to include all randomized patients if at all possible was used in all efficacy analyses. Only those patients who did not have baseline data or data following the initial dose were excluded from the analysis.

TABLE 3.5:1 Overview of Pivotal Phase 3 Studies: Primary Endpoint and Secondary Endpoints

Attributes	**Supporting study**	**Primary endpoint at specified timepoint; analysis method**	**Secondary endpoints; monitored over the duration of treatment; analysis method**
Primary: Bronchodilator efficacy with q.d. dosing vs. placebo and Atrovent **Supportive:** Dyspnea Health status Reduction in rescue medication Reduction in exacerbations	#114 #115 #122A #122B	**Prespecified:** Trough FEV_1 response at the end of 13 weeks in comparison to placebo or Atrovent; analysis of covariance with terms for treatment, center and baseline as covariate	**Prespecified:** **Bronchodilator efficacy, once-daily dosing:** Trough FEV_1 response at other timepoints, average and peak FEV_1 response: ANCOVA Trough, average and peak FVC response: ANCOVA Mean weekly morning and evening PEFRs: ANCOVA **Dyspnea:** TDI: ANCOVA **Health status:** SGRQ: ANCOVA (4 units change in Impact score as clinically meaningful difference) SF 36: physical dimensions as supportive of SGRQ used as exploratory measure: ANCOVA **Reduction in rescue medication:** Amount of albuterol therapy during treatment (weekly means): ANCOVA **Exacerbations:** Number and length
Exacerbations and Hospitalizations	Combined Analysis of replicate studies #114/#115 and #122A/#122B		**Exploratory:** As prespecified for analysis of #130/#137

TABLE 3.5:1 (continued) Overview of Pivotal Phase 3 Studies: Primary Endpoint and Secondary Endpoints (Page 2 of 2)

Attributes	Supporting study	Primary endpoint at specified timepoint; analysis method	Secondary endpoints; monitored over the duration of treatment; analysis method
Primary: Bronchodilator efficacy and relief of dyspnea with q.d. dosing vs placebo **Supportive:** Health status Reduction in rescue medication Comparison to salmeterol Reduction in exacerbations and hospitalizations	#130 #137 6 mo combined studies	Co-primary endpoints: Trough FEV_1 response (ANCOVA analysis as in 1-year studies) and Mahler Transitional Dyspnea Index (TDI) focal score at 6-months vs placebo (TDI focal score ≥1 from baseline was pre-specified as clinically meaningful improvement and responder analysis based on this criterion was pre-specified as primary analysis: logistic regression)	**Prespecified:** **Bronchodilator efficacy, once daily dosing:** Trough FEV_1 response at other timepoints, average and peak FEV_1 response: ANCOVA Trough, average and peak FVC response: ANCOVA Mean weekly morning and evening PEFRs: ANCOVA **Health status:** SGRQ: ANCOVA (4 units change in Total score as clinically meaningful difference) **Reduction in rescue medication:** Weekly mean of numbers of puffs per day of PRN- albuterol use; ANCOVA **Exacerbations and Hospitalizations:** It was pre-specified that the analysis would be conducted based on the combined data from the two 6-month studies. Kaplan-Meier estimates for COPD exacerbations over treatment period Number (proportion) of patients with at least one COPD exacerbation and number of patients with at least one hospitalization associated with COPD exacerbation during treatment period: logistic regression Time to first COPD exacerbation and time to first hospitalizations associated with COPD exacerbations: logrank test Number and number of days of COPD exacerbations and hospitalizations associated with COPD exacerbations per extent of exposure: Wilcoxon-Mann-Whitney test.

4. STUDY POPULATION OF PIVOTAL CLINICAL STUDIES

4.1 PATIENT PARTICIPATION

The tables below summarizes patient participation for the randomized population in the six pivotal studies. Descriptive statistics is used to describe differences.

TABLE 4.1:1 Patient Participation in Absolute Numbers and (%) in 1-Year Placebo- and Ipratropium-Controlled Studies

	#114		#115	
	Tiotropium	**Placebo**	**Tiotropium**	**Placebo**
Patients randomized	**N=279**	**N=191**	**N=271**	**N=180**
Completed (%)	235 (84.2)	139 (72.8)	212 (78.2)	129 (71.7)
Discontinued because of:				
Adverse event total (%)	23 (8.2)	26 (13.6)	30 (11.1)	25 (13.9)
Lack of efficacy (%)	7 (2.5)	13 (6.8)	6 (2.2)	13 (7.2)
Administrative (%)	14 (5.0)	12 (6.3)	15 (5.5)	10 (5.6)
Other (%)	0 (0.0)	1 (0.5)	8 (3.0)	3 (1.7)

	#122A		#122B	
Patients randomized	**Tiotropium**	**Ipratropium**	**Tiotropium**	**Ipratropium**
	N=191	**N=97**	**N=165**	**N=82**
Completed (%)	162 (84.8)	78 (80.4)	140 (84.8)	63 (76.8)
Discontinued because of:				
Adverse event total (%)	22 (11.5)	12 (12.4)	14 (8.5)	11 (13.4)
Lack of efficacy (%)	3 (1.6)	1 (1.0)	0 (0.0)	2 (2.4)
Administrative (%)	2 (1.0)	3 (3.1)	8 (4.8)	4 (4.9)
Other (%)	2 (1.0)	3 (3.1)	3 (1.8)	2 (2.4)

A total of 921 patients (550 on tiotropium and 371 on placebo) were randomized in the 1-year, placebo-controlled studies using a 3 to 2 allocation ratio for tiotropium and placebo to achieve a greater exposure for tiotropium. As evaluated by combined analysis, a greater percentage of patients ($p<0.05$, Fisher's Exact test) in the tiotropium group (81.3%) completed all visits compared to those in the placebo group (72.2%). Fewer patients ($p<0.05$, Fisher's Exact test) in the tiotropium group failed to complete due to adverse events (9.6%) and lack of efficacy (2.4%) than in the placebo group (13.7% and 7.0%, respectively).

A total of 535 patients (356 on tiotropium and 179 on ipratropium) were randomized in the 1-year, ipratropium-controlled studies using a 2 to 1 allocation ratio for tiotropium and ipratropium. The two replicate studies #122A and B appear to show one difference in that the

number of patients who discontinued because of an adverse event were similar between the tiotropium and ipratropium groups in Study #122A (11.5 versus 12.4 %), whereas the tiotropium group had a lower drop-out rate in Study #122B (8.5 versus 13.4 %).

TABLE 4.1:2 Patient Participation in Absolute Numbers and (%) in 6-Month, Placebo- and Salmeterol-Controlled Studies

	#130			#137		
	Tiotropium	**Placebo**	**Salmeterol**	**Tiotropium**	**Placebo**	**Salmeterol**
	N=209	**N=201**	**N=213**	**N=193**	**N=199**	**N=192**
Completed (%)	184 (88.0)	145 (72.1)	177 (83.1)	156 (80.8)	152 (76.4)	152 (79.2)
Discontinued because of:						
Adverse event total (%)	12 (5.7)	39 (19.4)	29 (13.6)	18 (9.3)	28 (14.1)	31 (16.1)
Administrative (%)	11 (5.3)	14 (7.0)	7 (3.3)	15 (7.8)	13 (6.5)	8 (4.2)
Other (%)	2 (1.0)	3 (1.5)	0 (0.0)	4 (2.1)	6 (3.0)	1 (0.5)

Lack of efficacy was not determined in this study.

A total of 1,207 patients (402 on tiotropium, 405 on salmeterol and 400 on placebo) were randomized in the six-month, placebo- and salmeterol-controlled studies with equal allocation for tiotropium, salmeterol, and placebo. In the two studies #130 and #137 the number of patients who discontinued because of an adverse event was always lower in the tiotropium groups versus the comparators (see TABLE 4.1:2). In combined analysis, a greater percentage of patients ($p<0.05$, Fisher's Exact test) in the tiotropium group (84.6%) completed all visits compared to those in the placebo group (74.3%). Also, fewer patients in the tiotropium group failed to complete due to adverse events (7.5%) compared to those in the placebo (16.8%) and salmeterol groups (14.8%) respectively ($p<0.05$, Fisher's Exact test). In particular, fewer patients in the tiotropium group failed to complete the studies due to worsening of COPD (5.0%) compared to those in the salmeterol group (10.1%) and in the placebo group (11.3%) (each nominal p-value <0.05, Fisher's exact test).

4.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS AT SCREENING VISIT

The most important demographic information of the six Phase 3 studies is summarized in TABLE 4.2:1.

TABLE 4.2:1 Demographic Characteristics at Screening Visit, Baseline Lung Function and Pulmonary Medication

	#114		#115	
	Tiotropium	**Placebo**	**Tiotropium**	**Placebo**
	N=279	N=191	N=271	N=180
Male [%]	66.7	63.4	66.4	62.2
Caucasian [%]	94.6	88	95.9	97.8
Age [year]: mean (range)	65 40-85	66 39-81	65 41-87	65 41-82
Smoking history [pack year]	65	61	61	57
Duration of COPD [year]: mean	9.3	8.6	8.0	7.7
FEV_1 [L]: mean (range)	1.04 0.37-3.03	1.00 0.30-2.63	1.05 0.31-2.97	1.01 0.29-2.62
FEV_1 %pred.:	39.2	37.7	39.1	38.6
FEV_1/FVC [%]	46.2	46.2	45.5	44.7
Inhaled anticholinergic [%]	53.4	56.5	56.5	60.6
Inhaled steroid [%]	41.9	34.6	45.0	46.1
Theophylline oral [%]	22.9	24.6	21.8	26.1

TABLE 4.2:1 (continued) Demographic Characteristics at Screening Visit, Baseline Lung Function and Pulmonary Medication (Page 2 of 3)

	#122A		#122B	
	Tiotropium	Ipratropium	Tiotropium	Ipratropium
	N=191	N=97	N=165	N=82
Male [%]	81.7	87.6	87.3	84.1
Age [year]: mean (range)	64 41-82	65 47-81	63 41-82	64 42-77
Smoking history [pack year]	33	35	36	32
Duration of COPD [year]: mean	10.7	12.3	12.3	9.8
FEV_1 [L]: mean (range)	1.24 0.40-2.50	1.19 0.60-2.30	1.26 0.29-2.60	1.16 0.47-2.45
FEV_1 %pred.:	42.2	40.2	41.6	38.5
FEV_1/FVC [%]	44.2	45.6	47.5	45.4
Inhaled anticholinergic [%]	64.9	60.8	57	57.3
Inhaled steroid [%]	77.0	80.4	84.2	81.7
Theophylline oral [%]	16.2	12.4	16.4	18.3

TABLE 4.2:1 (continued) Demographic Characteristics at Screening Visit, Baseline Lung Function and Pulmonary Medication (Page 3 of 3)

	#130			#137		
	Tiotropium	**Placebo**	**Salmeterol**	**Tiotropium**	**Placebo**	**Salmeterol**
	N=209	N=201	N=213	N=193	N=199	N=192
Male [%]	73.7	75.1	75.1	81.3	77.4	75.0
Age [year]: mean (range)	65 45-84	66 41-83	65 43-82	63 41-80	64 39-87	64 42-81
Smoking history [pack year]	47	46	49	41	39	41
Duration of COPD [y]: mean	9.2	9.7	10.4	8.9	9.9	9.4
FEV_1 [L]: mean (range)	1.11 0.33-2.05	1.06 0.44-2.14	1.07 0.26-2.23	1.14 0.37-2.51	1.13 0.37-2.20	1.06 0.35-2.06
FEV_1 %pred.:	41.0	39.9	39.7	41.0	41.3	39.2
FEV_1/FVC [%]	43.6	41.3	42.0	43.7	43.2	42.3
Inhaled anticholinergic [%]	55.5	52.7	51.2	50.3	47.7	48.4
Inhaled steroid [%]	65.6	66.2	67.6	64.2	63.3	71.9
Theophylline oral [%]	21.5	17.4	23.0	35.2	29.6	35.9

The baseline demographics and baseline disease characteristics were comparable across treatment groups in the 1-year studies and in the 6-month studies, respectively. In all studies, the mean age was about 65 years with an overall range of 39 to 87 years. In this patient population about 65% to 85% were males and more than 90% were Caucasian.

At the screening visit, the mean FEV_1 in the 1-year, placebo-controlled studies was 1.02 L and the mean percent of predicted normal FEV_1 was 38.7% based on the Morris equation. The 1-year ipratropium-controlled study patient population was made up of slightly milder COPD patients based on their mean screening FEV_1 of 1.23 L and mean percent of predicted normal FEV_1 of 43.1% based on the Morris equation. The mean FEV_1 at screening in the 6-month, placebo- and salmeterol-controlled studies was 1.09 L and the mean percent of predicted normal FEV_1 was 40.3% based on the Morris equation for this patient population.

Almost all patients used at least one pulmonary medication at the time they enrolled in the study. The use of these medications was well balanced between the treatment groups in each of the studies; however, prescribing similarities and differences between the 1-year placebo-controlled and ipratropium-controlled studies can be noted. While the use of anticholinergics was very similar between studies, there was a much lower use of inhaled steroid preparations in the U.S. placebo-controlled studies. Smaller differences were seen in theophylline use (greater in the placebo-controlled studies) and in oral beta adrenergics (greater in the ipratropium-controlled studies). A similar difference concerning theophylline use was seen between the placebo- and salmeterol-controlled replicate studies; in all three treatment groups oral theophylline use was lower in #130 compared to #137 (22, 17 and 23% versus 35, 30 and 36% in the tiotropium, placebo and salmeterol groups, respectively).

4.3 STUDY MEDICATION ADHERENCE

The table below presents study medication adherence data for the six pivotal studies based on the counts of used capsules in the medication record CRF. Due to differences in data collection, the method of calculating compliance was not the same across all studies and is explained in the footnote.

TABLE 4.3:1 Treatment Adherence for Pivotal Tiotropium Studies

	Tiotropium	Placebo	Ipratropium	Salmeterol
#114	**N=279**	**N=191**	**-**	**-**
Median rate (%)	98	98	-	-
≥90% adherence (% subjects)	78.1	79.6	-	-
#115	**N=271**	**N=180**	**-**	**-**
Median rate (%)	98	98	-	-
≥90% adherence (% subjects)	79.0	75.6	-	-
#122A	**N=191**	**-**	**N=97**	**-**
Median rate (%)	99	-	99	-
≥90% adherence (% subjects)	94.2	-	91.8	-
#122B	**N=165**	**-**	**N=82**	**-**
Median rate (%)	99	-	98	-
≥90% adherence (% subjects)	93.9	-	89.0	-
#130	**N=209**	**N=201**	**-**	**N=213**
Median rate (%)	99	98	-	99
≥90% adherence (% subjects)	91.9	87.6	-	88.3
#137	**N=193**	**N=199**	**-**	**N=192**
Median rate (%)	99	99	-	99
≥90% adherence (% subjects)	87.6	86.9	-	85.4

N is number of subjects randomized to treatment group.
Method of calculation: Placebo-Controlled Studies: The medication record CRF contained counts of used capsules. For each patient, the percent compliance was calculated as 100*(number of used capsules)/(number of days of treatment exposure). For any patient where the capsule count data was not known, the compliance was set to zero.
Active-Controlled Studies: In these studies the active comparator was delivered through an MDI. Therefore, there was no "pill count" data available for these treatments. However, on the daily patient record the number of capsules used as well as the number of puffs from the MDI were entered. These were the data used to calculate compliance.

Median treatment adherence was high (98 to 99%) and not different across all treatment groups in the six individual studies. Subjects adhering to treatment by more than 90% ranged from 76 to 94% across all studies, but there were no important differences within individual studies.

4.4 SUMMARY OF PIVOTAL PHASE 3 STUDY POPULATION

Analysis of the study population and their disposition during the conduct of the study supports the following conclusions:

- Most subjects completed each individual study (>71% placebo groups; >78% tiotropium groups).
- Demographics, baseline characteristics, and baseline spirometry data were similar across the treatment groups in each of the six studies, with occasional differences noted between studies or treatment groups.

- Medication adherence was high, with 76 to 94% of the patients showing ≥90% adherence across the studies with smaller differences between treatment groups.

5. EFFICACY RESULTS

Efficacy results are presented first for the primary endpoints in the individual studies followed by the supportive evidence from secondary endpoints or exploratory analyses. Integrated data of the replicate studies have been used occasionally, e.g. for subgroup analyses.

5.1 PRIMARY EFFICACY MEASURE: BRONCHODILATION WITH ONCE-A-DAY DOSING OF SPIRIVA

The bronchodilator efficacy was established by the spirometric responses, FEV_1 and FVC, measured in clinics following single and multiple doses and by morning and evening peak expiratory flow rates (PEFR) measured daily by the patient at home. The treatment groups were generally comparable at baseline in the three sets of two replicate studies. In addition, the treatment groups were evaluated using analysis of covariance with baseline as a covariate to eliminate any effect of differential baseline values.

The importance of trough FEV_1-response to demonstrate 24-hour duration of action has been explained in Section 3.3. This pulmonary function measure was chosen as the primary endpoint after 3 months of treatment in the 1-year studies and at the end of study in the 6-month studies. Peak and average FEV_1-measurements at 3 months as well as spirometric results at all other timepoints provide supportive evidence of bronchodilator efficacy following once-a-day inhalation of tiotropium.

5.1.1 Bronchodilator Efficacy in 1-Year, Placebo-Controlled Studies

FIGURE 5.1.1:1 shows the FEV_1-time profiles over all test days for tiotropium and placebo for the individual studies. Both 1-year studies #114 and #115 show comparable results. Following the first dose of tiotropium, patients showed a clinically and statistically significant bronchodilator response within 30 minutes, which was maintained over the 3-hour in-clinic assessment. At the next visit after 8 days on treatment, the trough was already elevated in the tiotropium-treated patients, so that the next dose effect was added on top of the already elevated baseline. The mean FEV_1 trough response was 0.12 L greater for tiotropium than placebo and about 12% above baseline FEV_1. The mean FEV_1 trough response increased by another 0.03 L over placebo with prolonged treatment at the later timepoints. The daily a.m. dose induced further increase of the mean FEV_1 response by 0.08 to 0.11 L.

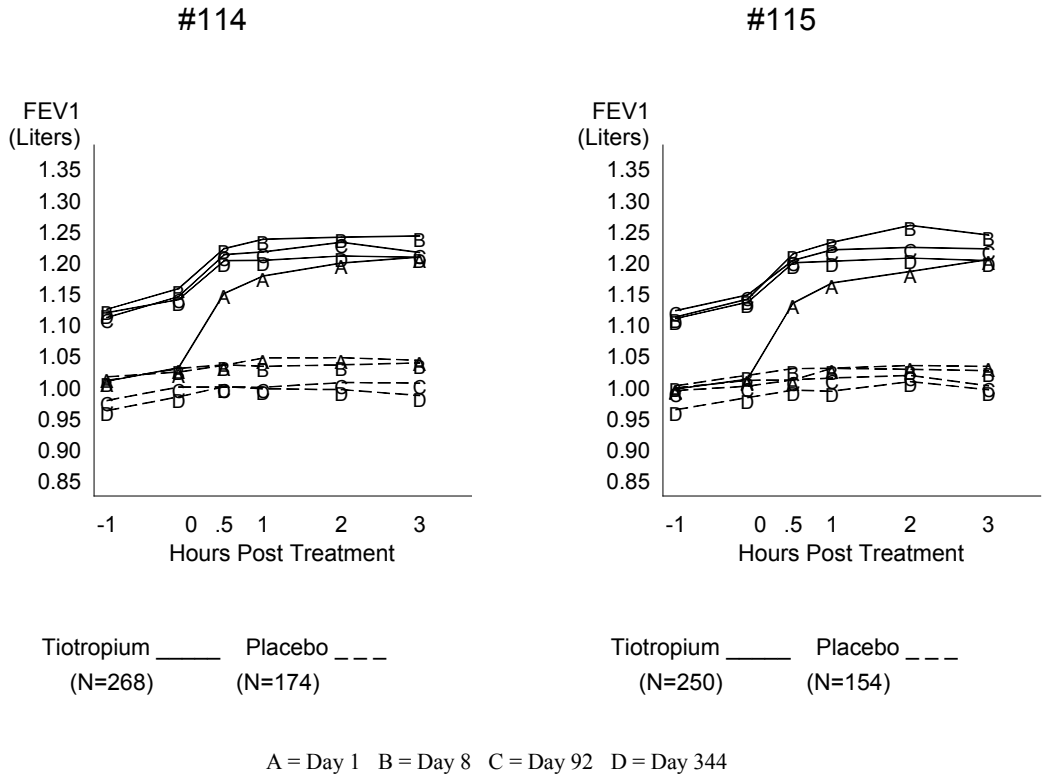


FIGURE 5.1.1:1 The Mean[1] FEV_1 (Ls) Over Time for COPD Phase 3, 1-Year, Placebo-Controlled Studies #114 and #115, Intent-to-Treat Data Sets

The primary endpoint, trough FEV_1-response at 92 days (average of two measurements at the end of the 24-hour dosing interval) was significantly superior following tiotropium compared to placebo in both studies. The magnitude of response as means was numerically identical in both studies and the improvement of 0.14±0.02 L over placebo in both studies is statistically significant and clinically meaningful (TABLE 5.1.1:1). A mean trough FEV_1 gain of 0.14 L with tiotropium over placebo ($p<0.0001$) means that the lung function status of a patient is re-established to the condition he had been in 2 to 5 years before, considering that the annual rate of decline of FEV_1 in COPD patients is about 62 mL per year in continuing smokers and 31 mL in sustained quitters (Scanlon et al., 2000).

TABLE 5.1.1:1 The Mean[1] (SE) FEV_1 Trough Response (L) Over Time for the COPD Phase 3, 1-Year, Placebo-Controlled Studies #114 and #115, Intent-to-Treat Data Sets

	Tiotropium	Placebo	Difference	P value
#114	N=268	N=174		
Baseline[2]	1.01	1.01		
Day 8	0.12 (0.01)	-0.00 (0.01)	0.12 (0.02)	0.0001
Day 50	0.11 (0.01)	-0.00 (0.01)	0.11 (0.02)	0.0001
Day 92	0.11 (0.01)	-0.03 (0.02)	0.14 (0.02)	0.0001
Day 176	0.11 (0.01)	-0.04 (0.02)	0.15 (0.02)	0.0001
Day 260	0.11 (0.01)	-0.04 (0.02)	0.15 (0.02)	0.0001
Day 344	0.11 (0.01)	-0.05 (0.02)	0.16 (0.02)	0.0001
#115	N=250	N=154		
Baseline[2]	1.00	1.00		
Day 8	0.12 (0.01)	0.01 (0.01)	0.12 (0.02)	0.0001
Day 50	0.15 (0.01)	0.01 (0.02)	0.13 (0.02)	0.0001
Day 92	0.13 (0.01)	-0.01 (0.02)	0.14 (0.02)	0.0001
Day 176	0.12 (0.01)	-0.04 (0.02)	0.16 (0.02)	0.0001
Day 260	0.13 (0.01)	-0.02 (0.02)	0.15 (0.02)	0.0001
Day 344	0.12 (0.01)	-0.03 (0.02)	0.15 (0.02)	0.0001

1 The means are adjusted for center effects and baseline FEV_1.
2 Common baseline mean
Shaded area indicates primary endpoint

The secondary endpoint trough FEV_1–response at other timepoints, as well as peak and average FEV_1-response at all timepoints, were also improved and significantly greater than placebo. The time-response data of the individual studies are summarized in TABLE 5.1.1:1 and 2.

