Boehringer Ingelheim

Briefing Document

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. ABBREVIATIONS

AMI	Acute Myocardial Infarction
AERS	Adverse Event Reporting System
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
ATS	American Thoracic Society
AUC	Area Under the Curve
BD	Bronchodilator
BMI	Body Mass Index
CHF	Congestive Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPMP	Committee for Proprietary Medicinal Products
CRP	C-reactive Protein
CVD	Cardiovascular Disease
DSMB	Data Safety Monitoring Board
EBGM	Empirical Bayes Geometrical Mean
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HLT	Higher Level Group Term
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonisation
IR	Incidence Rate
LABA	Long Acting B-agonist
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MI	Myocardial Infarction
NDA	New Drug Application
PADAC	Pulmonary and Allergy Division Advisory Committee

PEFR	Peak Expiratory Flow Rate
PFT	Pulmonary Function Test
PT	Preferred Term
RD	Rate Difference
RR	Rate Ratio
SD	Standard Deviation
SE	Standard Error
SGRQ	St. George's Respiratory Questionnaire
SMQ	Standardized MedDRA Query
sNDA	Supplemental NDA
SOC	System Organ Class
SVC	Slow Vital Capacity
TDI	Transition Dyspnea Index
UPLIFT®	Understanding the Potential Long-Term Impacts on Function with Tiotropium
VA	Veterans Affairs
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WHO	World Health Organization

2. EXECUTIVE SUMMARY

2.1 INTRODUCTION

Exacerbations of COPD - Clinical and Public Health Burden

Exacerbations of Chronic Obstructive Pulmonary Disease (COPD), including associated hospitalizations represent a significant clinical and public health burden involving patients, healthcare providers and society. Exacerbations of COPD lead to reduced quality of life, premature mortality and increased costs of healthcare.

2.2 BACKGROUND

This Briefing Document provides relevant information to the Pulmonary and Allergy Drugs Advisory Committee (PADAC) concerning the efficacy of tiotropium (Spiriva®) HandiHaler®, a once daily inhaled anticholinergic, on reducing exacerbations of chronic obstructive pulmonary disease (COPD). Tiotropium HandiHaler® is a dry powder delivery system that is the only approved formulation in the United States and is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD. Boehringer Ingelheim is currently seeking the additional indication for a reduction in exacerbations of COPD with tiotropium HandiHaler®.

The briefing document reviews the exacerbation data in the context of overall efficacy and safety. Relevant updated safety information is therefore being presented, which includes adverse event data from the UPLIFT trial, one of the largest COPD intervention trials performed, along with data from observational studies, spontaneous reports and an alternative formulation of tiotropium not available in the United States (tiotropium Respimat inhalation spray). The FDA posted an Early Communication regarding a potential association of tiotropium HandiHaler® with stroke in March 2008 based on information submitted by Boehringer Ingelheim. The Early Communication was updated in October 2008 and referred to recently published retrospective analyses suggesting that use of inhaled anticholinergics, including tiotropium HandiHaler®, may be associated with an increased risk of cardiovascular morbidity and mortality. Given the public health importance of the issues and the Early Communication, the presentation of adverse event data in this document focuses on cardiovascular safety including stroke and overall fatal events with tiotropium.

2.3 EXACERBATION ENDPOINT IN TWO RANDOMIZED TRIALS DESIGNED A PRIORI TO TEST THE HYPOTHESIS

Two large randomized trials, the Veterans Affairs (VA) Trial (205.266/U03-3575-01) and the Understanding Potential Long-Term Impacts in Function with Tiotropium (UPLIFT®) Trial (205.235/U08-3718-04) were designed to prospectively evaluate the effects of tiotropium HandiHaler® on exacerbations of COPD. The VA trial demonstrated that tiotropium HandiHaler® reduced exacerbations as a primary endpoint, whereas UPLIFT showed reductions in exacerbations as a secondary endpoint.

2.3.1 Veterans affairs trial (205.266/U03-3575-01)

The Veterans Affairs (VA) Trial was designed as a confirmatory trial following observations that tiotropium HandiHaler® reduced exacerbations of COPD in the original 1-year and 6-month registration trials in which exacerbation endpoints were prespecified secondary outcomes. The VA Trial was a six-month, randomized, double-blind, placebo-controlled, parallel group trial with tiotropium HandiHaler® once daily in 1,829 patients with COPD. All patients were receiving their medical care in the Veteran's Affairs Medical System. The only background respiratory medications excluded during the trial were inhaled anticholinergics. The co-primary endpoints of this trial were the proportion of patients experiencing exacerbation and the proportion of patients hospitalized due to exacerbation (tested in hierarchical order to protect the probability of type I error 0.05 level). As compared with placebo, tiotropium HandiHaler® significantly reduced the percentage of patients who experienced at least one COPD exacerbation during the six-month treatment period (28% vs. 32%, respectively, p = 0.040). Tiotropium HandiHaler® also reduced the percentage of patients who experienced one or more hospitalizations due to COPD exacerbation during the same period; however, statistical significance was not achieved (7.0% vs. 9.5%, respectively, p = 0.056). Tiotropium delayed the time to the first exacerbation (nominal p = 0.03) as well as the time to first hospitalization due to an exacerbation (nominal p = 0.05). The HRs (95% confidence intervals [CI]) for an exacerbation or exacerbation leading to hospitalization were 0.83 (0.71, 0.99) and 0.72 (0.52, 1.00), respectively. Tiotropium also reduced the number of exacerbations (0.71 (tiotropium) vs. 0.88 (placebo) exacerbations per patient-year, rate ratio (95%CI) = 0.81 (0.67, 0.99)). Only serious adverse events were collected in the protocol (i.e. non-serious events were not requested from investigational sites). The safety reporting in the VA trial was consistent with the overall tiotropium HandiHaler® safety database.

2.3.2 UPLIFT (205.235/U08-3718-04)

The UPLIFT trial was a four-year, multicenter, multinational, double-blind, randomized, placebo-controlled, parallel-group clinical trial involving 5,992 patients with COPD that investigated the effect of tiotropium on the accelerated loss of lung function in COPD. As with the VA trial, the only background respiratory medications excluded were inhaled anticholinergics. The co-primary endpoints were the rate of decline in pre and post-bronchodilator FEV_1 from steady state tiotropium (Day 30) to the last day of treatment. Tiotropium HandiHaler® 18 mcg once daily in comparison to placebo did not alter the rate of decline in FEV_1 in patients with COPD; however, tiotropium maintained improvements in lung function over 4 years.

Two key secondary endpoints were specified in the statistical analysis plan prior to database lock and unblinding: (a) time to first exacerbation, (b) time to exacerbation leading to hospitalization. Tiotropium delayed the time to the first exacerbation and the time to first hospitalization for an exacerbation. The HRs (95% confidence intervals [CI]) for an exacerbation or exacerbation leading to hospitalization were 0.86 (0.81, 0.91) and 0.86 (0.78, 0.95), respectively. The mean number of exacerbations was less for the tiotropium HandiHaler® group (0.73 (tiotropium) vs. 0.85 (placebo) exacerbations per patient-year, rate

ratio (95% CI) = 0.86 (0.81, 0.91)). While all statistical testing for exacerbations are considered descriptive given that the primary endpoint from UPLIFT did not achieve statistical significance, the UPLIFT exacerbation data is based on one of the largest and longest prospective interventional clinical trials