The FEV_1 measured at trough, average for 3 hours and peak after prolonged treatment periods does show a small decline versus the baseline values, however the decline in the placebo group is comparable or even more pronounced. These data demonstrate that the effect of tiotropium does not show tachyphylaxis.

TABLE 5.1.1:2 Mean[1] (SE) FEV_1 Average (3-hours following treatment) Response and Peak Response (L) Over Time for the COPD Phase 3, 1-Year, Placebo-Controlled Studies #114 and #115. Intent-to-Treat Data Sets

	Tiotropium	Placebo	P value	Tiotropium	Placebo	P value
	#114			**#115**		
Average	N=268	N=174		N=250	N=154	
Baseline[2]	1.01	1.01		1.00	1.00	
Day 1	0.16 (0.01)	0.02 (0.01)	0.0001	0.17 (0.01)	0.02 (0.01)	0.0001
Day 8	0.22 (0.01)	0.02 (0.01)	0.0001	0.23 (0.01)	0.02 (0.02)	0.0001
Day 50	0.20 (0.01)	0.01 (0.02)	0.0001	0.24 (0.01)	0.02 (0.02)	0.0001
Day 92	0.20 (0.01)	-0.02 (0.02)	0.0001	0.21 (0.01)	0.01 (0.02)	0.0001
Day 176	0.19 (0.01)	-0.02 (0.02)	0.0001	0.21 (0.01)	-0.02 (0.02)	0.0001
Day 260	0.19 (0.01)	-0.01 (0.02)	0.0001	0.20 (0.01)	-0.00 (0.02)	0.0001
Day 344	0.19 (0.01)	-0.01 (0.02)	0.0001	0.20 (0.02)	-0.01 (0.02)	0.0001
Peak						
Baseline[2]	1.01	1.01		1.00	1.00	
Day 1	0.24 (0.01)	0.08 (0.01)	0.0001	0.24 (0.01)	0.08 (0.02)	0.0001
Day 8	0.28 (0.01)	0.08 (0.01)	0.0001	0.31 (0.01)	0.09 (0.02)	0.0001
Day 50	0.27 (0.01)	0.08 (0.01)	0.0001	0.31 (0.01)	0.08 (0.02)	0.0001
Day 92	0.26 (0.01)	0.05 (0.02)	0.0001	0.28 (0.02)	0.07 (0.02)	0.0001
Day 176	0.26 (0.01)	0.04 (0.02)	0.0001	0.28 (0.02)	0.04 (0.02)	0.0001
Day 260	0.25 (0.01)	0.06 (0.02)	0.0001	0.26 (0.02)	0.06 (0.02)	0.0001
Day 344	0.26 (0.02)	0.04 (0.02)	0.0001	0.26 (0.02)	0.05 (0.02)	0.0001

1 The means are adjusted for center effects and baseline FEV_1.
2 Common baseline mean

For study #114, the mean FEV_1 average response during the first 3 hours after tiotropium administration was 0.16 L (0.14 L greater than placebo) on the first day of dosing and ranged from 0.19 L to 0.22 L over baseline (0.20-0.22 L greater than placebo) at steady state during the remainder of the 49-week study. The mean FEV_1 peak response following tiotropium was 0.24 L over baseline (0.16 L greater than placebo) on the first day of dosing and ranged from 0.25 to 0.28 L over baseline (0.19-0.22 L greater than placebo) at steady state during the remainder of the study. In each case the difference between the treatment groups was highly statistically significant ($p<0.01$). For study #115, the mean FEV_1 average response during the first 3 hours after tiotropium administration was 0.17 L (0.15 L greater than placebo) on the first day of dosing and ranged from 0.20 L to 0.24 L over baseline (0.20-0.23 L greater than placebo) at steady state during the remainder of the 49-week study. The mean FEV_1 peak response following tiotropium was 0.24 L over baseline (0.16 L greater than placebo) on the first day of dosing and ranged from 0.26 to 0.31 L over baseline (0.20-0.24 L greater than placebo) at steady state during the remainder of the study.

5.1.2 Bronchodilator Efficacy in 1-Year, Ipratropium-Controlled Studies

The patients in the two replicate studies were comparable concerning baseline characteristics. FIGURE 5.1.2:1 shows the FEV_1 profiles over all test days for tiotropium and ipratropium for each individual study. Note that the pulmonary function tests were conducted for 6 hours after treatment for the first three months and for 3 hours after treatment thereafter. The two replicate studies show comparable results. Following the first dose of tiotropium patients showed a clinically significant bronchodilator response within 30 minutes, peaking after 4 hours. The peak effect of ipratropium was seen after 1 hour. Following repeated administration the peak effect of tiotropium appeared after 2 to 3 hours, that of ipratropium remained unchanged after 1 hour. The trough FEV_1 responses are tabulated in TABLE 5.1.2:1. After eight days of treatment, the mean FEV_1 trough response for tiotropium was 0.15 L over baseline (0.14 L over ipratropium) in Study #122A and 0.13 L over baseline (0.11 L over ipratropium) in Study #122B. With the long-acting drug, the administration of the daily a.m. dose induced a further increase of the mean FEV_1 on top of the elevated morning baseline (trough) by 0.10-0.16 L. This profile was maintained throughout the yearlong treatment period. The patients receiving ipratropium always showed a similar time-response profile, unchanged throughout the course of the study (FIGURE 5.1.2:1).

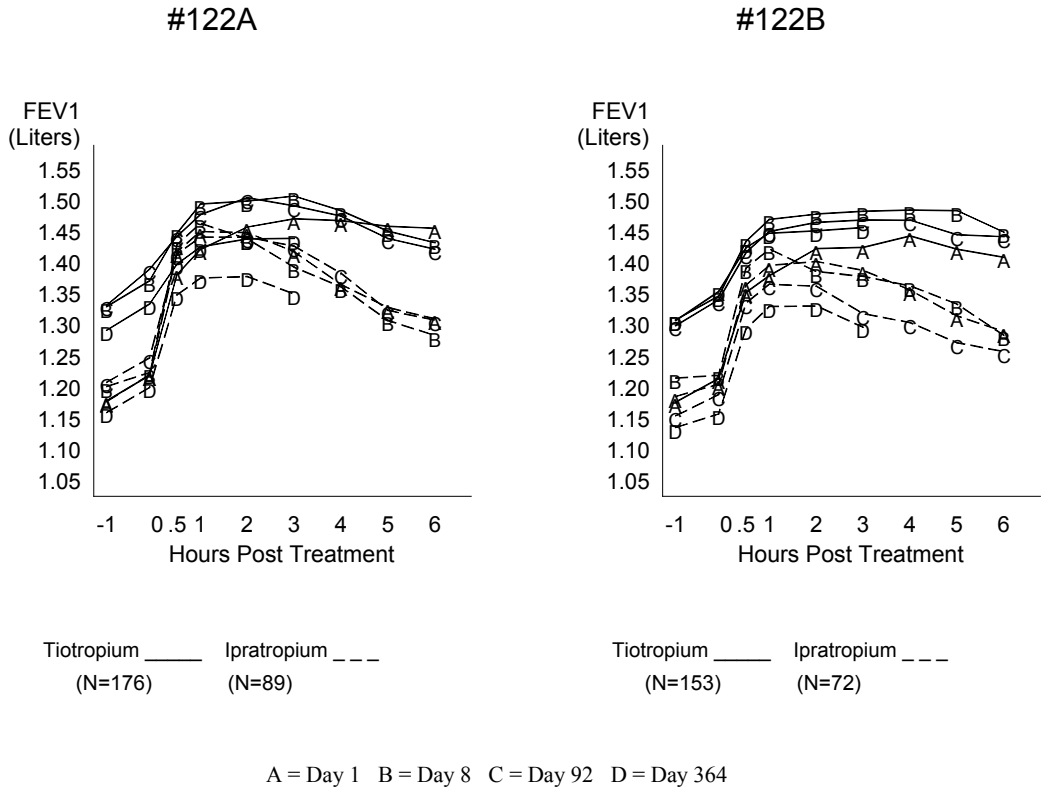


FIGURE 5.1.2:1 Mean[1] FEV_1 (L) Over Time for the COPD Phase 3, 1-Year Ipratropium-Controlled Studies #122A and #122B Intent-to-Treat Data Sets

1 Means are adjusted for center effects and baseline FEV_1.

The primary endpoint, trough FEV_1-response at 92 days, was significantly superior following tiotropium compared to the active comparator ipratropium in both studies (TABLE 5.1.2:1). The magnitude of response was comparable in both studies and the improvement of 0.16 L (0.13 L over ipratropium) in Study #122A and 0.12 (0.14 L over ipratropium) in Study #122B is a clinically meaningful improvement. Further, the superiority of tiotropium to ipratropium was statistically significant ($p<0.05$) at all time points on all test days, except for the first 2 hours following first dose and for the first hour post-dose 1 week later.

TABLE 5.1.2:1 The Mean[1] (SE) FEV_1 Trough Response (L) Over Time for the COPD Phase 3, 1-Year, Ipratropium-Controlled Studies #122A and #122B. Intent-to-Treat Data Sets

	Tiotropium	Ipratropium	Difference	P value
#122A	N=176	N=89		
Baseline[2]	1.19	1.19		
Day 8	0.15 (0.01)	0.01 (0.02)	0.14 (0.02)	0.0001
Day 50	0.15 (0.02)	0.01 (0.02)	0.14 (0.03)	0.0001
Day 92	0.16 (0.02)	0.03 (0.02)	0.13 (0.03)	0.0001
Day 182	0.15 (0.02)	-0.02 (0.02)	0.17 (0.03)	0.0001
Day 273	0.11 (0.02)	-0.02 (0.02)	0.13 (0.03)	0.0001
Day 364	0.11 (0.02)	-0.02 (0.03)	0.13 (0.03)	0.0001
#122B	N=153	N=72		
Baseline[2]	1.19	1.19		
Day 8	0.13 (0.02)	0.02 (0.02)	0.11 (0.03)	0.0001
Day 50	0.12 (0.02)	-0.00 (0.03)	0.12 (0.03)	0.0001
Day 92	0.12 (0.02)	-0.02 (0.02)	0.15 (0.03)	0.0001
Day 182	0.12 (0.02)	-0.04 (0.03)	0.16 (0.03)	0.0001
Day 273	0.12 (0.02)	-0.03 (0.03)	0.15 (0.03)	0.0001
Day 364	0.14 (0.02)	-0.05 (0.02)	0.18 (0.03)	0.0001

1 The means are adjusted for center effects and baseline FEV_1.

2 Common baseline mean. Shaded area indicates primary endpoint, Intent to Treat data set

As outlined in TABLE 5.1.2:2 tiotropium was superior to ipratropium as measured by the average response ($AUC_{0\text{-}6hours}$ until Day 92 then $AUC_{0\text{-}3hours}$) on all test days ($p<0.05$) and by the peak response on all test days, except Day 92 and Day 364 in Study #122A ($p<0.05$, following multiple dosing.

TABLE 5.1.2:2 The Mean[1] (SE) FEV_1 Average Response (0-6 hours until Day 92 then 0-3 hours) and FEV_1 Peak Response (L) Over Time for the COPD Phase 3, 1-Year Ipratropium-Controlled Studies #122A and #122B. Intent-to-Treat Data Sets

	Tiotropium	Ipratropium	P value	Tiotropium	Ipratropium	P value
	#122A			**#122B**		
Average	N=176	N=89		N=153	N=72	
Baseline[2]	1.19	1.19		1.19	1.19	
Day 1	0.22 (0.01)	0.22 (0.01)	0.9278	0.19 (0.01)	0.18 (0.02)	0.7255
Day 8	0.28 (0.02)	0.22 (0.02)	0.0187	0.26 (0.02)	0.19 (0.03)	0.0139
Day 50	0.28 (0.02)	0.21 (0.03)	0.0123	0.26 (0.02)	0.18 (0.03)	0.0201
Day 92	0.27 (0.02)	0.22 (0.02)	0.0354	0.25 (0.02)	0.14 (0.03)	0.0010
Day 182	0.26 (0.02)	0.14 (0.02)	0.0001	0.25 (0.02)	0.12 (0.03)	0.0001
Day 273	0.23 (0.02)	0.17 (0.03)	0.0344	0.24 (0.02)	0.12 (0.03)	0.0004
Day 364	0.22 (0.02)	0.15 (0.03)	0.0286	0.24 (0.02)	0.11 (0.03)	0.0001
Peak						
Baseline[2]	1.19	1.19		1.19	1.19	
Day 1	0.31 (0.01)	0.32 (0.02)	0.8684	0.28 (0.01)	0.27 (0.02)	0.5103
Day 8	0.36 (0.02)	0.30 (0.02)	0.0377	0.35 (0.02)	0.28 (0.03)	0.0238
Day 50	0.36 (0.02)	0.29 (0.03)	0.0286	0.35 (0.02)	0.26 (0.02)	0.0080
Day 92	0.35 (0.02)	0.31 (0.02)	0.1272	0.33 (0.02)	0.23 (0.03)	0.0040
Day 182	0.33 (0.02)	0.22 (0.02)	0.0001	0.34 (0.02)	0.20 (0.03)	0.0001
Day 273	0.31 (0.02)	0.25 (0.03)	0.0492	0.33 (0.02)	0.19 (0.03)	0.0001
Day 364	0.29 (0.02)	0.23 (0.03)	0.0578	0.32 (0.02)	0.18 (0.03)	0.0001

1 The means are adjusted for center effects and baseline FEV_1
2 Common baseline mean

5.1.3 Bronchodilator Efficacy in 6-Month, Placebo- and Salmeterol-Controlled Studies

The baseline FEV_1 values were comparable for the three treatment groups in the individual studies. FIGURE 5.1.3:1 shows the FEV_1-time profiles for the individual 6-month, placebo- and salmeterol-controlled Studies #130 and #137. The mean FEV_1 trough response, the average response over 12 or 3 hours post-treatment, and the peak response are displayed in TABLES 5.1.3:1 to 3.

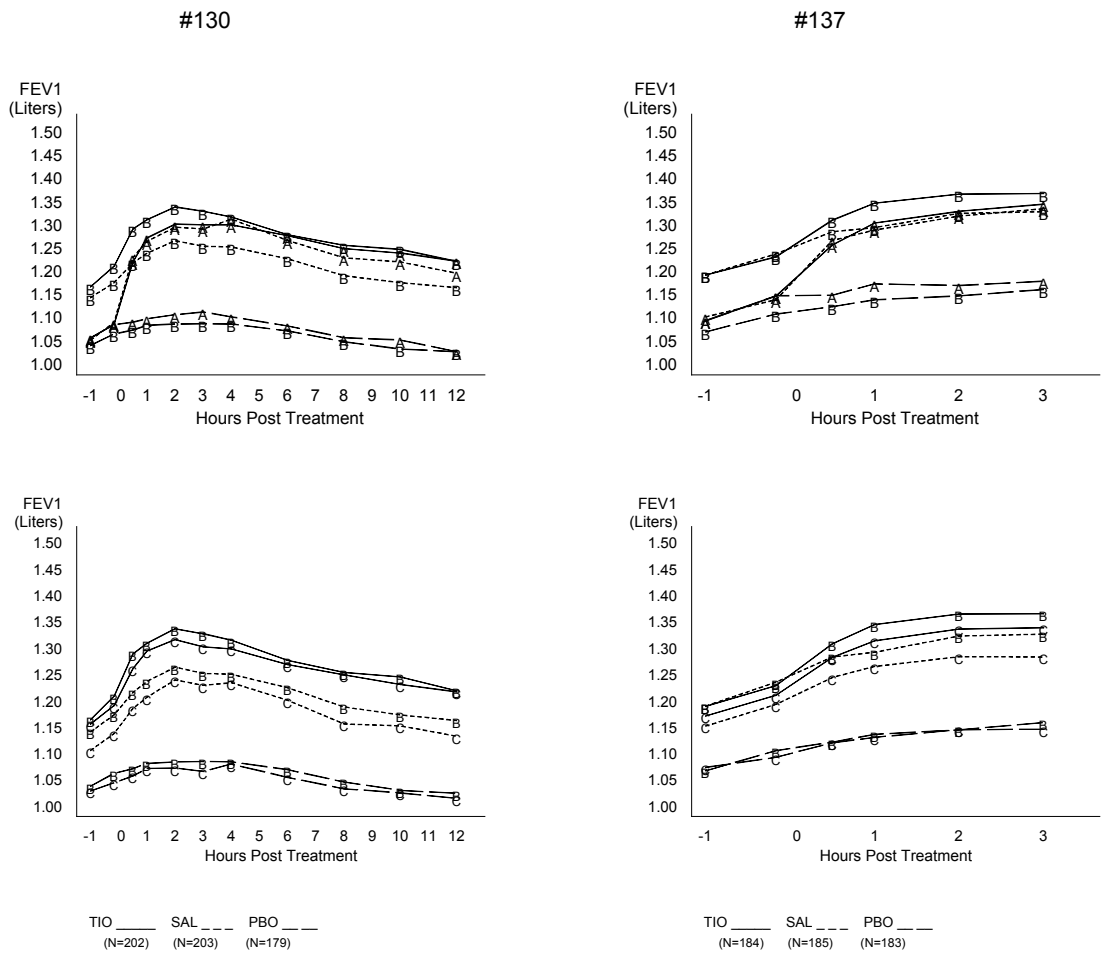


FIGURE 5.1.3:1 The Mean FEV_1 Over Time for COPD Phase 3, 6-Month Studies, #130 and #137, Intent-to-Treat Data Sets

TABLE 5.1.3:1 The Mean[1] (SE) FEV_1 Trough Response (L) Over Time for the COPD Phase 3, 6-Month, Placebo- and Salmeterol-Controlled Studies #130 and #137. Intent-to-Treat Data Sets.

	Tiotropium	Placebo	Salmeterol	P value		
	6 month, placebo- and salmeterol-controlled #130, trough					
Baseline[2]	1.06	1.06	1.06	TIO-PBO	TIO-SAL	SAL-PBO
Day 15	0.12 (0.01)	-0.02 (0.01)	0.09 (0.01)	0.0001	0.0788	0.0001
Day 57	0.12 (0.01)	-0.02 (0.01)	0.08 (0.01)	0.0001	0.0311	0.0001
Day 113	0.12 (0.01)	-0.02 (0.02)	0.08 (0.01)	0.0001	0.0329	0.0001
Day 169	0.11 (0.01)	-0.03 (0.02)	0.05 (0.01)	0.0001	0.0088	0.0001
	6 month, placebo- and salmeterol-controlled #137, trough					
Baseline[2]	1.11	1.11	1.11	TIO-PBO	TIO-SAL	SAL-PBO
Day 15	0.09 (0.01)	-0.03 (0.01)	0.09 (0.01)	0.0001	0.8532	0.0001
Day 57	0.10 (0.02)	-0.01 (0.02)	0.10(0.02)	0.0001	0.9971	0.0001
Day 113	0.10 (0.02)	-0.01 (0.02)	0.09 (0.02)	0.0001	0.8027	0.0001
Day 169	0.07 (0.02)	-0.03 (0.02)	0.05 (0.02)	0.0001	0.3934	0.0001

1 The means are adjusted for center effects and baseline FEV_1.
2 Common baseline mean
Shaded area indicates primary endpoint

TABLE 5.1.3:2 The Mean[1] (SE) FEV_1 Average (0-12h) Response (L) in Study #130 and The Mean[1] (SE) FEV_1 Average (0-3h) Response (L) in Study #137 Over Time for the COPD Phase 3, 6-Months, Placebo- and Salmeterol-Controlled Studies. Intent-to-Treat Data Sets.

	Tiotropium	Placebo	Salmeterol	P value		
	6-month, placebo- and salmeterol-controlled #130, 12 h average					
Baseline[2]	1.06	1.06	1.06	TIO-PBO	TIO-SAL	SAL-PBO
Day 1	0.19 (0.01)	0.01 (0.01)	0.18 (0.01)	0.0001	0.4539	0.0001
Day 15	0.21 (0.01)	-0.01 (0.01)	0.14 (0.01)	0.0001	0.0005	0.0001
Day 57	0.21 (0.01)	-0.02 (0.02)	0.14 (0.01)	0.0001	0.0003	0.0001
Day 113	0.21 (0.02)	-0.01 (0.02)	0.14 (0.02)	0.0001	0.0008	0.0001
Day 169	0.20 (0.02)	-0.02 (0.02)	0.12 (0.02)	0.0001	0.0004	0.0001
	6-month, placebo- and salmeterol-controlled #137, 3 h average					
Baseline[2]	1.11	1.11	1.11	TIO-PBO	TIO-SAL	SAL-PBO
Day 1	0.18 (0.01)	0.04 (0.01)	0.17 (0.01)	0.0001	0.5840	0.0001
Day 15	0.22 (0.02)	0.02 (0.02)	0.18 (0.02)	0.0001	0.0751	0.0001
Day 57	0.21 (0.02)	0.02 (0.02)	0.18 (0.02)	0.0001	0.2411	0.0001
Day 113	0.20 (0.02)	0.02 (0.02)	0.17 (0.02)	0.0001	0.1327	0.0001
Day 169	0.19 (0.02)	0.01 (0.02)	0.15 (0.02)	0.0001	0.0436	0.0001

1 The means are adjusted for center effects and baseline FEV_1.
2 Common baseline mean

TABLE 5.1.3:3 The Mean[1] (SE) FEV_1 Peak (0-3h) Response (L) Over Time for the COPD Phase 3, 6-Months, Placebo- and Salmeterol-Controlled Studies #130, #137. Intent-to-Treat Data Sets.

	Tiotropium	Placebo	Salmeterol	P value		
	6 month placebo- and salmeterol-controlled #130, peak in 1st 3 h					
Baseline[2]	1.06	1.06	1.06	TIO-PBO	TIO-SAL	SAL-PBO
Day 1	0.28 (0.01)	0.10 (0.01)	0.27 (0.01)	0.0001	0.6436	0.0001
Day 15	0.32 (0.01)	0.08 (0.02)	0.24 (0.01)	0.0001	0.0001	0.0001
Day 57	0.32 (0.02)	0.06 (0.02)	0.24 (0.02)	0.0001	0.0001	0.0001
Day 113	0.31 (0.02)	0.07 (0.02)	0.23 (0.02)	0.0001	0.0009	0.0001
Day 169	0.30 (0.02)	0.05 (0.02)	0.21 (0.02)	0.0001	0.0004	0.0001
	6 month placebo- and salmeterol-controlled #137, peak in 1st 3 h					
Baseline[2]	1.11	1.11	1.11	TIO-PBO	TIO-SAL	SAL-PBO
Day 1	0.27 (0.01)	0.11 (0.01)	0.26 (0.01)	0.0001	0.3931	0.0001
Day 15	0.30 (0.02)	0.09 (0.02)	0.25 (0.02)	0.0001	0.0206	0.0001
Day 57	0.29 (0.02)	0.09 (0.02)	0.25 (0.02)	0.0001	0.0944	0.0001
Day 113	0.28 (0.02)	0.09 (0.02)	0.23 (0.02)	0.0001	0.0667	0.0001
Day 169	0.27 (0.02)	0.08 (0.02)	0.21 (0.02)	0.0001	0.0097	0.0001

1 The means are adjusted for center effects and baseline FEV_1.
2 Common baseline mean

The efficacy of tiotropium in relation to baseline and placebo will be discussed first followed by the comparison to salmeterol.

Tiotropium compared to placebo and baseline:

The difference between tiotropium and placebo was highly statistically significant ($p<0.0001$) on all test days in each study for each FEV_1 endpoint, including the co-primary endpoint to dyspnea, trough FEV_1-response at Day 169.

Following the first dose of tiotropium, patients showed a clinically and statistically significant bronchodilator response within 30 minutes in both studies. The mean FEV_1 trough-response approached or reached steady state after 2 weeks on tiotropium treatment in both studies and ranged from 0.11 to 0.12 L over baseline in Study #130 (0.14 L over placebo) and 0.07 to 0.10 L over baseline (0.10-0.12 L over placebo) in Study #137. The mean FEV_1 increased further by another 0.09-0.14 L (0.10-0.12 L over placebo) following the daily tiotropium dose. This profile was maintained throughout the 6-month treatment period.

The mean FEV_1 average response during the first 12 hours after tiotropium administration ranged from 0.20 to 0.21 L over baseline (0.22-0.23 L over placebo) at steady state and for the remainder of the 24-week Study #130. The 3-hour average response in Study #137 was similar ranging from 0.19 to 0.22 L over baseline and 0.18-0.20 L over placebo.

The mean FEV_1 peak response in the first 3 hours following tiotropium was 0.28 (#130) to 0.27 L (#137) over baseline on the first day of dosing and ranged from 0.30 to 0.32 (#130) or and 0.27 to 0.30 L (#137) over baseline at steady state during the remainder of the study. Comparison to placebo ranged from 0.24-0.25 L (#130) and 0.19-0.21 L (#137) during this period.

Tiotropium compared to salmeterol:

Salmeterol also was significantly superior to placebo in both studies at all time points for trough FEV_1, average and peak. As previously noted, the primary comparison was trough FEV_1-response at Day 169: In Study #130 tiotropium was statistically significantly superior ($p=0.0088$) by 0.06 L to salmeterol. Furthermore, the trough FEV_1-response at all other time points after reaching steady state (except Day 15) showed statistically significant superiority ($p<0.05$). In Study #137 the trough FEV_1-response to tiotropium was similar to salmeterol. Comparisons for average response following multiple dosing revealed that tiotropium responses were higher than those of salmeterol (0.07-0.08 L in Study #130 and 0.03-0.04 L in Study #137). The differences were statistically significant on all test days in Study #130 and only on the last test day (Day 169) in Study #137.

In conclusion, even compared to the potent and long-acting active comparator salmeterol, tiotropium was statistically superior in one study and at least comparable in the second study.

5.1.4 Supportive Evidence for Bronchodilator Efficacy

FVC

The FVC response generally parallels that of the FEV_1 response.

In study #114 the mean response to tiotropium was 0.39 L at 1 hour (0.42 L study #115) and increased to 0.45 L (0.46 L study #115) in 3 hours following single dose administration. By the end of the first week the mean tiotropium FVC trough response was 0.27 L (0.26 L in study #115). The mean FVC increased by another 0.23 L in study #114 (0.26 L in study #115) following treatment. This profile was maintained throughout the 49-week treatment period. The difference between tiotropium and placebo was highly statistically significant ($p<0.01$) at all timepoints on all test days.

In study #122A, the mean FVC response to tiotropium 1 hour after dosing was 0.52 L (0.40 L study #122B) and increased to 0.60 L (0.44 L in study #122) in 3 hours following single dose administration. By the end of the first week the mean tiotropium trough FVC response was

0.36 L in study #122A (0.28 L in study #122B). The mean FVC increased by another 0.31 L in study #122A (0.24 L in study #122B) following treatment. The difference between tiotropium and ipratropium was statistically significant ($p<0.05$) starting with the 3-hour timepoint and for the pre-dose measurements (i.e., about 24 hours after treatment administration) with the exception of the baseline visit.

In study #130 the mean FVC response tiotropium 30 minutes after dosing was 0.34 L (0.31 L in study #137) and increased to 0.50 L (0.44 L in study #137) in 3 hours following single dose administration. After 2 weeks on treatment, the mean tiotropium trough response (about 24 hours after treatment administration) was 0.24 L in study #130 (0.19 L in study #137) for patients in the tiotropium group with an additional increase of 0.31 L in study #130 (0.29L in study #137) in the 3 hours following treatment administration. This profile was maintained throughout the 24-week treatment period.

PEFR

PEFRs were measured twice daily in the studies and weekly means were calculated. In Study #114, morning peak flows in the tiotropium group were on average 8-24 L/min greater than in the placebo group; these averages were statistically significant over 24 of the 49 weeks measured (marginally significant ($0.05 <p$ 0.10) for an additional 17 weeks. In Study #115 the mean differences were 12-31 L/min and were statistically significant for 48 of the 49 weeks.

Average weekly differences for evening PEFRs ranged from 13-24 L/min and were significantly greater in the tiotropium group for 41 of 49 weeks in study #114 and ranged from 19-40 L/min in Study #115 and were statistically significant for all 49 weeks. In the ipratropium-controlled studies the weekly averages in morning PEFR were greater in the tiotropium group, with mean differences ranging from 9-16 L/min in Study #122A and 9-22 L/min in Study #122B. These averages were statistically significantly greater for tiotropium throughout the 52 weeks in both studies. Average evening weekly PEFR differences ranged from 7-17 L/min. in Study #122A and 10-22 L/min. in Study #122B. In Study #122A these averages were statistically significantly greater in the tiotropium group throughout 30 of 52 weeks in Study #122A and in all weeks in Study #122B.

No rebound was observed following cessation of treatment as assessed by patient evaluations of PEFR and albuterol use over 3 weeks in any of the four 1-year studies.

The mean morning and evening PEFRs were greater for both tiotropium and salmeterol compared to placebo throughout the 24-week treatment period in each study. There was no difference between tiotropium and salmeterol throughout the 24-week period except for evening PEFR in study #130 where tiotropium was higher ($p<0.05$) in 23 of the 24 weeks.

5.1.5 Bronchodilator Efficacy Summary

Data from the two 1-year, placebo-controlled studies, two 1-year, ipratropium-controlled studies and two 6-month, placebo- and salmeterol-controlled studies demonstrated that tiotropium was a significantly more effective bronchodilator than placebo and ipratropium. This was shown with the primary endpoint trough FEV_1 at Day 92 in the 1-year studies and at Day 169 in the 6-month studies. Analysis of peak effects, average effects and of other time points provides consistent evidence of pronounced and sustained bronchodilator efficacy. Other lung function measures, FVC or PEFR, support these findings.

Tiotropium was significantly superior to salmeterol in one of two studies for most parameters and all time points after reaching steady state of tiotropium. In the second study tiotropium and salmeterol had comparable effects.

In summary, the effectiveness for tiotropium with once-a-day dosing was established by clinically meaningful and significant bronchodilator efficacy measured by appropriate measures of pulmonary function.

5.2 CO-PRIMARY EFFICACY MEASURE: RELIEF FROM DYSPNEA

5.2.1 Clinical Development Strategy to Evaluate Dyspnea

Dyspnea is the hallmark symptom of COPD and is the reason most COPD patients seek medical attention. In the clinical development program, the baseline and transition dyspnea index, BDI/TDI, were chosen to evaluate the effect of tiotropium. The instrument has been validated during its development and this validation was confirmed with the tiotropium database. Other supportive measures evaluated in the study included general symptom diaries, supplemental albuterol use, physician global evaluation, and health status measures.

Based on the evaluation of secondary endpoints characterizing dyspnea in the four 1-year studies, the superiority of tiotropium over its controls (placebo and ipratropium) in reducing dyspnea was clearly observed. In order to confirm these findings for a label indication, we included the transition dyspnea index (TDI) focal score as a co-primary endpoint along with trough FEV_1 response, in two additional independent studies. In agreement with an FDA recommendation, the protocols of the two 6-month, placebo- and salmeterol-controlled

Studies #130 and #137 were amended to include TDI focal score as co-primary endpoint with trough FEV_1-response. Improvement in TDI focal score of one unit or more was considered a priori as clinically meaningful and the primary analysis compared the percentage of patients between tiotropium and placebo with an improvement of one or more in TDI focal score (percent of responders) at the final visit on treatment, Day 169. The basis for one unit change in TDI focal score as clinically meaningful is outlined in Section 3.3.2.

5.2.2 Dyspnea as Co-Primary Endpoint to Trough FEV_1 Response: Transition Dyspnea Index (TDI) in 6-Months Studies

FIGURE 5.2.2:1 shows that in each of the two studies, tiotropium achieved a significantly greater percentage of responders than placebo on all test days including Day 169, the primary endpoint analysis. The response to tiotropium was consistent in each study.

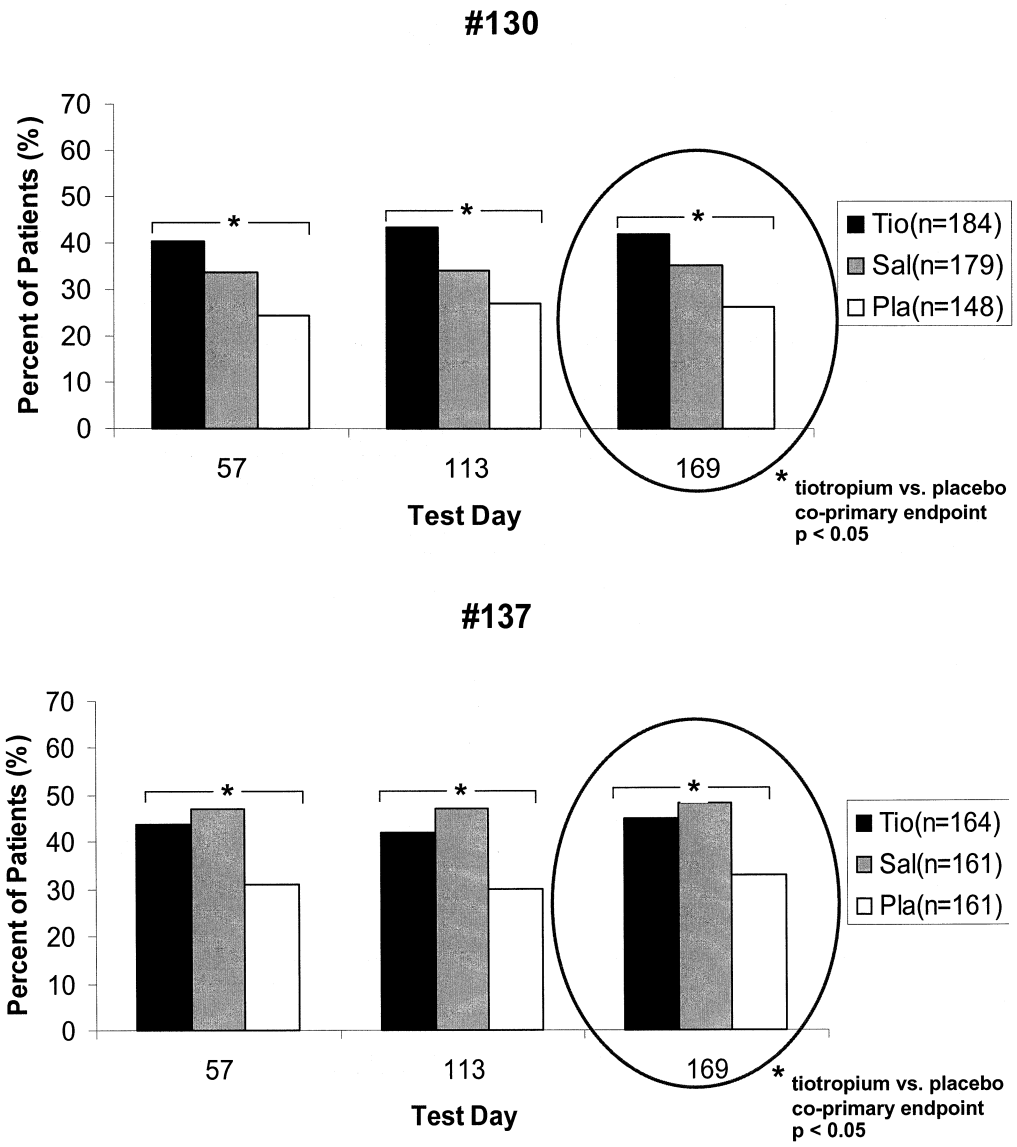
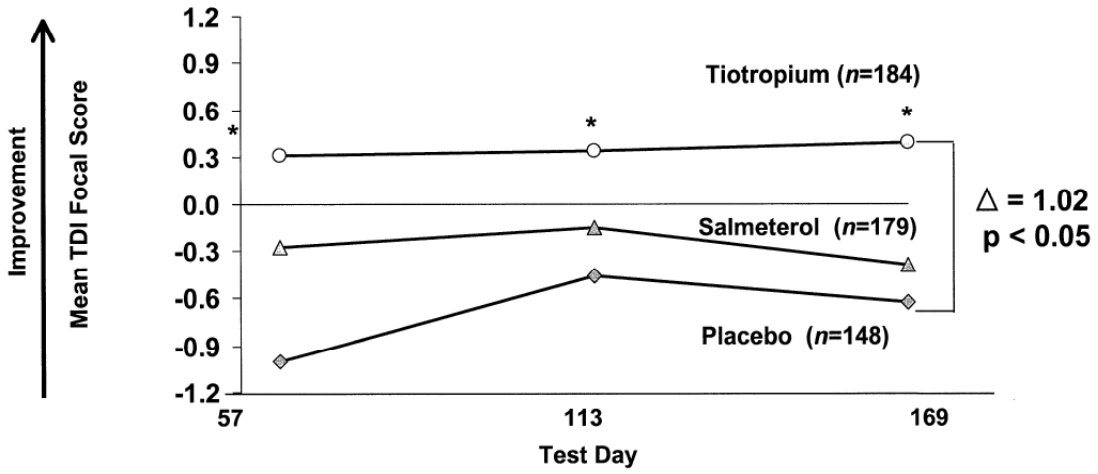


FIGURE 5.2.2:1 Percent of Patients Considered as TDI Responders

The analysis of means supported the responder analysis. Tiotropium was significantly more effective ($p<0.05$) than placebo in the focal score on all test days (FIGURE 5.2.2:2).

Study #130



Study #137

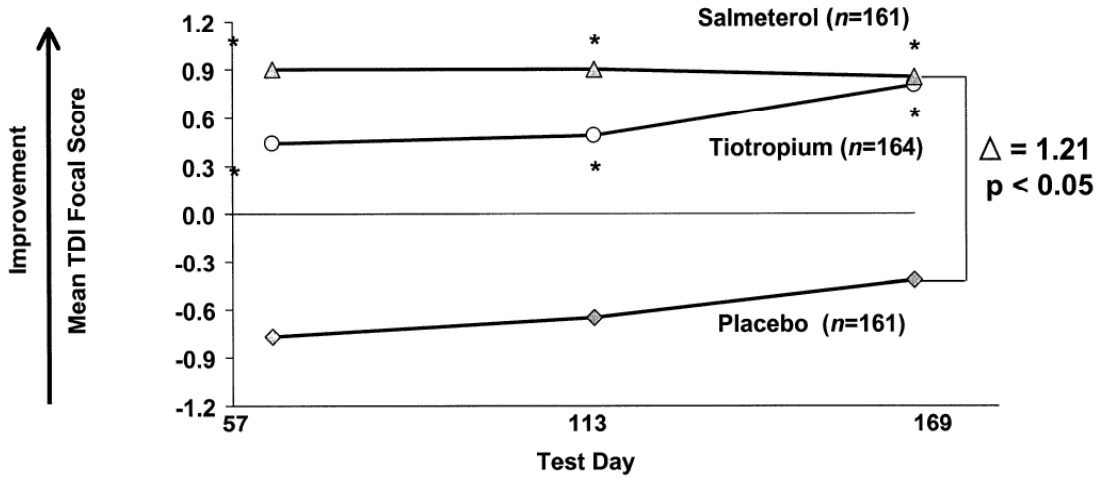


FIGURE 5.2.2:2 Mean TDI Focal Score Over 6 Months

TABLE 5.2.2:1 summarizes the evaluation of dyspnea across the study period. In addition to the significant effect on the proportion of patients improving ≥1 unit, the mean change versus placebo for TDI focal score was greater by more than one unit and statistically significant in the tiotropium treated patients versus placebo in both studies.

TABLE 5.2.2:1 The Baseline (BDI) and Transition Dyspnea Index (TDI) Focal Score in the 6-Months, Placebo- and Salmeterol-Controlled Studies #130 and #137

	Tiotropium	Placebo	Salmeterol	P[1]		
	#130					
N	184	148	179	TIO-PBO	TIO-SAL	SAL-PBO
BDI FS	6.65 (0.15)	6.21 (0.19)	6.62 (0.16)			
Day 57						
TDI FS	0.31 (0.26)	-1.00 (0.29)	-0.28 (0.26)	0.0007	0.1032	0.0603
%TDI ≥1	40.22	24.32	33.52	0.0040	0.1875	0.0968
Day 113						
TDI FS	0.34 (0.25)	-0.46 (0.28)	-0.15 (0.25)	0.0310	0.1547	0.4149
%TDI ≥1	43.48	27.03	34.08	0.0035	0.0668	0.2245
Day 169						
TDI FS	0.39 (0.28)	-0.63 (0.31)	-0.39 (0.28)	0.0134	0.0447	0.5596
%TDI ≥1	41.85	26.35	35.20	0.0049	0.1950	0.1067
	#137					
N	164	161	161	TIO-PBO	TIO-SAL	SAL-PBO
BDI FS	6.43 (0.20)	6.88 (0.19)	6.47 (0.20)			
Day 57						
TDI FS	0.44 (0.26)	-0.77 (0.26)	0.90 (0.26)	0.0007	0.1997	0.0001
%TDI ≥1	43.90	31.06	47.20	0.0163	0.5519	0.0030
Day 113						
TDI FS	0.49 (0.29)	-0.65 (0.27)	0.90 (0.28)	0.0026	0.2712	0.0001
%TDI ≥1	42.07	29.81	47.20	0.0156	0.3576	0.0010
Day 169						
TDI FS	0.80 (0.28)	-0.42 (0.29)	0.85 (0.29)	0.0021	0.9031	0.0015
%TDI ≥1	44.51	32.92	47.83	0.0232	0.5569	0.0046

Shaded area indicates primary endpoint.

Throughout the six-months treatment period the tiotropium group showed an improvement in mean focal score by 0.3 to 0.4 units, whereas the placebo group worsened by 0.46 to 1.0 units in Study #130 (Study #137: Tiotropium +0.44 to + 0.8, placebo –0.42 to -0.77). The percentage of patients achieving an improvement of more than one unit from baseline ranges from 40 to 45% in the tiotropium groups compared to only 24 to 33% in the placebo groups considering both studies and all timepoints. All aforementioned comparisons to placebo had p-values <0.05. The effect is stable with time and there is no evidence of tachyphylaxis.

The analysis of three components of the Dyspnea Index, viz. Functional Impairment, Magnitude of Task and Magnitude of Effort shows that the improvement in focal score is composed of similar improvements in all three components in both studies.

In conclusion, in addition to achieving statistically significant superiority in mean FEV_1 trough response, tiotropium achieved statistical superiority in the co-primary endpoint in improvement in dyspnea, achieving the pre-specified clinically meaningful difference from placebo.

5.2.3 Dyspnea: Supportive Evidence from Transition Dyspnea Index in 1-Year Studies

One-year, placebo- and ipratropium-controlled Studies #114/#115 and #122A/#122B

Evaluation of mean TDI score in comparison of tiotropium versus placebo or ipratropium was prespecified as a secondary endpoint in the four 1-year studies. A clinically meaningful difference in mean TDI focal scores was not pre specified. For consistency of evaluation with the
6-month studies, the percentage of patients achieving an improvement of one unit in focal score was retrospectively evaluated in the 1-year studies.

In the placebo-controlled, 1-year Studies #114 and #115, the mean focal score as well as the percent of patients achieving a clinically meaningful change of TDI FS ≥1 (responders) were superior following tiotropium treatment versus placebo at all time points in both studies ($p<0.05$), except the percent responders on Day 50 ($p=0.084$). Differences in mean TDI focal scores between tiotropium and placebo ranged from 0.58-1.15 in Study #114 and 0.89-1.14 in Study #115. The percent responders with clinically meaningful improvement ranged from 40 to 46 % in the tiotropium groups versus 30 to 34 % in the placebo groups in Study #114 (Study #115, tiotropium: 44-49%, placebo: 26-35%). The higher variability of mean focal score as well as the percent responders between the replicate studies is not surprising as there is a drop (worsening) in score over the study period of 1 year (TABLE 5.2.3:1).

In comparison to the active comparator ipratropium, one of the replicate studies, Study #122B, showed superiority of tiotropium in mean TDI FS at all time points ($p<0.05$) and the percent responders was numerically more positive at all timepoints (Day 92, 182 and 364: $p<0.05$, Day 8: $p=0.051$, Day 50: $p=0.10$, Day 273: $p=0.07$). The second ipratropium-controlled Study #122A showed superiority of tiotropium for the mean of TDI FS on Days 8, 182, 273 and 364 ($p<0.05$), with positive trends on Days 50 and 92. The percent responders was numerically more favourable for tiotropium, but only at Day 182 achieved $p<0.05$ (TABLE 5.2.3:2).

In conclusion, both placebo-controlled studies consistently support the efficacy of tiotropium in relieving dyspnea. Also, one of the active controlled studies demonstrated the superiority

of tiotropium over ipratropium. The results favored tiotropium in the second study, but did not achieve statistical significance. The "weaker" results in the ipratropium-controlled studies are not surprising, because ipratropium is an active comparator. The four 1-year studies support the evidence from evaluation of the primary endpoint in the six months studies that tiotropium is effective in relieving dyspnea.

TABLE 5.2.3:1 The Baseline (BDI) and Transition Dyspnea Index (TDI) Focal Score in the 1-Year, Placebo-Controlled Studies #114 and #115

	#114			**#115**		
	Tiotropium	Placebo	P value	Tiotropium	Placebo	P value
N	258	171		249	154	
BDI FS	5.96 (0.12)	6.09 (0.17)		6.11 (0.13)	6.34 (0.17)	
Day 50						
TDI FS	0.95 (0.14)	0.14 (0.17)	0.0002	1.42 (0.15)	0.53 (0.15)	0.0001
%TDI ≥1	41.47	32.75	0.0840	49.00	32.47	0.0013
Day 92						
TDI FS	1.09 (0.15)	0.16 (0.18)	0.0001	1.50 (0.15)	0.55 (0.19)	0.0001
%TDI ≥1	45.74	33.92	0.0162	47.79	34.42	0.0096
Day 176						
TDI FS	0.78 (0.16)	0.05 (0.19)	0.0028	1.11 (0.16)	0.15 (0.21)	0.0002
%TDI ≥1	40.31	27.49	0.0072	44.18	25.97	0.0003
Day 260						
TDI FS	0.59 (0.17)	0.01 (0.21)	0.0268	1.29 (0.17)	0.22 (0.22)	0.0001
%TDI ≥1	42.25	32.16	0.0423	47.39	29.22	0.0004
Day 344						
TDI FS	0.86 (0.17)	-0.29 (0.21)	0.0001	1.25 (0.18)	0.11 (0.23)	0.0001
%TDI ≥1	45.35	30.41	0.0024	46.59	26.62	0.0001

TABLE 5.2.3:2 The Baseline (BDI) and Transition Dyspnea Index (TDI) Focal Score in the 1-Year, Ipratropium-Controlled Studies #122A and #122B

	#122A			**#122B**		
	Tiotropium	Ipratropium	P[1]	Tiotropium	Ipratropium	P
N	172	85		148	67	
BDI FS	7.12 (0.18)	7.18 (0.26)		7.16 (0.23)	7.70 (0.29)	
Day 8						
TDI FS	1.13 (0.17)	0.47 (0.24)	0.0182	0.89 (0.24)	-0.34 (0.35)	0.0028
%TDI ≥1	44.77	38.82	0.4219	44.59	29.85	0.0506
Day 50						
TDI FS	1.05 (0.20)	0.49 (0.28)	0.0824	1.51 (0.25)	0.54 (0.36)	0.0198
%TDI ≥1	45.35	34.12	0.1064	46.62	34.33	0.1030
Day 92						
TDI FS	0.83 (0.21)	0.33 (0.29)	0.1328	1.50 (0.22)	0.69 (0.32)	0.0283
%TDI ≥1	38.95	35.29	0.5874	47.97	31.34	0.0258
Day 182						
TDI FS	0.24 (0.18)	-0.49 (0.25)	0.0107	1.35 (0.24)	0.08 (0.35)	0.0020
%TDI ≥1	25.00	10.59	0.0079	45.95	28.36	0.0166
Day 273						
TDI FS	0.07 (0.16)	-0.68 (0.23)	0.0049	0.98 (0.26)	-0.27 (0.38)	0.0047
%TDI ≥1	20.35	11.76	0.1158	40.54	26.87	0.0660
Day 364						
TDI FS	-0.02 (0.18)	-0.67 (0.25)	0.0216	0.96 (0.28)	-0.25 (0.40)	0.0102
%TDI ≥1	22.67	15.29	0.1891	40.54	22.39	0.0131

[1] P are the p-values of comparisons tiotropium (TIO) versus ipratropium (IPRA), %TDI ≥1 refers to focal score and defines responder

5.2.4 Dyspnea: Supportive Evidence from Rescue Medication Use and COPD Symptoms

This improvement in dyspnea was further supported by the analysis of severity of COPD symptoms recorded by investigators after reviewing patients' daily records. This showed that tiotropium was consistently more effective than placebo in reducing wheezing and shortness of breath.

In addition, patients treated with tiotropium used significantly less albuterol than patients treated with placebo or ipratropium. FIGURE 5.2.4:1 gives an example of rescue albuterol use in the 1-year, placebo-controlled studies. They had significantly fewer nighttime awakenings because of COPD symptoms. In response to the Energy – Fatigue questionnaire patients treated with tiotropium showed a greater improvement over the 1-year period compared to both placebo and ipratropium. They also had superior physician global evaluations compared to patients treated with placebo.

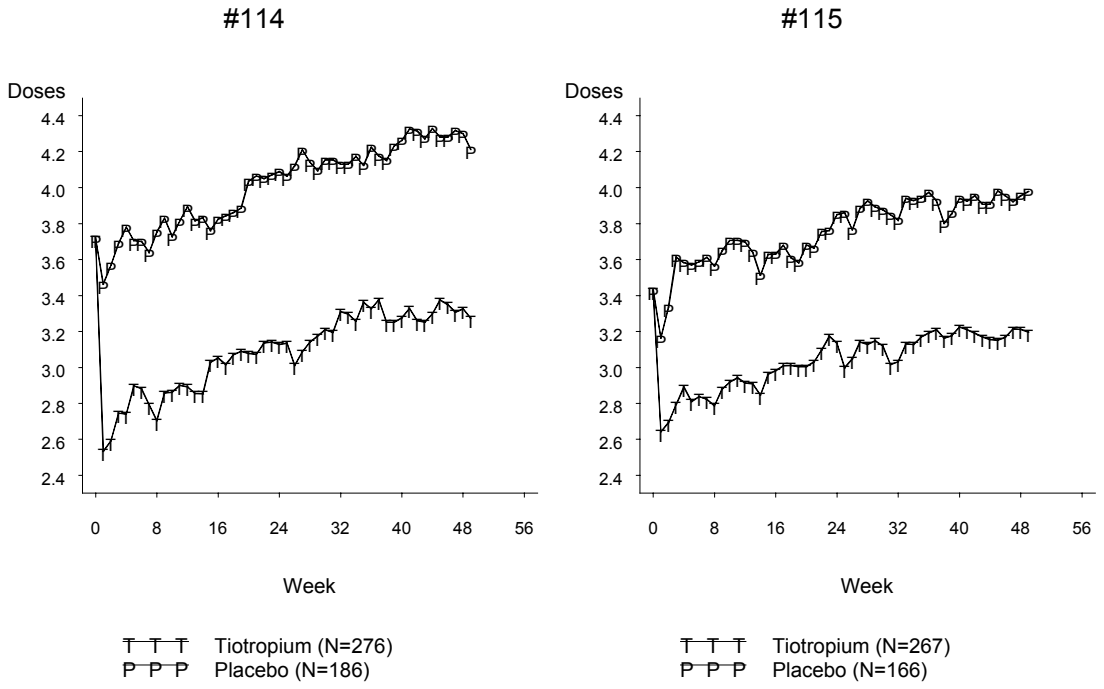


FIGURE 5.2.4:1 Rescue albuterol use in the 1-year, placebo-controlled studies

In summary, the secondary endpoints from all long-term studies support the conclusion that tiotropium is highly effective in reducing dyspnea associated with airflow limitation in COPD. This result is consistent across different endpoints, timepoints and studies. The beneficial effect was observed as early as Day 8 of treatment (first visit in one ipratropium-controlled study), became more consistent with prolonged treatment and did not fade within the observation period of up to 1 year.

5.2.5 Conclusion on Dyspnea

The minimally clinically important difference in the TDI focal score was defined as one unit (see Section 3.3.2). Improvements or worsenings of this magnitude can be expressed as either the proportion of patients achieving meaningful changes (i.e., at least one unit) or as mean changes. When expressed as proportions, it is explicitly known how many patients will achieve that specific treatment goal. A one unit change in TDI focal score results from a one unit change in at least one of the three components – functional impairment, magnitude of task or magnitude of effort in the individual patient, thereby reflecting perceivable change. The validity and clinical relevance of a one unit change in TDI focal score has been summarized by Witek and Mahler (J Clin Epidemiol, 2002 in press). Construct validity was

demonstrated by significant correlations ($p<0.05$) between BDI and other baseline measures between TDI and changes in other related measures at the end of one year. Concurrent validity was observed by the significant correlation between TDI and dyspnea diary responses. Changes in mean TDI focal score were in the range of one unit when the group was stratified by a unit change in the physician's global evaluation (perceivable change by the practitioner). Significantly less ($p<0.05$) supplemental albuterol was observed in the group of responders defined by at least one unit improvement in TDI. Those who improve dyspnea based on the TDI also had fewer exacerbations and better health status.

The percentage of patients achieving the clinically meaningful change of TDI focal score ≥1 was significantly higher following treatment with tiotropium than placebo in two independent studies, for which this measurement was the prespecified co-primary endpoint at the final day of treatment, Day 169. A statistically significant one unit change of mean TDI focal score in comparison of tiotropium versus placebo was also achieved. The other timepoints in the studies showed similarly positive results. The two 1-year studies, in which change in the mean TDI focal score was prespecified as a secondary endpoint have shown similarly consistent positive results at all timepoints. Even versus the active comparator ipratropium there is some indication of superior relief from dyspnea with tiotropium in one of the studies. The beneficial effect may occur as soon as at Day 8 on treatment, became more consistent with prolonged treatment, and did not fade within the observation period of up to 1 year. Other endpoints, health status, energy-fatigue questionnaire, physicians global evaluation and reduction of rescue medication support the positive findings with the transition dyspnea index (TDI).

The relief from dyspnea was always associated with improvement of spirometric values, FEV_1, FVC, and PEFR. Tiotropium was effective more consistently across studies and timepoints than either ipratropium or salmeterol, although both are effective bronchodilators. Because of the long duration of action and the once-a-day regimen, the effectiveness of tiotropium is less dependent on a patient's compliance. The explanation for relief from dyspnea may be seen in the magnitude and quality of stable, long-lasting, 24-hour bronchodilation achieved especially by tiotropium, which allows the respiratory muscles to recover.

Dyspnea is a cardinal and disabling symptom of COPD. It is the primary reason patients present to physicians. In the current development program tiotropium demonstrated substantial evidence of efficacy in the relief of this symptom using a specific and validated disease instrument, and supported by related changes in other outcome parameters. For this

reason, the sponsor proposes that dyspnea should be included in the Indications and Usage section of tiotropium product labeling.

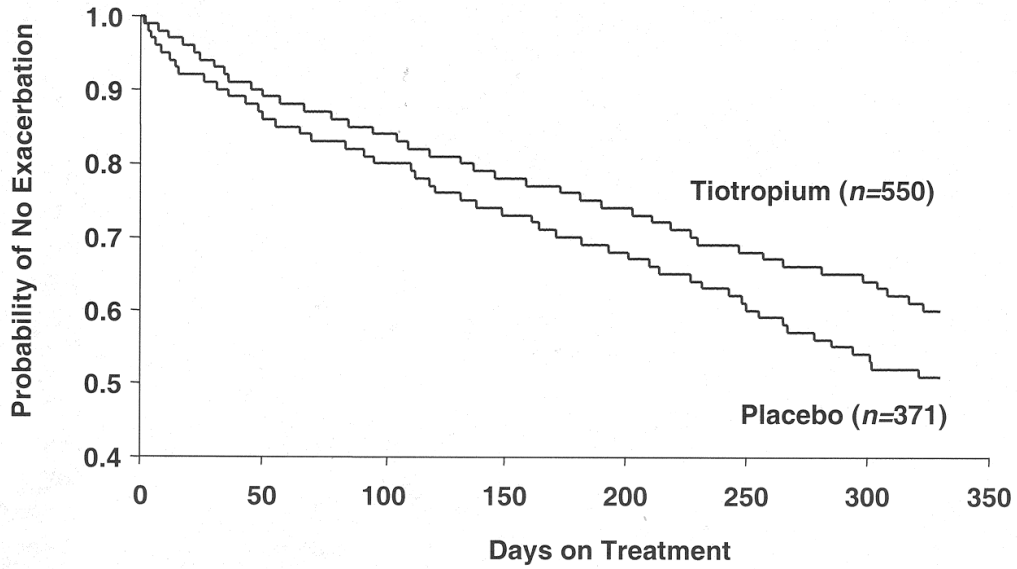
5.3 SECONDARY EFFICACY MEASURES AND EXPLORATORY ANALYSES EVIDENCE OF OVERALL THERAPEUTIC BENEFIT OF SPIRIVA

5.3.1 COPD Exacerbations

The analysis of exacerbations including pneumonia was prespecified as a secondary endpoint for combined analysis of the two replicate, 6-months, placebo- and salmeterol-controlled studies. Several compelling ways to evaluate exacerbations of COPD have been selected and prespecified: percentage of patients with at least one exacerbation, time to first exacerbation, number of exacerbations per 100 patient years and number of exacerbation days per 100 patient years. The sequence of these evaluations was not prespecified, so the alpha-level could not be protected. Therefore, special labeling claims cannot be made. In the 1-year studies this evaluation was not prespecified, and should be considered only exploratory in nature. For comparability, these evaluations were performed combining data for each replicate set of studies.

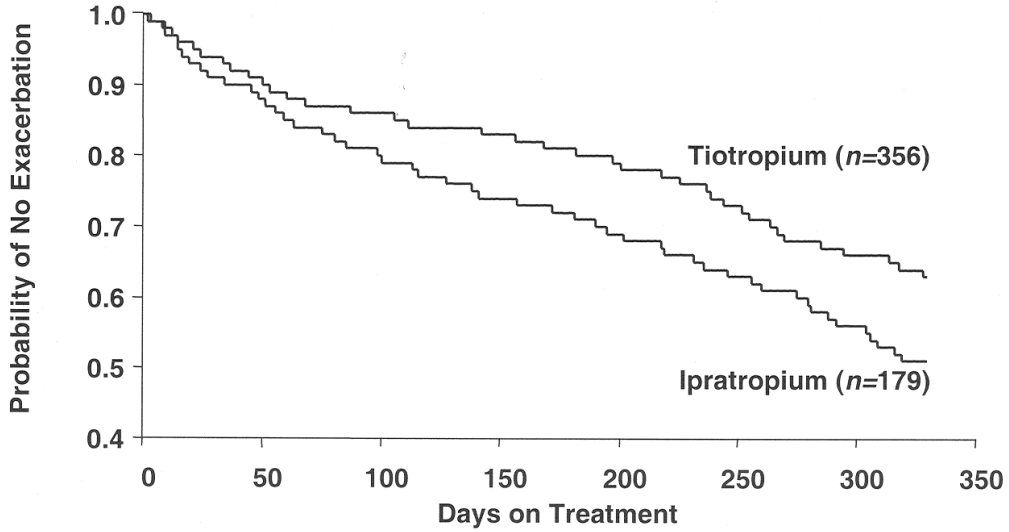
The different approaches to evaluation gave similar results that are summarized in TABLE 5.3.1:1. As an example, the Kaplan-Meier curves depicting the probability of no COPD exacerbation for all three sets of combined studies are shown (FIGURE 5.3.1:1), demonstrating that tiotropium reduced the propensity for a COPD exacerbation in all sets of studies. Overall, tiotropium treatment groups fared more favourably compared to placebo or ipratropium as comparator in all study sets and endpoints: in 9 out of 12 comparisons nominal p-values <0.05 could be assigned.

Combined Analysis of Studies #114/115



Time to first COPD exacerbation p=0.011 (log rank test)

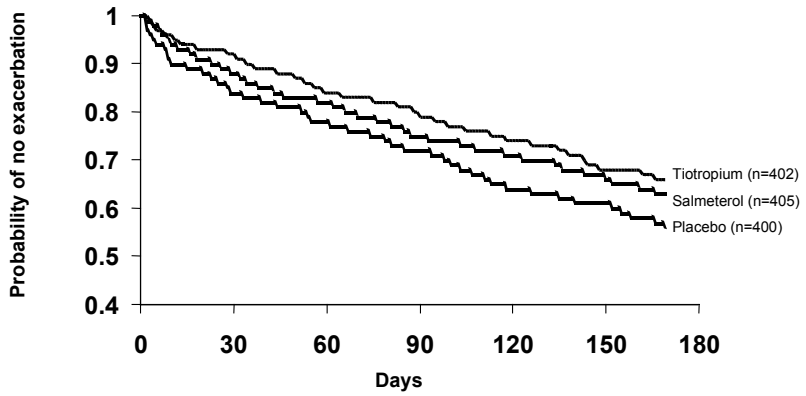
Combined Analysis of Studies #122A/122B



Time to first COPD exacerbation p=0.008 (log rank test)

Vincken W et al. Eur Respir J (2002)

Combined Analysis of Studies #130/137



Time to first COPD exacerbation *p*=0.005, tiotropium vs pbo (log rank test)

FIGURE 5.3.1:1 Kaplan-Meier Estimates of Probability of no COPD Exacerbation for the COPD Phase 3, 1-year, Placebo-Controlled, Ipratropium-Controlled and 6-Month, Placebo- and Salmeterol-Controlled Studies - All Randomized Patients

TABLE 5.3.1:1 Summary of Exacerbation Variables in the 6- Months and 1-Year Controlled Studies (Combined Analysis of Replicate Studies). Limitations of the analysis are described in Section 5.3.1. Numbers indicate the nominal p-value associated with the comparison of tiotropium with the control (placebo or ipratropium)

Study/Variable	**#114/115 49 weeks**	**#122A/B 52 weeks**	**#130/137 26 weeks**
Treatment	**Tiotropium/Placebo**	**Tiotropium/Ipratropium**	**Tiotropium/Placebo**
% Patients with at least 1 exacerbation (p)	36 42 (0.03)	35 46 (0.015)	32 39 (0.064)
Time to first exacerbation (p)	(0.011)	(0.008)	(0.005)
Number of exacerbations per 100 years (p)	76 95 (0.045)	73 96 (0.006)	107 149 (0.025)
Number of exacerbation days per 100 years (p)	1470 1495 (0.117)	1076 1769 (0.002)	1724 2500 (0.025)

5.3.2 Health Status: SGRQ and SF-36

Health-related quality of life (QOL) was evaluated using two different instruments. These were the disease specific quality of life instrument, SGRQ and a generic quality of life instrument, SF-36™ that was used in addition in the 1-year studies.

Quality of life measures were secondary endpoints in the four 1-year placebo- or ipratropium-controlled studies, with prespecification for a change in the impact domain score of four units. QOL measures were also secondary endpoints in the two 6-month placebo- and salmeterol-controlled studies, with prespecification for a change in the total score of four units. QOL measures were monitored over the full duration of the study.

Tiotropium was superior to placebo and ipratropium in the 1-year studies in improving the SGRQ impact domain score as well as total score: the difference in mean for the impact domain score between tiotropium and placebo ranged from 2.9 to 4.0 and that between tiotropium and ipratropium ranged from 2.5 to 4.3 over the last six months during the 1-year treatment period, with $p<0.05$ on all test days. Not unexpectedly, the difference between tiotropium and comparator increased with the duration of treatment. The difference in mean for the total score between tiotropium and placebo ranged from 3.0 to 3.7 and that between tiotropium and ipratropium ranged from 2.1 to 3.3 over the last six months during the 1-year treatment period. Although $p<0.05$ was reached on all test days for the impact domain as well as total score, the predefined difference of clinical meaningful change of four points was approached but often not reached.

Statistically significant differences between tiotropium and placebo were also noted for all domains of the SGRQ over the last six months during the 1-year treatment period. In an exploratory analysis, a significantly greater number of patients in the tiotropium groups compared to placebo showed a clinically meaningful improvement of four units in both impact and total scores in the final six months of the 1-year studies.

In the 6-month, placebo- and salmeterol-controlled studies, tiotropium was superior to placebo in total and impact SGRQ scores. The difference in mean for the total score between tiotropium and placebo ranged from 1.7 to 2.8 ($p<0.05$) on all test days. In these studies, tiotropium was also superior to placebo in symptom score on all test days.

These results were confirmed by the patient responses to the generic health-related quality of life questionnaire, SF-36™ assessed in the 1-year studies. Tiotropium was superior to placebo

in all physical domains except Bodily Pain. In mental health domains tiotropium was superior to placebo in Vitality and Social Function.

Overall, the assessment of health status with a disease specific and a generic instrument show the superiority of tiotropium to placebo and less clearly, to ipratropium. Although the predefined clinically meaningful difference was approached but often not reached, these results are consistent with the demonstrated improvement by tiotropium in lung function, dyspnea, COPD symptoms, and reduction of exacerbations of COPD.

5.4 ADDITIONAL ASPECTS OF THE CLINICAL PROFILE OF SPIRIVA

5.4.1 Onset of Effect and Onset of Steady State

One center in Study #122A performed additional pulmonary function testing to determine the onset of pharmacodynamic steady state with respect to FEV_1 improvement. This subset of the study was reported as Study #129.

Thirty-one patients were randomized into the 8-day portion of the 1-year, double-blind, double-dummy study to tiotropium or ipratropium (one capsule from the HandiHaler® q.d. + two puffs from the MDI q.i.d.). The baseline demographics of the subset is not different from the complete study population reported in Section 4.

Onset of a clinically and statistically significant increase in trough FEV_1 response occurred within 24 hours after the first dose of tiotropium. Trough FEV_1 response, i.e., the response 23-24 hours post-dose, reached pharmacodynamic steady state within the 8-day observation period with an increase in mean of 0.19 L (18%) over baseline on Test-Day 8. Most of this increase was achieved by Test-Day 3 (0.14 L, 13% over baseline) and was maintained at the 7-week visit of the 1-year study. This confirmed that in terms of FEV_1, pharmacodynamic steady state was achieved within 1 week of daily dosing with tiotropium. Peak and average FEV_1 response showed similar trends, further demonstrating that for the acute response (1-6 hours post-dose), pharmacodynamic steady state was achieved within 1 week of daily dosing with tiotropium.

The results for FVC parallel those for FEV_1, with an increase in mean trough of 0.67 L on Test-Day 8. Again, most of the improvement was seen by Test-Day 3 (0.47 L) and also maintained after 7 weeks of treatment. Peak and average FVC response again showed similar trends to trough response.

Daily morning PEFR data provided additional support showing achievement of steady state by Test-Day 6, with about half of the effect seen by Test-Day 4. Daily evening PEFR data were stable by Test-Day 3.

In summary, the data from this study showed that pharmacodynamic steady state was achieved within 1 week of daily dosing with tiotropium.

5.4.2 Timing of Dosing, AM/PM Dosing Study

The purpose of this multi-center, double-blind, parallel-group, placebo-controlled study (#123) was to determine whether the time of dosing (a.m. or p.m.) at steady state influences the bronchodilator response of tiotropium in patients with COPD.

The inclusion criteria were similar to those in the 1-year studies. Following an initial screening and a 7-day run-in period, 121 patients entered the double-blind phase of the study. The baseline features of the three treatment groups (tiotropium a.m. dosing; tiotropium p.m. dosing; and placebo) were very similar. The overall mean age was 65.8 years and 62% of the study population was male. All patients were Caucasian. The mean FEV_1 at screening was 1.08 L and mean percent predicted according to the ECCS criteria was 40.8%. The mean FEV_1/FVC was 50.8%.

Patients attended a baseline clinic visit of 24-hours duration. FEV_1 was measured for a full 24 hours at 3 hour intervals. Patients received their first morning dose of study medication on completion of this visit. Patients continued to take their morning and evening medications for a period of 6-weeks and completed diary cards with twice daily PEFR readings, COPD symptoms scores, and rescue medication usage. At the final clinic visit, 3 hourly FEV_1 measurements were repeated for 24 hours.

Of the 121 patients randomised, 105 (86.8%) completed all 3 visits; 35 (81.4%) in the tiotropium p.m. group, 38 (100%) in the tiotropium a.m. group and 32 (80%) in the placebo group.

The steady state bronchodilator effect at the time of dosing of tiotropium was primarily determined by the early morning dip in FEV_1 following the last dose of study medication (43 ±3 days after initiation of therapy). The morning dip in FEV_1 response was defined as the mean of the FEV_1 values recorded at 3 a.m. and 6 a.m. Baseline FEV_1 was derived from the measurements recorded at 3 a.m. and 6 a.m. prior to the administration of study drug on Test-Day 1.

The overall steady state bronchodilator efficacy of tiotropium was determined by the average FEV_1 measured over a specified 24-hour time interval at the last visit (i.e., from 9 a.m. on Day 42 to 9 a.m. on Day 43). The average FEV_1 at baseline was calculated as the mean of the 3-hourly FEV_1 readings measured over 24-hours from 9 a.m. on Day 0 to 9 a.m. on Day 1.

The data for the morning dip (3-6 a.m.) showed that the FEV_1 for both tiotropium dosing groups was highly statistically significantly ($p<0.01$) greater in comparison with placebo (a difference from placebo in mean of 0.21 L for both). The difference in mean morning dip FEV_1 response of 0.01 L between the two tiotropium dosing groups (p.m.–a.m.) at steady state (Day 43) was not statistically significant.

The differences between each tiotropium dosing group and placebo in the overall 24-hour steady state FEV_1 response after 6 weeks of treatment (Days 42/43) were highly statistically significant ($p<0.01$). The difference between the tiotropium p.m. group and the tiotropium a.m. group was not statistically significant.

In conclusion, the data from this study support the claim that 18 µg tiotropium lactose inhalet orally inhaled is an effective once-a-day bronchodilator for maintenance treatment of bronchospasm in patients with COPD. The 24-hour lung function profile shows that efficacy is maintained throughout the 24-hour dosing interval regardless of the time of dosing.

5.5 ANALYSIS OF WITHDRAWAL OF THERAPY

Following the end of therapy in the 1-year studies, patients were followed for an additional 3 weeks during which they continued to perform their PEFRs and record their use of albuterol inhalation aerosol in their daily record cards. In addition to these data, quality of life questionnaires as well as COPD symptoms and global evaluations (only in placebo-controlled studies) were evaluated. Only those patients who had a valid baseline measurement, who completed the study, and who had at least some post-treatment data, were included in these evaluations.

With the exception of the albuterol use in the 1-year, ipratropium-controlled studies, the post-treatment data gradually moved toward baseline. For both treatment groups in the ipratropium-controlled studies, the number of puffs per day of albuterol showed an initial increase from baseline during the first washout week that remained stable for the remainder of the washout period. However, since this increase was seen for both groups, less occurred in the tiotropium group and was not seen in the placebo-controlled studies or for the other endpoints, it was not seen as evidence of rebound.

In the 6-month placebo- and salmeterol-controlled studies patients were also followed for an additional 3 weeks. The same rules as in the 1-year studies were followed to evaluate if there was any rebound effect. These data confirm that there is no evidence for a rebound effect following withdrawal of tiotropium.

5.6 EFFICACY IN POPULATION SUBGROUPS

Efficacy results were evaluated for the following population subgroups: smoking status (current smokers, former smokers), severity of disease (FEV_1 <35%, ≥35 to 50%, ≥50% predicted), inhaled glucocorticoid use (yes, no), gender (male, female), age (40-64 years, ≥65 years, ≥75 years). There were only few subjects in the non-White (Black or Other) subgroups to determine a response to treatment.

The subgroup analyses showed that tiotropium was similarly effective in all subgroups based on the demographic variables mentioned above. The data showed that the effect of tiotropium on spirometric response and health related quality of life was more pronounced in moderate COPD patients (FEV_1 between 35% to 50% predicted). The use of steroids had no impact on the effect of tiotropium in COPD patients. Tiotropium was effective in patients who used theophylline as well as those who did not use theophylline.

5.7 SUMMARY OF EFFICACY

The tiotropium clinical study database provides robust evidence to support the proposed labeling that the 18 mcg dose of tiotropium 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. Improvement in FEV_1 and TDI focal score provide the primary support for this indication. Supportive evidence of overall benefit of treatment with tiotropium is provided by improvement of health status, COPD symptoms, and reduced exacerbations of COPD.

6. SAFETY

6.1 INTRODUCTION

Tiotropium is an inhaled quaternary anticholinergic bronchodilator developed for the treatment of bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The inhalation powder capsules proposed for market introduction contain 18 mcg of tiotropium diluted with lactose monohydrate. Tiotropium shares several positive properties attributable to the class of N-quaternary anticholinergic agents such as ipratropium. Ipratropium has been marketed globally by Boehringer Ingelheim for more than 25 years and has established a successful benefit/risk profile. As with ipratropium, tiotropium has limited oral bioavailability and does not cross the blood-brain barrier to an appreciable extent. The limited systemic exposure of tiotropium provides the pharmacologic rationale for a favorable safety profile.

Toxicity studies in various animal species and by different routes of administration confirmed the expected toxicology profile for this potent, long-acting anticholinergic agent. In rabbits, rats and dogs, the systemic administration of supra-therapeutic doses of tiotropium induced several non-CNS antimuscarinic effects, such as inhibition of salivation and lacrimation, mydriasis, coprostasis and increased heart rate. This experience provides a basis for evaluating the clinical safety of tiotropium.

The clinical safety of tiotropium is described by analyses of adverse events (AEs) in large, controlled randomized clinical studies. The core safety population comprises patients with objective evidence of airway obstruction participating in 1-year placebo-controlled and ipratropium-controlled studies and 6-month studies with both placebo and salmeterol controls. The population in terms of its size and demographics is described in Section 4.1; the duration of exposure is detailed in Section 6.2 below. The adverse event profile presents an overview of the important categories of adverse events and shows that tiotropium is comparable to placebo with regard to proportion of patients who had an adverse event. A smaller proportion of tiotropium patients than placebo patients had serious adverse events including fatal events, and adverse events leading to discontinuation of treatment. Detailed analyses of specific adverse events present the most common adverse events, followed by those events that are clinically significant. We consider as clinically significant those adverse events classified as serious, including fatal adverse events, or adverse events leading to discontinuation of therapy. Guided by these analyses and its well-understood pharmacology, we characterize the safety profile and identify adverse events possibly associated with tiotropium by pooling the

1-year and 6-month placebo-controlled studies for selected adverse events, and computing incidence rates expressed per unit time on treatment. Finally, we discuss supplementary safety data on electrocardiography, vital signs, laboratory tests, physical examinations and mucociliary clearance.

This safety assessment shows that the adverse events most likely to be associated with tiotropium are those that are expected from its pharmacology, most commonly dry mouth (Mintzer and Burns; 2000). Other possible anticholinergic events including upper respiratory symptoms, tachyarrhythmias, urinary symptoms, and constipation, occur less frequently and, like dry mouth, are rarely serious and usually do not require discontinuation of medication.

6.2 CLINICAL SAFETY

6.2.1 Population

The primary support of safety for tiotropium 18 mcg in COPD patients is demonstrated by six large Phase 3 studies: two 1-year studies in comparison with placebo, two 1-year studies in comparison with ipratropium bromide (40 mcg qid by inhalation aerosol), and two 6-month studies in comparison with both salmeterol (50 mcg by inhalation aerosol) and placebo. In each study, 18 mcg tiotropium powder capsules were orally inhaled once daily via the HandiHaler® by patients with COPD.

The patient participation is detailed in Section 4. In all, these long-term studies include information on 1,308 tiotropium patients, as well as 771 placebo patients, 405 salmeterol patients, and 179 ipratropium patients. The pooled placebo-controlled studies include 952 subjects contributing 679 person-years of exposure to tiotropium and 771 subjects contributing 483 person-years of exposure to placebo.

The protocols for the 1-year and 6-month studies were similar. These studies sought patients who had a diagnosis of COPD with objective documentation of airflow limitation, were at least 40 years of age, and a smoking history of at least 10 pack-years. Patients with a history of asthma were excluded as were patients judged by investigators to have significant disease other than COPD. Specifically excluded by protocol were patients with symptomatic prostatic hypertrophy or bladder neck obstruction, narrow-angle glaucoma, as well as patients who experienced heart failure within the past three years, myocardial infarction within the past year, or who had a cardiac arrhythmia requiring drug therapy.

The study populations, as described in TABLE 4.2:1, were balanced between the tiotropium and control groups within these studies. The mean age for all patients in these studies was

approximately 64 years. Most of the patients were Caucasian in both populations. In the placebo-controlled studies, 65% of the patients were male compared with 85% in the ipratropium-controlled studies. In the 6-month studies, all but 5 of the 1,207 patients were Caucasian, and 76% were male. There was no difference between treatment groups in duration of COPD (a mean for all patients of 9.6 years) and smoking history (mean for all patients of 43.7 pack years). The mean FEV_1 of the population was approximately 1.1 L (40% predicted).

TABLE 6.2.1:1 presents the distribution of patients by duration of exposure in the core studies. In the placebo-controlled studies, 482 patients (87.6%) received tiotropium 18 mcg once daily for at least 200 days and 302 patients (54.9%) received tiotropium for at least 330 days. The median exposure was 10 days longer for the tiotropium patients than the placebo patients (338 days *vs* 328 days) owing to greater discontinuations among the placebo patients. In the 1-year ipratropium-controlled studies, 316 patients (88.8%) received tiotropium for more than 200 days and 260 patients (73%) received tiotropium for more than 330 days. The median exposure was similar for both groups (365 days *vs* 364 days). In the 6-month studies, 353 patients (87.8%) received tiotropium 18 mcg for at least 101 days, and the median treatment exposure was 169 days for each treatment group.

TABLE 6.2.1:1 Patient Exposure in 1-Year and 6-Month Studies

	1-year studies								6-month studies					
	Placebo-controlled				Active-controlled									
	Tiotropium		Placebo		Tiotropium		Ipratropium		Tiotropium		Placebo		Salmeterol	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total treated	550	(100)	371	(100)	356	(100)	179	(100)	402	(100)	400	(100)	405	(100)
Exposure (days)														
1	2	(0.4)	2	(0.5)	2	(0.6)	1	(0.6)	2	(0.5)	6	(1.5)	2	(0.5)
2-7	3	(0.5)	10	(2.7)	9	(2.5)	3	(1.7)	5	(1.2)	12	(3.0)	2	(0.5)
8-60	27	(4.9)	34	(9.2)	16	(4.5)	14	(7.8)	26	(6.5)	50	(12.5)	37	(9.1)
61-100	17	(3.1)	14	(3.8)	4	(1.1)	5	(2.8)	15	(3.7)	14	(3.5)	14	(3.5)
101-200	19	(3.5)	18	(4.9)	9	(2.5)	7	(3.9)	353	(87.8)	318	(79.5)	350	(86.4)
201-330	180	(32.7)	110	(29.6)	56	(15.7)	31	(17.3)	1	(0.2)	0	(0.0)	0	(0.0)
> 330	302	(54.9)	183	(49.3)	260	(73.0)	118	(65.9)						
Median	338.0		328.0		365.0		364.0		169.0		169.0		169.0	
Range	1.00-408.0		1.00-371.0		1.00-388.0		1.00-386.0		1.00-210.0		1.00-193.0		1.00-190.0	

6.2.2 Adverse Event Profile

Safety assessment is based primarily on clinical endpoints as assessed by adverse events in the core studies. Adverse events were reported at each visit in response to the question, "How have you felt since your last visit?" The type of event was recorded on the case report form, along with date of onset, event end date, intensity, treatment required, investigator's assessment of whether or not the event was possibly related to the study drug, action taken with the study drug, and outcome of the event. Adverse event preferred terms were classified to system organ class according to a standard coding dictionary developed by the World Health Organization (WHO). The respiratory system was divided into upper and lower respiratory system disorders by preferred term, as determined by the clinical monitor.

The adverse event profile from the 1-year and 6-month studies is shown in TABLES 6.2.2:1 and 6.2.2:2. The proportion of patients experiencing all adverse events was similar across treatment groups. The proportion of patients experiencing serious adverse events, adverse events leading to discontinuation, and fatal adverse events was smaller among patients receiving tiotropium compared with patients receiving placebo. Adverse events judged by the investigator to be drug-related were more common among patients receiving tiotropium compared with placebo due to reports of dry mouth.

Compared with ipratropium, the proportion of tiotropium patients experiencing any adverse event was similar. A smaller number of patients receiving tiotropium had serious adverse events and adverse events leading to discontinuation, while the proportion of patients experiencing fatal adverse events was slightly lower for patients receiving ipratropium. Contrasted with salmeterol, a smaller proportion of tiotropium patients experienced all adverse events, fatal adverse events, serious adverse events, and adverse events leading to discontinuation, while the proportion of patients with drug-related adverse events was greater among tiotropium patients due to reports of dry mouth.

TABLE 6.2.2:1 Adverse Event Profile: Number of Patients with Adverse Events in 1-Year Studies

	Placebo-controlled				Active-controlled			
	Tiotropium		Placebo		Tiotropium		Ipratropium	
	N	(%)	N	(%)	N	(%)	N	(%)
Total Treated	550	(100)	371	(100)	356	(100)	179	(100)
Total with any adverse event	495	(90.0)	338	(91.1)	318	(89.3)	162	(90.5)
Drug-related adverse events	104	(18.9)	34	(9.2)	73	(20.5)	22	(12.3)
Serious adverse events	99	(18.0)	78	(21.0)	57	(16.0)	46	(25.7)
Adverse events leading to discontinuation	53	(9.6)	50	(13.5)	35	(9.8)	22	(12.3)
Fatal adverse events	7	(1.3)	7	(1.9)	9	(2.5)	3	(1.7)

TABLE 6.2.2:2 Adverse Event Profile: Number of Patients with Adverse Events in 6-Month Studies

	Tiotropium		Placebo		Salmeterol	
	N	(%)	N	(%)	N	(%)
Total Treated	402	(100)	400	(100)	405	(100)
Total with any adverse event	298	(74.1)	307	(76.8)	305	(75.3)
Drug-related adverse events	44	(10.9)	31	(7.8)	33	(8.1)
Serious adverse events	37	(9.2)	55	(13.8)	50	(12.3)
Adverse events leading to discontinuation	29	(7.2)	64	(16.0)	60	(14.8)
Deaths	1	(0.2)	5	(1.3)	6	(1.5)

6.2.3 Common Adverse Events

The most common adverse events are those events most likely to be seen in clinical practice. Adverse events observed in at least 3% of tiotropium patients are tabulated in TABLE 6.2.3:1 for the 1-year studies, and in TABLE 6.2.3:2 for the 6-month studies. Events are presented alphabetically by system organ class and preferred term, as reported by the investigator. For each event, we tabulate the number of events and proportion of patients with each event by treatment group. In computing the proportion of patients with an event, a patient can appear only once for each event. Patients with multiple adverse events are tabulated for each event that occurred. In the discussion below we identify differences between treatment groups of at least 1% in proportions of patients who had an adverse event.

In the 1-year placebo-controlled studies, a higher proportion of tiotropium patients (by more than 1%) experienced accidents, chest pain, edema, abdominal pain, constipation, dyspepsia,

dry mouth, vomiting, infection, moniliasis, epistaxis, pharyngitis, sinusitis, upper respiratory tract infection, rash and urinary tract infection. By contrast, a smaller proportion of tiotropium patients (by more than 1%) experienced fatigue, headache, diarrhea, nausea, COPD exacerbations, and pneumonia.

Compared with ipratropium, a larger proportion of tiotropium patients had back pain, chest pain, dry mouth, moniliasis, pharyngitis, sinusitis, upper respiratory tract infection, and urinary tract infection. A smaller proportion of tiotropium patients than ipratropium patients experienced accidents, edema, headache, influenza-like symptoms, dizziness, nausea, infection, COPD exacerbation, coughing, and dyspnea.

In the 6-month studies, when compared with placebo, a larger proportion of tiotropium patients had accidents, back pain, headache, influenza-like symptoms, dry mouth, coughing, pharyngitis, and upper respiratory tract infection. A smaller proportion of tiotropium patients than placebo patients experienced COPD exacerbations and dyspnea.

Compared with salmeterol, a larger proportion of tiotropium patients had influenza-like symptoms, dry mouth, pharyngitis, sinusitis, and upper respiratory tract infection. A smaller proportion of tiotropium patients than salmeterol patients had accidents and COPD exacerbations.

For all long-term studies, the largest difference between the tiotropium group and control group was for dry mouth, a recognized anticholinergic effect. Dry mouth had a median onset of about 3 weeks, was usually judged as mild or moderate, often resolved during continued therapy, and rarely resulted in discontinuation of therapy.

TABLE 6.2.3:1 Number of Patients with Adverse Events in 3% or More of Tiotropium Patients in 1-Year Studies

		Placebo-controlled				Active-controlled			
		Tiotropium		Placebo		Tiotropium		Ipratropium	
WHO system organ class	WHO preferred term	N	(%)	N	(%)	N	(%)	N	(%)
Total treated		550	(100)	371	(100)	356	(100)	179	(100)
Total with any adverse event		495	(90.0)	338	(91.1)	318	(89.3)	162	(90.5)
Body as a whole-general disorders									
	Accidents[a]	73	(13.3)	42	(11.3)	16	(4.5)	14	(7.8)
	Back pain	36	(6.5)	26	(7.0)	27	(7.6)	9	(5.0)
	Chest pain	38	(6.9)	17	(4.6)	19	(5.3)	4	(2.2)
	Edema[b]	25	(4.5)	13	(3.5)	10	(2.8)	9	(5.0)
	Fatigue	19	(3.5)	17	(4.6)	12	(3.4)	5	(2.8)
	Headache	44	(8.0)	44	(11.9)	40	(11.2)	25	(14.0)
	Influenza-like symptoms	45	(8.2)	30	(8.1)	39	(11.0)	25	(14.0)
	Pain	21	(3.8)	16	(4.3)	16	(4.5)	7	(3.9)
Cardiovascular disorders, general									
	Hypertension [c]	18	(3.3)	14	(3.8)	13	(3.7)	7	(3.9)
Cent & peripheral nervous system disorders									
	Dizziness	29	(5.3)	20	(5.4)	6	(1.7)	8	(4.5)
Gastrointestinal system disorders									
	Abdominal pain	26	(4.7)	11	(3.0)	20	(5.6)	11	(6.1)
	Constipation	19	(3.5)	6	(1.6)	2	(0.6)	2	(1.1)
	Diarrhea	31	(5.6)	25	(6.7)	10	(2.8)	5	(2.8)
	Dyspepsia	32	(5.8)	17	(4.6)	5	(1.4)	1	(0.6)
	Dry mouth	88	(16.0)	10	(2.7)	43	(12.1)	11	(6.1)
	Nausea	25	(4.5)	27	(7.3)	10	(2.8)	7	(3.9)
	Vomiting	19	(3.5)	9	(2.4)	3	(0.8)	3	(1.7)

a Accidents- Includes accidents household, accidents vehicular and falls
b Edema - Includes edema, edema dependent, edema generalized, edema legs, edema peripheral
c Hypertension- Includes hypertension and hypertension aggravated

TABLE 6.2.3:1 (continued) Number of Patients with Adverse Events in 3% or More of Tiotropium Patients in 1-Year Studies (Page 2 of 2)

		Placebo-controlled				Active-controlled			
		Tiotropium		Placebo		Tiotropium		Ipratropium	
WHO system organ class	WHO preferred term	N	(%)	N	(%)	N	(%)	N	(%)
Musculoskeletal system disorders									
	Arthritis[d]	26	(4.7)	17	(4.6)	15	(4.2)	7	(3.9)
	Myalgia	21	(3.8)	11	(3.0)	13	(3.7)	6	(3.4)
Resistance mechanism disorders									
	Infection[e]	23	(4.2)	12	(3.2)	5	(1.4)	5	(2.8)
	Moniliasis[f]	20	(3.6)	9	(2.4)	10	(2.8)	3	(1.7)
Respiratory system disorders (lower)									
	COPD exacerbation	196	(35.6)	148	(39.9)	124	(34.8)	85	(47.5)
	Coughing	26	(4.7)	17	(4.6)	30	(8.4)	17	(9.5)
	Dyspnoea	25	(4.5)	20	(5.4)	39	(11.0)	27	(15.1)
	Pneumonia	24	(4.4)	24	(6.5)	18	(5.1)	10	(5.6)
Respiratory system disorders (upper)									
	Epistaxis	20	(3.6)	7	(1.9)	4	(1.1)	2	(1.1)
	Pharyngitis	49	(8.9)	27	(7.3)	23	(6.5)	5	(2.8)
	Rhinitis	30	(5.5)	20	(5.4)	9	(2.5)	4	(2.2)
	Sinusitis	62	(11.3)	35	(9.4)	12	(3.4)	4	(2.2)
	Upper respiratory tract infection	226	(41.1)	138	(37.2)	153	(43.0)	62	(34.6)
Skin and appendages disorders									
	Rash[g]	23	(4.2)	8	(2.2)	7	(2.0)	4	(2.2)
Urinary system disorders									
	Urinary tract infection[h]	40	(7.3)	19	(5.1)	14	(3.9)	4	(2.2)

d Arthritis- Includes arthritis, arthritis aggravated, arthralgia and arthrosis
e Infection- Includes infection, infection bacteria and infection viral
f Moniliasis- Includes moniliasis and moniliasis genital
g Rash- Includes rash, rash erythematous and rash maulo-papular
h Urinary tract infection- Includes urinary tract infection and cystitis

TABLE 6.2.3:2 Number of Patients with Adverse Events in 3% or More of Tiotropium Patients in 6-Month Studies

		Tiotropium		Placebo		Salmeterol	
WHO system organ class	WHO preferred term	N	(%)	N	(%)	N	(%)
Total treated		402	(100)	400	(100)	405	(100)
Total with any adverse event		298	(74.1)	307	(76.8)	305	(75.3)
Body as a whole-general disorders							
	Accidents[a]	17	(4.2)	10	(2.5)	21	(5.2)
	Back pain	16	(4.0)	12	(3.0)	16	(4.0)
	Chest pain	16	(4.0)	15	(3.8)	14	(3.5)
	Headache	26	(6.5)	18	(4.5)	28	(6.9)
	Influenza-like symptoms	27	(6.7)	16	(4.0)	21	(5.2)
Gastrointestinal system disorders							
	Dry mouth	33	(8.2)	9	(2.3)	7	(1.7)
Respiratory system disorders (lower)							
	COPD exacerbation	135	(33.6)	163	(40.8)	149	(36.8)
	Coughing	21	(5.2)	14	(3.5)	24	(5.9)
	Dyspnoea	26	(6.5)	36	(9.0)	25	(6.2)
Respiratory system disorders (upper)							
	Pharyngitis	18	(4.5)	12	(3.0)	14	(3.5)
	Rhinitis	11	(2.7)	13	(3.2)	13	(3.3)
	Sinusitis	13	(3.2)	10	(2.5)	1	(0.2)
	Upper respiratory tract infection	78	(19.4)	64	(16.0)	69	(17.0)

[a] Accidents- Includes accidents household, accidents vehicular and falls.
Abbreviations:

6.2.4 Clinically Significant Adverse Events

6.2.4.1 Serious Adverse Events

Adverse events are classified as serious if they are considered immediately life-threatening, result in death, require or prolong hospitalization, are incapacitating or a significant disability, a congenital anomaly, or otherwise deemed serious according to the medical judgment of the investigator. Serious adverse events from the 1-year studies and from the 6-month studies are shown in TABLES 6.2.4.1:1 and 6.2.4.1:2. Patients are counted only once for each event, and patients who experience multiple events are counted as cases for each event that occurred. To simplify the presentation, we present events that occurred in more than one patient in any treatment group. Our rationale is that an event that occurs in no more than one patient in any treatment group provides an unreliable basis for inference.

In both the 1-year studies and the 6-month studies, the most common serious adverse event was COPD exacerbation, and COPD exacerbation was also the only serious adverse event that

occurred with a difference of 1% or more between comparison groups. COPD exacerbations occurred less frequently among tiotropium patients than among patients who receive placebo, ipratropium, or salmeterol. Among other serious adverse events occurring in more than 1% of any group, chest pain occurred in a slightly larger proportion of tiotropium patients than placebo patients (1.5% v. 1.1%), and basal cell carcinoma occurred in a slightly larger proportion of placebo patients (1.3% v. 0.5%). In the ipratropium-controlled studies, among serious adverse events occurring in at least 1% of patients in any treatment group, pulmonary neoplasms occurred in a larger proportion of tiotropium patients (1.1% v. 0.6%), while a smaller proportion of tiotropium patients experienced atrial fibrillation (0% v. 1.1%) or angina pectoris (0.8% v. 1.7%). Each of these differences is based on a small number of cases.

Dehydration was reported in five (0.9%) tiotropium patients in the 1-year placebo controlled studies and in none of the placebo patients. In all cases, dehydration occurred in the setting of a systemic illness that contributed to the clinical outcome. No cases of dehydration occurred in the 1-year ipratropium-controlled studies or in the 6-month studies.

There are several events for which numerical imbalances occurred between treatment groups that were inconsistent across studies. For instance, in the 1-year placebo-controlled studies, there were four cases (0.7%) classified as “neoplasm, malignant” in the tiotropium group, and none in the placebo group; in the ipratropium studies there was one case (0.6%) in the ipratropium group and no cases in any group in the 6-month studies. In the 1-year studies there were three (0.5%) cases of cardiac failure in the tiotropium group as compared with three (0.8%) cases in the placebo group, and in the ipratropium-controlled studies there were no cases in the tiotropium group versus one case (0.6%) in the ipratropium group. In the 6-month studies, there were no cases of cardiac failure with tiotropium, but there two cases (0.5%) with placebo and six (1.5%) cases in the salmeterol group. Finally, in the 1-year studies there were three cases (0.5%) of myocardial infarction in the tiotropium group compared with one case (0.3%) in the placebo group, and three cases (0.8%) in the tiotropium group as compared with no cases in the ipratropium group; in the 6-month studies there was one case (0.2%) of myocardial infarction in the tiotropium group and three cases (0.8%) in the placebo group and two cases (0.5%) in the salmeterol group. In the 1-year placebo-controlled studies, there were three cases (0.5%) of syncope in the tiotropium group and none in the placebo group, while in the ipratropium-controlled studies there were two cases of syncope in the tiotropium group and one case in the ipratropium group (0.6% in each group). No cases of syncope were reported in the 6-month studies.

In summary, overall serious adverse events occur more frequently in each comparator group than in the tiotropium groups. This decreased risk of serious adverse events with tiotropium is due primarily to a lower risk of COPD exacerbations associated with tiotropium. Other serious adverse events, including events considered possible anticholinergic effects, tend to occur rarely or with similar frequency among treatment groups.

TABLE 6.2.4.1:1 Number of Patients with Serious Adverse Events for 1-Year Studies

		Placebo-controlled				Active-controlled			
		Tiotropium		Placebo		Tiotropium		Ipratropium	
WHO system organ class	WHO preferred term	N	(%)	N	(%)	N	(%)	N	(%)
Total treated		550	(100)	371	(100)	356	(100)	179	(100)
Total with any serious adverse event		99	(18.0)	78	(21.0)	57	(16.0)	46	(25.7)
Body as a whole General disorders	Accident vehicular	2	(0.4)	0	(0)	3	(0.8)	0	(0)
	Chest pain	8	(1.5)	4	(1.1)	1	(0.3)	0	(0)
	Fall	0	(0)	2	(0.5)	0	(0)	0	(0)
Cardiovascular disorders, general	Cardiac failure	3	(0.5)	3	(0.8)	0	(0)	1	(0.6)
	Syncope	3	(0.5)	0	(0)	2	(0.6)	1	(0.6)
Gastrointestinal system Disorders	Abdominal pain	0	(0)	2	(0.5)	1	(0.3)	0	(0)
	Diverticulitis	0	(0)	2	(0.5)	0	(0)	0	(0)
	GI hemorrhage	2	(0.4)	2	(0.5)	0	(0)	0	(0)
	Pancreatitis	1	(0.2)	2	(0.5)	0	(0)	0	(0)
Heart rate and rhythm disorders	Atrial fibrillation	2	(0.4)	1	(0.3)	0	(0)	2	(1.1)
Metabolic and nutritional disorders	Dehydration	5	(0.9)	0	(0)	0	(0)	0	(0)
	Diabetes mellitus, aggravated	2	(0.4)	0	(0)	1	(0.3)	0	(0)
	Hyperglycaemia	2	(0.4)	0	(0)	0	(0)	0	(0)
Myo endo pericardial & valve disorders	Angina pectoris	2	(0.4)	1	(0.3)	3	(0.8)	3	(1.7)
	Coronary artery disorder	4	(0.7)	3	(0.8)	0	(0)	0	(0)
	Myocardial infarction	3[a]	(0.5)	1	(0.3)	3	(0.8)	0	(0)
Neoplasms	Basal cell carcinoma	3	(0.5)	5	(1.3)	0	(0)	0	(0)
	Neoplasm malignant	4	(0.7)	0	(0)	0	(0)	1	(0.6)
	Oral neoplasm malignant	0	(0)	2	(0.5)	0	(0)	0	(0)
	Pulmonary carcinoma	2	(0.4)	2	(0.5)	4	(1.1)	1	(0.6)
	Skin neoplasm malignant	1	(0.2)	3	(0.8)	0	(0)	0	(0)

TABLE 6.2.4.1:1 (continued) Number of Patients with Serious Adverse Events for 1-Year Studies (Page 2 of 2)

		Placebo-controlled				Active-controlled			
		Tiotropium		Placebo		Tiotropium		Ipratropium	
WHO system organ class	WHO preferred term	N	(%)	N	(%)	N	(%)	N	(%)
Platelet bleeding & clot disorders	Embolism pulmonary	0	(0)	0	(0)	2	(0.6)	0	(0)
Psychiatric disorders	Manic reaction	2	(0.4)	0	(0)	0	(0)	0	(0)
Reproductive disorders, male	Prostatic disorder	2	(0.4)	0	(0)	0	(0)	1	(0.6)
Resistance mechanism disorders	Infection	2	(0.4)	0	(0)	0	(0)	0	(0)
Respiratory system disorders (lower)	COPD exacerbation	32	(5.8)	30	(8.1)	23	(6.5)	21	(11.7)
	Dyspnoea	0	(0)	1	(0.3)	0	(0)	2	(1.1)
	Pneumonia	13	(2.4)	14	(3.8)	6	(1.7)	4	(2.2)
Vascular (extracardiac disorders)	Cerebrovascular disorder	4	(0.7)	1	(0.3)	1	(0.3)	1	(0.6)

TABLE 6.2.4.1:2 Number of Patients with Serious Adverse Events in 6-Month Studies

		Tiotropium		Placebo		Salmeterol	
WHO System Organ Class	WHO Preferred Term	N	(%)	N	(%)	N	(%)
Total treated		402	(100)	400	(100)	405	(100)
Total with any serious adverse event		37	(9.2)	55	(13.8)	50	(12.3)
Body as a whole - general disorders	Accident household	1	(0.2)	0	(0)	2	(0.5)
	Chest pain	1	(0.2)	1	(0.3)	2	(0.5)
Cardiovascular disorders, general	Cardiac failure	0	(0)	2	(0.5)	6	(1.5)
Gastrointestinal system disorders	Gastroenteritis	2	(0.5)	0	(0)	0	(0)
Heart rate and rhythm disorders	Cardiac arrest	0	(0)	2	(0.5)	0	(0)
Musculoskeletal disorders	Arthritis	0	(0)	2	(0.5)	0	(0)
Myo endo pericardial & valve disorders	Angina pectoris aggravated	0	(0)	0	(0)	2	(0.5)
	Myocardial infarction	1	(0.2)	3	(0.8)	2	(0.5)
Neoplasm	Pulmonary carcinoma	2	(0.5)	4	(1.0)	1	(0.2)
Platelet, bleeding & clotting disorders	Embolism pulmonary	0	(0)	0	(0)	2	(0.5)
Resistance mechanism disorders	Infection	0	(0)	2	(0.5)	0	(0)
Respiratory system disorders (lower)	COPD exacerbation	14	(3.5)	23	(5.8)	24	(5.9)
	Dyspnoea	0	(0)	0	(0)	2	(0.5)
	Pneumonia	4	(1.0)	2	(0.5)	5	(1.2)
	Pneumothorax	0	(0)	2	(0.5)	1	(0.2)
	Respiratory insufficiency	0	(0)	1	(0.3)	2	(0.5)
Respiratory system disorders (upper)	Upper resp tract infection	2	(0.5)	0	(0)	0	(0)
Vascular (extracardiac) disorders	Cerebrovascular disorder	1	(0.2)	2	(0.5)	2	(0.5)

6.2.4.2 Adverse Events Leading to Discontinuation

Adverse events leading to discontinuation of treatment are shown for the 1-year studies in TABLE 6.2.4.2:1 and for the 6-month studies in TABLE 6.2.4.2:2. In both the 1-year and 6-month studies, the most common adverse events leading to discontinuation are COPD exacerbations and other respiratory symptoms, most of which tend to occur more frequently among active and placebo comparator patients than among patients receiving tiotropium. Otherwise, discontinuations tend to be distributed sparsely among various adverse events and in a balanced fashion between treatment groups with one or two cases per treatment group for any individual adverse event. Dry mouth, the most common adverse event associated with tiotropium, resulted in discontinuation of treatment for only three tiotropium patients.

TABLE 6.2.4.2:1 Number of Patients with Adverse Events Leading to Discontinuation in 1-Year Studies

		Placebo-controlled				Active-controlled			
WHO System Organ Class	WHO Preferred Term	Tiotropium		Placebo		Tiotropium		Ipratropium	
		N	(%)	N	(%)	N	(%)	N	(%)
Total Treated		550	(100)	371	(100)	356	(100)	179	(100)
Total with any adverse event leading to discontinuation		53	(9.6)	50	(13.5)	35	(9.8)	22	(12.3)
Cardiovascular disorders-general	Cardiac failure	2	(0.4)	3	(0.8)	0	(0)	0	(0)
Gastrointestinal system disorders	Dry mouth	3	(0.5)	1	(0.3)	0	(0)	0	(0)
Myo endo pericardial & valve disorders	Coronary artery disorder	2	(0.4)	1	(0.3)	0	(0)	0	(0)
	Myocardial infarction	2	(0.4)	0	(0)	2	(0.6)	1	(0.6)
Neoplasms	Pulmonary carcinoma	1	(0.2)	2	(0.5)	3	(0.8)	0	(0)
Respiratory system disorders (lower)	COPD exacerbation	20	(3.6)	19	(5.1)	10	(2.8)	9	(5.0)
	Coughing	2	(0.4)	0	(0)	1	(0.3)	0	(0)
	Dyspnoea	0	(0)	5	(1.3)	4	(1.1)	1	(0.6)
	Pneumonia	4	(0.7)	5	(1.3)	0	(0)	1	(0.6)
Respiratory system disorders (upper)	Upper respiratory tract infection	1	(0.2)	2	(0.5)	0	(0)	0	(0)

TABLE 6.2.4.2:2 Number of Patients With Adverse Events Leading to Discontinuation in 6-Month Studies

WHO System Organ Class	WHO Preferred Term	Tiotropium N	Tiotropium (%)	Placebo N	Placebo (%)	Salmeterol N	Salmeterol (%)
Total Treated		402	(100)	400	(100)	405	(100)
Total with any adverse event leading to discontinuation		29	(7.2)	64	(16.0)	60	(14.8)
Body as a whole-general disorders	Accident household	0	(0)	0	(0)	2	(0.5)
Cardiovascular disorders, general	Cardiac failure	0	(0)	2	(0.5)	0	(0)
Gastro-intestinal system disorders	Nausea	0	(0)	0	(0)	2	(0.5)
Myo endo pericardial & valve disorders	Myocardial infarction	0	(0)	2	(0.5)	2	(0.5)
Neoplasms	Pulmonary carcinoma	2	(0.5)	0	(0)	0	(0)
Psychiatric disorders	Agitation	0	(0)	2	(0.5)	0	(0)
	Anxiety	0	(0)	0	(0)	2	(0.5)
Respiratory system disorders (lower)	Bronchospasm	0	(0)	2	(0.5)	0	(0)
	COPD exacerbation	14	(3.5)	31	(7.8)	31	(7.7)
	Dyspnoea	5	(1.2)	13	(3.3)	7	(1.7)

6.2.5 Fatal Adverse Events

Fatal adverse events for the 1-year studies are shown in TABLE 6.2.5:1 and for the 6-month studies in TABLE 6.2.5:2. All fatal events are tabulated, and patients with multiple fatal adverse events appear in multiple rows of these tables. A smaller proportion of tiotropium patients had a fatal adverse event than did placebo patients in both the 1-year studies and the 6-month studies. In studies with active comparators, the proportion of tiotropium patients with a fatal event was greater than for ipratropium patients and smaller than for salmeterol patients. Deaths were distributed among various types of events and, in a population comprising chronic smokers, it is not surprising that the only events that were fatal for more than one patient were myocardial infarction and pulmonary carcinoma. Neither in number of deaths nor in the characteristics of the cases did any cause of death distinguish itself as suggesting a relation with treatment.

TABLE 6.2.5:1 Number of Patients with Fatal Adverse Events in 1-Year Studies

		Placebo-controlled				Active-controlled			
		Tiotropium		Placebo		Tiotropium		Ipratropium	
WHO system organ class	WHO preferred term	N	(%)	N	(%)	N	(%)	N	(%)
Total treated		550	100	371	100	356	100	179	100
Total with any fatal adverse event		7	(1.3)	7	(1.9)	9	(2.5)	3	(1.7)
Body as a whole, general disorders	Back pain	0	(0)	0	(0)	0	(0)	1	(0.6)
	Malaise	0	(0)	1	(0.3)	0	(0)	0	(0
	Sudden death	1	(0.2)	0	(0)	0	(0)	0	(0)
Cardiovascular disorders	Cardiac failure	1	(0.2)	1	(0.3)	0	(0)	0	(0)
	Cor Pulmonale	0	(0)	1	(0.3)	0	(0)	0	(0)
Heart rate and rhythm disorders	Arrhythmia	1	(0.2)	0	(0)	0	(0)	0	(0)
	Cardiac arrest	1	(0.2)	0	(0)	0	(0)	0	(0)
Myo endo pericardial and valve disorders	Aneurysm	0	(0)	0	(0)	0	(0)	1	(0.6)
	Cardiomyopathy	1	(0.2)	0	(0)	0	(0)	0	(0)
	CAD	1	(0.2)	1	(0.3)	0	(0)	0	(0)
	Myocardial infarction	1	(0.2)	0	(0)	3	(0.8)	0	(0)

Abbreviations:
NOS: Not otherwise specified
CAD: Coronary artery disease

TABLE 6.2.5:1 (continued) Number of Patients with Adverse Events Leading to Death in 1-Year Studies (Page 2 of 2)

		Placebo-controlled				Active-controlled			
		Tiotropium		Placebo		Tiotropium		Ipratropium	
WHO system organ class	WHO preferred term	N	(%)	N	(%)	N	(%)	N	(%)
Neoplasms	Adenocarcinoma NOS	0	(0)	1	(0.3)	0	(0)	0	(0)
	Gastric carcinoma	0	(0)	0	(0)	1	(0.3)	0	(0)
	Hepatic neoplasm malignant	0	(0)	1	(0.3)	0	(0)	0	(0)
	Pulmonary carcinoma	0	(0)	2	(0.5)	2	(0.6)	0	(0)
Psychiatric disorders	Suicide attempt	1	(0.2)	0	(0)	0	(0)	0	(0)
Platelet, bleeding & clotting disorders	Embolism pulmonary	0	(0)	0	(0)	1	(0.3)	0	(0)
Resistance mechanism disorders	Meningitis	0	(0)	0	(0)	1	(0.3)	0	(0)
Respiratory system disorders (lower)	COPD exacerbation	0	(0)	1	(0.3)	0	(0)	0	(0)
	Pneumonia	0	(0)	0	(0)	0	(0)	1	(0.6)
	Resp Insuff	0	(0)	0	(0)	1	(0.3)	0	(0)
Urinary system disorders	Renal failure	0	(0)	0	(0)	1	(0.3)	0	(0)
Vascular disorders (extracardiac)	Cerebral haemorrhage	0	(0)	0	(0)	1	(0.3)	0	(0)
White cell and RES disorder	Leucopenia	0	(0)	0	(0)	0	(0)	1	(0.6)

Abbreviations:
CAD: Coronary artery disease
NOS: Not otherwise specified

TABLE 6.2.5:2 Number of Patients with Fatal Adverse Events in 6-Month Studies

		Tiotropium		Placebo		Salmeterol	
WHO system organ class	WHO preferred term	N	(%)	N	(%)	N	(%)
Total treated		402	(100)	400	(100)	405	(100)
Total with any fatal adverse event		1	(0.2)	5	(1.3)	6	(1.5)
Body as a whole-general disorders	Death	0	(0)	1	(0.3)	0	(0)
	Sudden death	0	(0)	0	(0)	1	(0.2)
Cardiovascular disorders, general	Cardiac failure	0	(0)	0	(0)	1	(0.2)
Gastrointestinal system disorders	Gastric ulcer	0	(0)	0	(0)	1	(0.2)
Heart rate and rhythm disorders	Cardiac arrest	0	(0)	2	(0.5)	0	(0)
Myo endo pericardial & valve disorders	Aneurysm	1	(0.2)	0	(0)	0	(0)
Neoplasms	Bronchial carcinoma	0	(0)	1	(0.3)	0	(0)
Platelet, bleeding & clotting disorders	Embolism pulmonary	0	(0)	0	(0)	1	(0.2)
Respiratory system disorders (lower)	COPD exacerbation	0	(0)	0	(0)	1	(0.2)
	Respiratory insufficiency	0	(0)	1	(0.3)	2	(0.5)

6.2.6 Selected Adverse Events

To conduct a more rigorous assessment of tiotropium safety, in which we sought to minimize random error to enhance detection of possible adverse events that are not necessarily common or serious, we pooled data from the 1-year and 6-month placebo-controlled studies. We computed incidence rates as the number of patients experiencing an event divided by the person-years at risk (Rothman and Greenland, 1998:31). To enhance ascertainment of possible drug-related adverse events including events that might occur soon after discontinuing treatment, person-time is accumulated from onset of treatment until 30 days after the last day of treatment. In a person-time analysis, the numerator is the same as in

analyses of incidence proportions: the number of patients experiencing a particular adverse event. Patients contribute person-time to the denominator only as long as they are in the study receiving treatment and at risk of being identified with an adverse event. Thus, a patient who drops out after 1-week contributes much less person-time than a patient who completes 48 weeks of treatment. In this way, each patient's contribution to the incidence rate denominator is proportional to his or her time at risk.

We compute rate differences as the rate in the tiotropium group minus the rate in the placebo group, expressed per 100 person-years. To ensure detection of adverse events occurring soon after discontinuing treatment, patients were included in the analysis for thirty days after discontinuing treatment. Prior to pooling, we compared incidence of events over time, demonstrating that the risk of adverse events did not increase over time. To account for possible differences between studies, we used the Mantel Haenszel procedure to adjust rate differences for whether subjects participated in the 1-year studies or the 6-month studies (Rothman and Greenland, 1998:269). Rate differences with positive values indicate the extent to which there is a higher rate for tiotropium patients, and rate differences less than zero quantify the magnitude of the higher rate for placebo patients. For descriptive purposes, P-values are provided to help assess the statistical reliability of each rate difference. P-values were computed using exact methods that do not require large sample assumptions and, therefore, are appropriate for sparse data (Rothman and Greenland, 1998:267).

Analyses of the most common adverse events, serious adverse events, and adverse events leading to discontinuation, identified adverse events of interest in several system organ classes, including gastrointestinal system disorders, urinary tract disorders, and respiratory system disorders. In addition to adverse events that emerged from previous analyses, we also included in this analysis those events possibly related to antimuscarinic effects, such as increased heart rate, and events of public health importance, such as myocardial infarction and cardiac arrest. Results from the pooled analysis of placebo-controlled studies are presented in TABLE 6.2.6:1 for selected adverse events. We show in TABLE 6.2.6:2 the subset of these selected adverse events that are classified as serious adverse events. Patients with multiple adverse events appear in analyses of each event.

TABLE 6.2.6:1 Selected Adverse Events from Pooled 1-Year and 6-Month Placebo-Controlled Studies

	Tiotropium			Placebo				
WHO system organ class/preferred term	N	Pyrs	Rate (*100 pyrs)	N	Pyrs	Rate (*100 pyrs)	RD (*100 pyrs)	P-value
Body as a whole								
Accidents	90	636	14.14	52	460	11.30	2.85	0.20
Chest pain	54	651	8.29	32	469	6.82	1.47	0.38
Edema	37	664	5.57	19	477	3.99	1.59	0.24
Gastrointestinal								
Abdominal pain	35	662	5.29	19	475	4.00	1.29	0.33
Constipation	23	668	3.44	8	480	1.67	1.78	0.07
Dry mouth	121	598	20.23	19	473	4.02	16.22	<0.01
Dyspepsia	41	660	6.21	22	474	4.64	1.57	0.27
Heart rate and rhythm								
Arrhythmia	4	678	0.59	1	483	0.20	0.38	0.38
Atrial fibrillation	7	677	1.03	3	482	0.62	0.41	0.49
Cardiac arrest	1	679	0.15	2	483	0.41	-0.27	0.45
Palpitation	5	677	0.74	6	480	1.25	-0.51	0.40
SVT	3	679	0.44	1	483	0.21	0.23	0.57
Tachycardia	8	675	1.19	2	482	0.41	0.77	0.18
Myo/Endo/Pericardial								
Angina pectoris	9	676	1.33	3	482	0.62	0.71	0.26
Angina pectoris aggravated	2	678	0.30	0	483	0.00	0.29	0.34
Myocardial infarction	5	678	0.74	5	483	1.04	-0.30	0.60
Resistance mechanism								
Moniliasis*	26	666	3.91	12	478	2.51	1.39	0.21
Respiratory system (upper)								
Epistaxis	23	666	3.46	11	479	2.30	1.16	0.27
Laryngitis	7	676	1.03	1	483	0.21	0.83	0.10
Pharyngitis	67	648	10.33	39	467	8.35	1.99	0.29
Sinusitis	75	641	11.70	45	465	9.69	2.02	0.32
URTI	304	534	56.92	202	398	50.73	6.18	0.21
Respiratory system (lower)								
COPD exacerbation	331	542	61.06	311	368	84.51	-23.44	<0.01
Dyspnea	51	664	7.68	56	467	11.99	-4.31	0.02
Urinary system								
Cystitis	6	677	0.89	7	480	1.46	-0.57	0.38
Micturition disorders	4	677	0.59	0	483	0.00	0.59	0.12
Urinary incontinence	1	679	0.15	4	481	0.83	-0.68	0.11
Urinary retention	5	677	0.74	0	483	0.00	0.74	0.07
Urinary tract infection	41	661	6.21	17	476	3.57	2.63	0.05
Visual								
Glaucoma	3	678	0.44	3	483	0.62	-0.18	0.69

Abbreviations: RD: Rate difference estimate
CI: Confidence Interval
N: Number of patients
Pyrs: person-years
SVT: Supraventricular tachycardia
URTI: Upper Respiratory Tract Infection

The largest rate differences are, from largest absolute value to the smallest, a lower incidence among tiotropium patients of lower respiratory events (COPD exacerbation and dyspnea), followed by a greater increased incidence among tiotropium patients of dry mouth, upper respiratory events (including upper respiratory tract infection), and urinary events (including urinary tract infection). Smaller increases with tiotropium are observed for accidents, constipation, edema, dyspepsia, chest pain, and moniliasis. Adverse events are considered further below according to system organ class.

Within the system organ class body as a whole, small increases with tiotropium were observed for chest pain, accidents, and edema. Accidents and edema are relatively common events in this population, and differences are imprecise. Chest pain could originate in the respiratory, cardiovascular, or musculoskeletal systems.

Among gastrointestinal events, dry mouth and, less commonly, constipation and dyspepsia likely represent antimuscarinic effects.

Cardiovascular effects are categorized as heart rate and rhythm disorders and myocardial, endocardial, pericardial and valve disorders. There is a larger incidence of angina in the tiotropium group, but there is no increased incidence of cardiac arrest, nor is there an increased incidence of myocardial infarction. Among heart rate and rhythm disorders, there is no increased incidence of palpitations, but there is a slightly larger incidences of tachycardia, supraventricular tachycardia, arrhythmia, and atrial fibrillation. Tachycardia is a recognized antimuscarinic effect.

Tiotropium is weakly associated with several common respiratory symptoms, including epistaxis, laryngitis, pharyngitis, sinusitis, and upper respiratory tract infection. These conditions are not recognized as classic antimuscarinic effects, but may be consistent with drying of epithelial tissues. The weak association with the resistance mechanism disorder event, moniliasis, might also be secondary to such a phenomenon.

A small number of patients appear to experience a decrease in bladder contractility, which manifests as several adverse events, including a larger incidence among tiotropium patients of micturition disorders, micturition frequency, urinary retention, and a smaller incidence among tiotropium patients of urinary incontinence. A review of individual cases indicated that urinary retention was concentrated among elderly men with predisposing factors such as benign prostatic hyperplasia. A larger incidence among tiotropium patients of urinary tract infections also was observed.

Few of the selected adverse events were classified as serious (TABLE 6.2.6:2). Specifically, possible anticholinergic events such as dry mouth, upper respiratory infection, constipation, supraventricular tachyarrhythmias, and urinary events were rarely serious. Chest pain was sometimes considered serious, although serious cases of chest pain were unrelated to tiotropium. The most common serious adverse event was COPD exacerbation, and a smaller incidence of COPD exacerbation among tiotropium patients was the largest difference between treatment groups among serious adverse events. Conditions that are inherently serious, such as overall mortality, cardiovascular mortality, cardiac arrest and myocardial infarction did not occur more frequently among patients receiving tiotropium.

TABLE 6.2.6:2 Serious Selected Adverse Events From Pooled 1-Year and 6-Month Placebo-Controlled Studies

	Tiotropium			Placebo				
WHO system organ class/preferred term	N	Pyrs	Rate (*100 pyrs)	N	Pyrs	Rate (*100 pyrs)	RD (*100 pyrs)	P-value
Fatal adverse events								
Total with any fatal adverse event	8	679	1.18	12	483	2.48	-1.31	0.11
Any fatal CV adverse event	7	679	1.03	5	483	1.03	0.00	0.98
Body as a whole								
Accidents	4	678	0.59	3	482	0.62	-0.03	0.93
Chest pain	9	673	1.34	5	481	1.04	0.30	0.67
Edema	0	679	0.00	0	483	0.00	--	--
Gastrointestinal								
Abdominal pain	0	679	0.00	3	482	0.62	-0.62	0.07
Constipation	1	679	0.15	0	483	0.00	0.15	0.58
Dry mouth	0	679	0.00	0	483	0.00	--	--
Dyspepsia	0	679	0.00	0	483	0.00	--	--
Heart rate and rhythm								
Arrhythmia	1	678	0.15	0	483	0.00	0.15	0.58
Atrial fibrillation	2	678	0.29	1	483	0.21	0.09	0.82
Cardiac arrest	1	679	0.15	2	483	0.41	-0.27	0.45
Palpitation	0	679	0.00	0	483	0.00	0.00	--
SVT	2	679	0.29	0	483	0.00	0.29	0.34
Tachycardia	1	679	0.15	0	483	0.00	0.15	0.58
Myo/Endo/Pericardial								
Angina pectoris	3	678	0.44	2	483	0.41	0.03	0.96
Angina pectoris aggravated	1	678	0.15	0	483	0.00	0.15	0.58
Myocardial infarction	4	678	0.59	4	483	0.83	-0.24	0.64
Respiratory system (upper)								
Epistaxis	1	679	0.15	0	483	0.00	0.15	0.58
Laryngitis	0	679	0. 00	0	483	0.00	--	--
Pharyngitis	0	679	0.00	0	483	0.00	--	--
Sinusitis	1	679	0.15	0	483	0.00	0.15	0.58
URTI	2	679	0.29	0	483	0.00	0.29	0.34
Respiratory system (lower)								
COPD exacerbation	46	666	6.91	53	470	11.28	-4.37	0.02
Dyspnea	0	679	0.00	1	483	0.21	-0.21	0.42
Resistance mechanism								
Moniliasis	0	679	0.00	0	483	0.00	--	--

Abbreviations:
RD: Rate difference estimate
CI: Confidence Interval
N: Number of Patients
Pyrs: person-years at risk
COPD: Chronic obstructive pulmonary disease
CV: Cardiovascular
SVT: Supraventricular tachycardia
URTI: Upper Respiratory Tract Infection

TABLE 6.2.6:2 (continued) Serious Selected Adverse Events From Pooled 1-Year and 6-Month Placebo-Controlled Studies (Page 2 of 2)

WHO system organ class/preferred term	Tiotropium N	Tiotropium Pyrs	Tiotropium Rate	Placebo N	Placebo Pyrs	Placebo Rate	RD	P-value
Fatal adverse events								
Total with any fatal adverse event	8	679	1.18	12	483	2.48	-1.31	0.11
Any fatal CV adverse event	7	679	1.03	5	483	1.03	0.00	0.98
Urinary system								
Cystitis	0	679	0.00	0	483	0.00	--	--
Micturation disorders	0	679	0.00	0	483	0.00	--	--
Urinary incontinence	0	679	0.00	1	483	0.21	-0.21	0.42
Urinary retention	0	679	0.00	0	483	0.00	0.00	--
Urinary tract infection	0	679	0.00	1	483	0.21	-0.21	0.42
Visual								
Glaucoma	0	679	0	0	483	0	--	--

Abbreviations:
RD: Rate difference estimate
CI: Confidence Interval
N: Number of Patients
Pyrs: person-years at risk
COPD: Chronic obstructive pulmonary disease
CV: Cardiovascular
SVT: Supraventricular tachycardia
URTI: Upper Respiratory Tract Infection

In summary, assessment of adverse events shows tiotropium to be most strongly associated with a decreased incidence of COPD exacerbations and dyspnea. The most common unintended adverse events are dry mouth and upper respiratory symptoms, including upper respiratory tract infection. Less common adverse events include constipation, supraventricular tachyarrhythmias, urinary tract infection and urinary retention. Events possibly associated with tiotropium and not generally recognized as direct antimuscarinic effects include accidents, angina and edema. Although one cannot eliminate the possibility that any of these adverse events could, in unusual circumstances, be clinically serious, there is little if any indication of a relationship between tiotropium and any serious adverse event, apart from a reduced incidence of COPD exacerbations.

6.2.7 Supplementary Safety Data

6.2.7.1 Subgroup Analysis

To identify any subgroups that may have a higher incidence of adverse events, we examined the incidence of adverse events according to subgroups defined by age (≤60 years, 61-70 years and ≥71 years), race, gender, smoking status, COPD severity (based on percent predicted FEV_1), and concomitant use of common respiratory medications (data not shown). With regard to age, tiotropium was associated with a greater incidence of dry mouth and constipation among elderly patients. Other adverse events where trends existed to a lesser

degree that suggested the possibility of a relationship to age included abdominal pain, depression, pharyngitis and urinary retention.

With regard to gender, dry mouth was reported proportionately more often in women. Urinary retention and micturition disorders were only reported by men, which may be related to benign prostatic hyperplasia.

There was no association between baseline smoking status and tiotropium with regard to adverse events.

Dry mouth was reported least often among subjects with the most severe COPD (FEV_1 <35%). There was a rank ordering according to disease severity for COPD exacerbations and upper respiratory tract infections in the placebo and ipratropium-controlled studies, a finding that would be expected in COPD. Upon review of all other adverse events, particularly those associated with anticholinergic effects, no consistent patterns of rank ordering was evident that suggested an interaction between tiotropium and disease severity.

In general, there was no difference in the percent of patients with adverse events between oral steroid users and non-users with the exception of COPD exacerbation and dyspnea, which occurred at a greater frequency in the steroid-users vs. steroid non-users. This observed difference is likely secondary to prescriptions of steroids for more severe disease at baseline. There appeared to be no interaction of tiotropium with oral steroids on reported adverse events. An increased incidence of oral moniliasis was seen in those using inhaled steroids, a known adverse effect of corticosteroid therapy. No interaction between tiotropium and inhaled steroids was observed.

With regard to theophyllines, no interactions based on adverse events were observed. An increased frequency of nausea was seen in those receiving theophylline in the 1-year studies that did not appear to be modified by tiotropium.

6.2.7.2 Mucociliary Clearance

Systemically absorbed anticholinergic drugs like atropine have been reported to decrease mucociliary clearance in contrast to N-quarternary drugs like ipratropium, which were reported to have no influence on the mucociliary clearance. The effects of tiotropium on mucociliary clearance were studied in Study #116. In this study, the influence of 3-week treatment of patients with COPD with 18 mcg tiotropium once-daily on tracheobronchial clearance (TBC) was assessed. TBC was measured using an objective non-invasive radioaerosol technique. The effect of tiotropium on TBC was primarily determined by the

area under the tracheobronchial retention curve for 0-6 hours (AUC_{0-6}) with the initial deposition (penetration index) reflecting airway patency and the AUC_{0-6h} reflecting TBC. Following treatment with tiotropium compared to placebo, there was a significant increase in FEV_1 and FVC, and improved radioaerosol penetration into the lung compared to a decrease with placebo. Tracheobronchial retention was unchanged in the tiotropium group compared to a significant change in the placebo group. Whole lung retention of radioaerosol at 6, 24 and 48 hours post-inhalation was higher with tiotropium than placebo (difference of 16%, 14% and 10%). To summarize the observations, once daily inhaled tiotropium resulted in improved penetration of radioaerosol but did not change TBC compared to baseline; however, TBC following tiotropium was apparently delayed compared to placebo. The deeper penetration of radioaerosol is attributable to the effectiveness of tiotropium as a bronchodilator among patients with COPD, and the likely cause of the apparent slower TBC in the tiotropium group. The deeper radioaerosol penetration into the lung would be expected to decreased clearance in the tiotropium group because (a) there is a reduction and/or absence of cilia in the peripheral airways/alveolar area, (b) cilia from peripheral bronchioles have a lower beat frequency by 35% than cilia from the proximal bronchi and (c) the clearance starting point for the particles was deeper into the lung. Thus, in the tiotropium group particles had to travel a longer distance before being cleared by the TBC mechanism. Any clinically relevant reduction of TBC, if present, might be expected to manifest as an increased frequency of lower respiratory tract events; however, tiotropium was associated with a marked reduction in frequency of COPD exacerbations and dyspnea.

6.2.7.3 Electrocardiography

In the 1-year placebo and 1-year ipratropium-controlled studies 12-lead ECGs were done at baseline and every 90 days for the duration of the study. Two-minute rhythm recordings were part of the safety evaluation in the multidose dose-ranging study (#108). Holter monitoring was performed during the AM/PM dosing study (#123).

ECGs from the 1-year placebo controlled studies were sent retrospectively to a central laboratory (eResearchTechnology, Inc. Philadelphia, PA, USA) for a high-resolution measurement of the cardiac intervals. ECGs were obtained from clinical sites for approximately 94% of the participants in each treatment group. There were 2,359 ECG's completed by tiotropium patients and 1,505 completed by the placebo patients. ECG's were performed at visit 1, 7, 9, 11, and 13. ECG measurements were performed using digitization software with magnification of the ECG and point-to-point determination on the digitizing pad by experienced technicians and a centralized cardiologist who was blinded to the tracings.

The reproducibility of this system was 1.4 +/- 2.2 milliseconds (msec). In addition to the analyses of the measured intervals (RR, PR, QRS and QT) a calculated QTc interval was determined using both Bazett's (QTcB) and Fridericia's formula (QTcF).

The analyses of the ECG intervals of heart rate, PR, QRS, QT, QTcB, and QTcF included change from baseline to the average of on-treatment values for a given patient and change from baseline to the maximum of on-treatment values for a given patient. For QT parameters, change from baseline to an average of on-treatment values for a given patient and a determination of those patients who attain QT values >500 msec when not present at baseline (new onset) was assessed. For QTc, analyses were conducted for new onset of QTc >500 msec as well as QTc, categorizations of changes <30 msec, 30-60 msec and >60 msec in QTc from baseline (described as the proportion of patients meeting these criteria for each treatment group).

Outlier analyses for PR, QRS and heart rate used the following criteria:

PR change from baseline: ≥25% when PR >200 msec vs. Not (determined from individual time points, but each patient is tallied as having at least one notable PR change or no notable PR changes)

QRS change from baseline: ≥25% when QRS >100 msec vs. Not (determined from individual time points, but each patient is tallied as having at least one notable QRS change or no notable QRS changes)

Heart Rate (HR) changes reflecting a 25% decrease from baseline to a HR < 50 bpm (Brady event) or a 25% increase from baseline reflecting a HR > 100 bpm (Tachy event) (determined from individual time points, but each patient is tallied as having at least one notable HR change or no notable HR changes). Results are shown in TABLE 6.2.7.3:1.

TABLE 6.2.7.3:1 ECG Monitoring in the 1-Year Placebo Controlled Studies

	Tiotropium Group	Placebo Group
N	518	343
Heart Rate		
Mean change in bpm	0	0
Maximum change in bpm	7	6
% with Brady Events	0.2	0.3
% with Tachy Events	2.3	1.7
PR		
Mean change in msec	1	1
% outliers	0.2	0.9
QRS		
Mean change in msec	1	0
% outliers	1	1
QT		
Mean change in msec	0	0
% New QT> 500 msec	0	0
QTc by Bazett		
Mean change in msec	1	0
Maximum change in msec	14	13
% new QTcB >500 msec	0.8	0.3
% Change of 30-60 msec	21	22
% Change > 60 msec	2.7	1.5
QTc by Fridericia		
Mean change in msec	1	0
Maximum change in msec	12	11
% new QTcB >500 msec	0.2	0.3
% Change of 30-60 msec	15	15
% Change > 60 msec	1.4	0.3

There was no indication of any effect of tiotropium on heart rate, PR, QRS, or QT intervals. The QTc interval by Bazett and Fridericia corrections gave comparable results (within only 1 msec or for outliers about a 1% difference). The incidence of an abnormal rhythm was 9% in the tiotropium group and 10.1% in the placebo group. A change in conduction was observed in 2.9% of the tiotropium group and in 4.2% of the placebo group. In summary, centralized analysis of ECGs for 518 tiotropium patients and 343 placebo patients did not detect any effect of tiotropium on ECG intervals, heart rhythm or conduction.

In each of the long-term studies, abnormalities in the ECGs were recorded as adverse events if they were considered clinically significant, required treatment, or lead to discontinuation of the study drug. These data are shown in TABLE 6.2.7.3:2. In the 1-year placebo-controlled studies 14 patients developed ECG changes: 5 (1%) patients receiving tiotropium, and 9 (2.4%) patients receiving placebo. In the 1-year ipratropium-controlled studies, ECG changes were observed in 13 patients: 8 (2.3%) tiotropium patients and 5 (2.8%) ipratropium patients. There were no significant imbalances noted with regard to the type of ECG abnormalities between the tiotropium and control groups. In addition, there were no

ventricular tachyarrhythmias. In the 6-month studies, 19 patients developed clinically significant ECG changes, 8 (2%) tiotropium patients, 3 (0.7%) placebo patients, and 8 (2%) salmeterol patients. There were no significant imbalances noted with regard to the type of ECG abnormalities between the tiotropium and control groups.

TABLE 6.2.7.3: 2 ECG Changes Reported as Adverse Events in Long-Term Studies

	1-year studies								6-month studies					
	Tiotropium		Placebo		Tiotropium		Ipratropium		Tiotropium		Placebo		Salmeterol	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total treated	550	(100.0)	371	(100.0)	356	(100.0)	179	(100.0)	402	(100.0)	400	(100.0)	405	(100.0)
Total with any ECG adverse event	5	(0.9)	9	(2.4)	8	(2.3)	5	(2.8)	8	(2.0)	3	(0.7)	8	(2.0)
Extrasystoles	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.5)	2	(0.5)	2	(0.5)
Atrial fibrillation	0	(0.0)	2	(0.5)	3	(0.8)	2	(0.6)	2	(0.5)	0	(0.0)	1	(0.2)
MAT	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Sinus tachycardia	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Myocardial infarction	0	(0.0)	2	(0.5)	0	(0.0)	2	(0.6)	2	(0.5)	0	(0.0)	2	(0.5)
Other changes	4	(0.7)	5	(1.5)	4	(1.1)	1	(0.6)	2	(0.5)	1	(0.2)	3	(0.7)

The most intensive cardiac monitoring comes from 24-hour Holter data collected in the 6-week, double-blind, placebo-controlled, parallel group AM/PM dosing study (#123). Three treatment groups were studied (tiotropium administered in the morning, tiotropium administered in the evening, and placebo). For all treatment groups, no pattern in supraventricular tachycardia events and no incidences of atrial flutter or fibrillation were observed during the Holter monitoring. In addition, no differences in ventricular dysrhythmias were observed among treatment groups. There was no marked shift in aberrant count frequency (atrial or ventricular) noted in any of the treatment groups. In summary, the Holter data indicated that treatment with tiotropium was not associated with adverse effects on cardiac rhythm or heart rate.

In the four-week placebo-controlled, parallel group, multidose dose-ranging study (#108), a 12-lead ECG and a 2-minute rhythm strip were performed prior to drug administration and at 1, 3 and 5 hours post drug administration at the randomization visit and after 1, 2 and 4 weeks of treatment. The changes seen were predominantly premature atrial and ventricular contractions. No differences were noted between placebo and the active treatment groups. Most changes were either transient or intermittent. Only one patient exhibited progressive changes, a placebo patient with borderline changes in the PR interval. One case of each of the following tachyarrhythmias was observed in the tiotropium treatment groups: sinus tachycardia (18 mcg dose), atrial fibrillation (9 mcg dose) and ventricular tachycardia (4.5 mcg dose). One case of sinus tachycardia was observed in the placebo group. All tachyarrhythmias were transient in nature.

In summary, no clinically significant abnormalities in electrocardiographic evaluations were associated with tiotropium in the 1-year studies or dose-ranging study. With regard to heart rate and rhythm, none of the groups showed any relevant change in overall heart rate and rhythm parameters among Holter studies.

6.2.7.4 Clinical Laboratory Tests

Tiotropium is administered as an inhaled medication with low systemic bioavailability. As such, significant abnormalities in laboratory evaluations would not be expected. Laboratory tests were performed on all patients at baseline and at three-month intervals throughout the treatment period in the 1-year studies, and at baseline and the end of treatment in the 6-month studies. Tests were performed by a central laboratory and included hematology, clinical chemstries, and urinalysis. Abnormal laboratory events were not considered adverse events

unless action was taken with the study drug, therapy was required, and the abnormal value was not already associated with a reported adverse event.

The mean values for all parameters both at baseline and conclusion of patient participation were similar between treatment groups in each of the combined 1-year studies as well as being similar between combined 1-year studies. The changes in the mean values from the beginning to the end of the study were equally well balanced with no indication of a clinically significant effect in either the 1-year or the 6-month studies. Marked changes in laboratory values were identified as those final values which were outside the reference range as determined by the central laboratory, having been within the reference range at baseline and showing a change greater than the amount determined prior to the study initiation. The percent of patients with marked changes was small in all groups. In summary, no laboratory abnormalities were observed that could be attributed to tiotropium.

6.2.7.5 Physical Examinations and Vital Signs

Vital signs were measured at the screening visit and on test days prior to pulmonary function testing, and physical examinations were conducted at baseline and the final visit. Throughout the 1-year and 6-month studies, a comparable percent of patients in each treatment group had clinically significant changes in physical examinations from baseline to the final examination that were considered adverse events. These events were not different in nature or frequency from the range of adverse events reported overall and no serious adverse events were discovered upon physical examination.

Heart rate and blood pressure were monitored at regularly scheduled intervals in all six long-term clinical studies. The mean values for each parameter are similar between tiotropium 18 mcg and the comparator treatment groups. Pre-defined settings were established for marked changes in vital signs. The marked changes were generally balanced between treatment groups except for fewer increases in both systolic and diastolic blood pressure in the tiotropium group compared to the control group in the 1-year ipratropium-controlled studies but not in the 1-year placebo-controlled studies or in the 6-month studies. There were no differences in pulse rates.

6.2.7.6 Adverse Events in Other Clinical Studies in COPD

Studies in this group include the AM/PM dosing study (#123), the mucociliary clearance study (#116), the sleep study (#124) and the dose ranging studies (#119, #120, #108). The

study of tiotropium in the elderly (#133) was a pharmacokinetic study in COPD patients. The overall adverse event profile in these other studies in COPD was not significantly different from that seen in the 1-year placebo, 1-year ipratropium-controlled studies and 6-month placebo- and salmeterol-controlled studies. The sample size in these studies was small relative to the 1-year studies and to the 6-month studies.

There was one death in each of the following studies: dose ranging Study #120 non-Hodgkin's Lymphoma 108 days following the two-week study period; sleep Study #124 respiratory failure, placebo patient; and tiotropium in the elderly Study #133 myocardial infarction approximately 11 weeks after the patient's last dose of tiotropium.

In general the type of serious adverse events were not different from those occurring in the one-year and in the 6-month studies. The number of patients and the durations were relatively short, thus the frequency of serious adverse events was low in these studies. One event occurred in the AM/PM dosing study (#123) in a tiotropium treated patient. No serious adverse events occurred in the mucociliary study (#116). In the sleep study (#124) there were seven serious adverse events reported; three (4.6%) in the tiotropium groups and four (13.3%) in the placebo group. Two serious adverse events (one each for placebo and tiotropium treated patients) were reported in the 4-week dose-ranging study (#108). In Study #120, two serious events were reported. In addition to the death reported 108 days post drug, a placebo patient experienced a serious adverse event.

There were few adverse events leading to discontinuation observed in these clinical studies. In the AM/PM study (#123) four patients (9.3%) in the tiotropium p.m. group and five patients (13%) in the placebo group discontinued the study due to an adverse event during the treatment period. In addition, one patient in the placebo group discontinued due to COPD exacerbation that had started during the baseline period and deteriorated post randomization. In the sleep study (#124) eight patients discontinued due to adverse events; two (6.3%) in the tiotropium groups and six (20%) in the placebo group. Four of the six in the placebo group and none in the tiotropium group withdrew due to a COPD exacerbation. In the multiple-dose, dose-ranging study (#108), a patient discontinued from the study due to worsening anxiety after one week on placebo.

6.3 ADVERSE EVENTS INCLUDED IN PROPOSED PACKAGE INSERT

Based on detailed aggregate and individual analyses of all adverse events, the following table has been proposed for inclusion in the package insert. The table includes adverse events in the 1-year studies that occurred in at least 3% of tiotropium patients and with an excess of at least 1% greater than placebo patients:

TABLE 6.3:1 Adverse Experience Incidence (% Patients) in 1-Year COPD Clinical Studies

	Placebo-Controlled Studies		Ipratropium-Controlled Studies	
	SPIRIVA [n=550]	Placebo [n=371]	SPIRIVA [n=356]	Ipratropium [n=179]
Body System (Event)				
Body as a Whole				
Accidents	13 %	11 %	5 %	8 %
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Vomiting	4	2	1	2
Musculo-Skeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (upper)				
Epistaxis	4	2	1	1
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Sinusitis	11	9	3	2
Upper Respiratory Tract Infection	41	37	43	35
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

In addition, the following less common events also are listed:

Body as a whole:	allergic reaction, influenza-like symptoms, leg pain
CNS:	dysphonia, paraesthesia
Gastrointestinal:	gastrointestinal disorder not otherwise specified, gastroesophageal reflux, stomatitis
Heart rate and rhythm:	increased heart rate, atrial fibrillation, supraventricular tachycardia
Metabolic and nutritional:	hypercholesterolemia, hyperglycemia
Musculoskeletal:	arthritis, skeletal pain
Myocardial, endocardial, pericardial and valve disorders:	angina pectoris
Psychiatric:	depression
Resistance mechanism disorders:	herpes zoster
Respiratory:	coughing, laryngitis
Skin:	angioedema
Urinary:	urinary difficulty, urinary retention
Visual:	blurred vision, glaucoma

6.4 CONCLUSION OF SAFETY EVALUATION FROM CLINICAL STUDIES

Tiotropium is a once daily, inhaled quaternary anticholinergic bronchodilator developed for the treatment of bronchospasm and dyspnea associated with chronic obstructive lung disease, including chronic bronchitis and emphysema. Analyses of adverse events demonstrate that the most prominent effect of tiotropium is a decreased incidence of COPD exacerbations and dyspnea. This difference is seen compared with ipratropium and the long acting β-agonist, salmeterol, as well as with placebo. Other adverse events are understood in the context of antimuscarinic pharmacology, and include dry mouth, upper respiratory infections and related symptoms, urinary tract infection and urinary symptoms, and constipation (Mintzer and Burns, 2000). These events are rarely serious or require discontinuation of therapy. There is no indication of an increased risk of any life-threatening event or death from any cause. In addition, evaluation of electrocardiography including Holter monitoring, laboratory test, vital signs and physical examinations indicate no association between tiotropium and any clinically important abnormality.

6.5 SUMMARY OF SAFETY FROM CLINICAL STUDIES

- Large clinical development program with 1,308 patients treated with 18 mcg in the core studies, 50% of whom were treated for at least 300 days.
- Safety profile consistent with antimuscarinic pharmacology

- Possible antimuscarinic adverse events include dry mouth, upper respiratory symptoms, constipation, supraventricular tachyarrhythmias, urinary tract infections and urinary retention.
- These events usually do not require discontinuation of treatment.
- There is no indication of an increased rate of any fatal event.
- Laboratory evaluations, ECGs, vital signs and physical examinations indicate no imbalance in abnormal findings of clinical importance.

7. DISCUSSION OF BENEFIT/RISK

In summary, tiotropium provides clinically important benefits for the treatment of COPD, both in terms of bronchodilation and dyspnea. These important benefits are associated with adverse effects similar to those seen with currently available treatments for COPD. Therefore, tiotropium exhibits a favorable risk-benefit ratio.

FDA regulations (21 CFR 201.57(c) iii) allow labeling of relief of symptoms associated with a disease in the Indications and Usage section of product labeling. As previously noted, dyspnea is the reason most patients seek medical attention and it is a major cause of disability and anxiety associated with the disease. The importance of this information to the prescribing physician warrants its inclusion in the Indication section of the labeling.

In conclusion, the favorable clinical profile and benefit-risk ratio for tiotropium, as well as the importance of dyspnea as the key symptom of COPD, support the proposed Indication statement.

8. OVERVIEW NON-CLINICAL STUDIES

A comprehensive program of non-clinical investigations of tiotropium bromide monohydrate was conducted to characterize its pharmacological, toxicological, and ADME profiles. The data demonstrate a lack of relevant toxicity for humans, good tolerability, and support its safety for long-term clinical administration in man.

8.1 PHARMACOLOGY AND PHARMACOKINETICS

The results of *in vitro* and *in vivo* pharmacological studies are consistent with the proposed clinical indication for this drug (once daily treatment for COPD). These experiments show that tiotropium is a potent and long-acting M_3 muscarinic receptor antagonist having high affinity for the receptor together with slow dissociation kinetics. The slow dissociation of tiotropium from the M_3-receptor (dissociation half-life is 27 hours) is thought to be responsible for the long duration of action of this drug. Affinity for M_2- and M_1-receptors at relevant concentrations.

In vivo experiments performed by intravenous or inhalation administration demonstrated that tiotropium protected against bronchospasm induced by intravenous or inhaled acetylcholine. The bronchoprotective effects were dose-dependent with an estimated ED_{50} (dose-inhibiting spasms by 50%) of approximately 1 µg/kg. Inhalation of pharmacologically effective doses was shown to be devoid of systemic anticholinergic side effects.

In general pharmacology studies, systemic administration of tiotropium induced several expected non-CNS anticholinergic effects such as inhibition of salivation, lacrimation, gastric secretion, increase in heart rate, mydriasis and antimiosis. The increased heart rate was accompanied by the expected reduction in the Q-T interval (not corrected for heart rate) but with no concomitant change in systolic blood pressure. Tiotropium had no effect on action potential duration in preparations of guinea pig papillary muscle or on HERG-mediated potassium ion channels in HEK293 cells.

Characterization of the absorption, distribution, metabolism and excretion (ADME) properties of tiotropium show that the maximum plasma levels achieved in the animal toxicity studies are significantly greater than human plasma levels expected after once daily administration by dry powder inhalation. The pharmacokinetic studies with tiotropium show: good absorption in the lung; dose proportionality of plasma concentrations; a rapid and broad distribution; no crossing of the blood-brain barrier; a high systemic clearance without accumulation in the plasma; elimination primarily by renal clearance; a relatively low protein binding in animals

(20%) compared to humans (71%); and metabolism by non-esterase hydrolytic cleavage. In addition, there is no evidence of cytochrome P-450 induction or adverse drug-to-drug interactions.

8.2 TOXICOLOGY

In single dose studies a low acute toxicity was noted in the inhalation studies with exposures lasting up to 4 hours. The approximate LD_{50} values were >131 mg/kg in mice, >300 mg/kg in rats and dogs. The oral (gavage) and intravenous (bolus injection) approximate LD_{50} in mice was in the range of 1200 to>5000 mg/kg and 15.5 and 21.5 mg/kg respectively. The oral approximate LD_{50} in mice and rats was respectively about 2×10^5 and 1×10^6 times greater than the MRHD on a mg/m^2 basis.

The repeated dose toxicology program of tiotropium included numerous studies focused primarily on aqueous aerosol inhalation in rats and dogs for periods of up to 12 months. This program was supplemented by 13-week tiotropium/lactose-powder formulation bridging studies. No significant toxicological or toxicokinetic differences were seen between the two formulations. Consequently, the aqueous aerosol inhalation studies were included in the safety assessment of the tiotropium powder formulation.

In the repeat dose studies most of the observed effects reflected the exaggerated pharmacological action typical of an anticholinergic compound. These changes included: dry oral and nasal mucosa caused by the inhibition of salivation which resulted in decreased in food consumption and body weight gain; decreased lacrimal secretion; tachycardia; mydriasis and coprostasis. Tachycardia was accompanied by a reduced Q-T interval (not corrected for heart rate) but no change in systolic blood pressure. Additional animal species-specific findings regarded as of little or negligible relevance for therapeutic use in human patients included proteinaceous deposits in the urinary bladder (male rats), anterior subscapular lenticular opacities/cataracts (rats) and keratoconjunctivitis (dogs). In rats, a no observable toxic effect level (NOTEL) of 10, 70 and 100 µg/kg was established for intravenous, inhalation, and oral administration, respectively, in repeated dose toxicity studies over periods up to 52 weeks. In dogs, the NOTEL was evaluated to be 5, 5 and 4 µg/kg of tiotropium for inhalation, oral and intravenous administration, respectively, in repeated dose toxicity studies over periods up to 52 weeks. Signs of overt toxicity caused by inhalation of tiotropium were observed at relatively high dose levels, when compared to the daily human therapeutic dose of 22.5 µg tiotropium, ≈ 0.45µg/kg (50 kg individual). Consequently, for inhalation use, a NOTEL of 5 µg/kg of tiotropium (derived from the dog data) represents a satisfactory safety margin for the intended human therapeutic use.

Reproduction toxicity studies showed no evidence of teratogenic potential or reproductive abnormalities. The studies performed were an inhalation fertility study (segment I) in rats, embryo-fetal toxicity studies (segment II) in rats (oral) and in rabbits (oral and inhalation) and inhalation peri- and post-natal studies (segment III) in rats. In the rat inhalation studies the NOTEL for maternal and fetal toxicity (exaggerated anticholinergic effects) was 10 µg/kg (approximately 22 times the maximum daily therapeutic dose).

Carcinogenicity bioassays in mice and rats revealed no neoplastic or carcinogenic potential of tiotropium following inhalation in mice and rats at target doses up to 0.0025, 0.180 and 0.074 mg/kg/day (male mice, female mice and male/female rats respectively). These dosages correspond approximately to 0.45, 92, and 27 times the MRHD on a mg/m^2 basis. In the 2-year rat carcinogenicity study, epithelial changes in the nasal cavity and larynx were observed that were regarded as adaptive responses to sustained mild irritation caused by the inhalant and drying of the mucosa. The risk of any adverse respiratory tract epithelial changes in patients is considered negligible, because the rat changes were clearly adaptive in nature, did not progress to neoplasia in a valid life-span study, and occurred at high doses compared to the human dose. Other minor histopathological changes were observed in the harderian gland (incidence and severity of pigment deposits), in the lacrimal gland (increased incidence of cellular alteration), in the submandibular lymph node (increased incidence of plasmacytosis), in the prostate (increased incidence of prostatitis), in the stomach (increased incidence of dilated/cystic glands), and in the urinary bladder (transitional epithelial hyperplasia and inflammation in males).

Genotoxicity studies performed on tiotropium included the Ames assay (*S. typhimurium* and *E. coli* bacterial gene mutation test), *in vivo* micronucleus test, *in vitro* gene mutation test in V79 Chinese hamster cells, *in vitro* cytogenetic study with human lymphocytes and an *in vitro* unscheduled DNA-synthesis test. These tests showed no evidence of a genotoxic potential.

Single and repeat- dose local tolerance studies showed that tiotropium was well tolerated in rabbits (eye irritation, intraarterial and intravenous injection) and in rats (paravenous administration). Administration of tiotropium into the conjunctival sac of rabbits induced no irritant effects even at high doses, although mydriasis was observed.

8.3 CONCLUSION

The extensive non-clinical data indicate an absence of relevant toxicity for man, and the data support the safety of daily inhalation of 22.5 µg tiotropium bromide (corresponding to 18 µg tiotropium) by patients.

9. DRUG PRODUCT INFORMATION

The active substance is tiotropium bromide, which is a new chemical entity, structurally related to ipratropium bromide.

The system for administration of tiotropium by oral inhalation involves the drug product, a formulated powder in a pharmaceutical capsule, in conjunction with a device referred to as "HandiHaler®". This system, as applied to tiotropium, is a refinement of well-established, propellant-free, technology for dry powder inhalation from Boehringer Ingelheim.

Marketing Authorisations have been granted in other countries for tiotropium using the HandiHaler® device.

9.1 COMPOSITION

The active ingredient, tiotropium, is present in the formulation as bromide in a crystalline monohydrate form whereas the label claim is expressed in terms of the mass of the cation entity, which is the pharmacologically active species. It is incorporated as fine particles in the preferred range for inhalation, generally less than 5 µm. The remainder of the formulation consists of crystalline lactose monohydrate.

The formulated powder is filled into a two-piece, imprinted, light green, opaque hard gelatin capsule. The total powder content for each pre-dispensed tiotropium dose of 18 µg is 5.5 mg.

9.2 CONTAINER/CLOSURE SYSTEM

The capsules are packaged in an aluminum foil, moisture resistant blister. One blister card consists of two, five cavity strips joined along a perforated line. Each five cavity strip contains five cavities made of PVC, sealed with an aluminium peel-off foil on the top and a molded aluminum based protective foil on the bottom. A picture of the container/closure system is provided on the next page.

9.3 INHALATION DEVICE

The capsules will be administered with the HandiHaler® inhalation device that enables extraction of the dose from the capsules and dispersion of the drug substance in the inhalation airstream of a patient. The HandiHaler® is a high resistance device working along the following principle:

The hard gelatin capsule is placed into the inhalation device. By pressing a knob the capsule is pierced with the aid of needles. During inhalation the contents of the capsule are aerosolised due to vibration forces and will follow the airstream to the patient's lung. A picture of the HandiHaler® inhalation device is provided on the next page.

9.4 STORAGE AND SHELF-LIFE

The product should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). An expiration dating period of 24 months is proposed for the product.

Container/Closure System

HandiHaler Inhalation Device

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APPENDIX: LIST OF CLINICAL STUDIES

CLINICAL PHARMACOLOGY

Human Pharmacology Studies

Study No.	Description of Study	Total No. Subjects
#101	Tolerability and pharmacokinetics of single increasing doses (0.8–160 mcg).	24
#102	Tolerability and pharmacokinetics of single increasing doses (35.2–281.6 mcg).	16
#103	Tolerability and pharmacokinetics of multiple doses (70.4, 140.8 mcg) over 7 days.	12
#104	Tolerability and pharmacokinetics of multiple doses (8.8, 17.6, 35.2 mcg) over 14 days.	15
#105	Pharmacokinetic study after single administration of 64 mcg p.o., 108 mcg by inhalation and 14.4 mcg by i.v. infusion.	36
#106	Tolerability and pharmacokinetics of single increasing doses (8–64 mcg) p.o.	15
#107	Tolerability and pharmacokinetics after doses of 2.4 mcg and 14.4 mcg (administered once) and 4.8 mcg and 9.6 mcg (administered twice at 24 hr interval by i.v.).	16
#112	Tolerability and pharmacokinetics of multiple doses (8–32 mcg) over 14 days.	36
#133	Effect of age on pharmacokinetics of tiotropium 18 mcg in COPD patients.	29
#134	Effect of renal insufficiency on the pharmacokinetics of tiotropium.	24
#138	Ocular administration, single dose (0.02–0.4 mcg)	48

COPD-Dose Ranging Studies

Study No.	Description of Study	Total No. Subjects
#119	Pilot dose-escalation (8, 16, 32, 64, 128 mcg) study in COPD.	6
#120	Dose and time responses in COPD (8.8, 17,6, 35.2, 70.4 mcg). Double-blind, placebo-controlled crossover.	35
#108	Double-blind, placebo-controlled, parallel group chronic dose ranging study over 4 weeks (4.4, 8.8, 17.6 and 35.2 mcg) in COPD.	169
#139	Dose ranging, placebo-controlled, double-blind, four-way crossover (9, 18, 36 mcg) in COPD	27

CONTROLLED STUDIES

COPD 1-Year Studies

Study No.	Description of Study	Total No. Subjects
#114	Efficacy/safety one-year safety study in COPD (18 mcg). Double-blind, randomized, placebo-controlled, parallel group.	470
#115	Efficacy/safety one-year safety study in COPD (18 mcg). Double-blind, randomized, placebo-controlled, parallel group.	451
#122A	Efficacy/safety one-year safety study in COPD: 18 mcg comparison to Atrovent MDI. Double-blind, randomized, parallel group.	288
#122B	Efficacy/safety one-year safety study in COPD: 18 mcg comparison to Atrovent MDI. Double-blind, randomized, parallel group.	247

COPD 6-Month Studies

Study No.	Description of Study	Total No. Subjects
#130	Efficacy/safety six-month study in COPD (18 mcg). Double-blind, randomized, salmeterol and placebo-controlled (12 hr PFTs)	623
#137	Efficacy/safety six-month study in COPD (18 mcg). Double-blind, randomized, salmeterol and placebo-controlled (3 hr PFTs)	584

CONTROLLED STUDIES

COPD Special Studies

Study No.	Description of Study	Total No. Subjects
#116	Safety of 18 mcg on mucociliary clearance in COPD: a four- week, double-blind, randomized, placebo-controlled, parallel group.	38
#123	Effect of dosing A.M. vs P.M. in COPD: a six-week, double-blind, randomized, placebo-controlled, parallel group, 18 mcg.	121
#124	Effect of tiotropium, 18 mcg, on sleep architecture in patients with COPD compared with placebo. Double-blind , randomized , placebo-controlled , parallel group	95
#129 (Subset of #122A)	Multiple dose, double-blind, Atrovent controlled study of 18 mcg tiotropium to assess the onset of pharmacodynamic steady state in adults with COPD (investigated in one center of #122A).	31
#132	Study of the flow rate characteristics of the HandiHaler® in patients with COPD	26

COPD Non-Inhalation Powder Capsules Formulation Studies

Study No.	Description of Study	Total No. Subjects
#127	Double-blind placebo-controlled parallel group chronic dose ranging study over 3 weeks in COPD 1.0, 2.0, 4.0, 8.0, 16.0 mcg RESPIMAT formulation and 18 mcg DPI	202

Asthma Studies

Study No.	Description of Study	Total No. Subjects
#121	A double-blind, placebo-controlled crossover study to determine the effect increasing single doses (8.8, 35.2 and 70.4 mcg) on methacholine responsiveness in patients with mild asthma	13
#201	The effect of 21-day dosing of tiotropium (4.5, 9, 18, 36 mcg) on bronchomotor tone in patients with moderate to severe asthma, a randomized, double-blind, placebo-controlled, multiple-dose, parallel study	204
#202	The effect of tiotropium (4.5, 9, 18, 36 mcg) on nocturnal asthma, a randomized, double-blind, placebo-controlled, multiple-dose, parallel study	223
#203	The effect of tiotropium 36 mcg on exercise-induced bronchoconstriction, a randomized, double-blind, placebo-controlled, parallel study	31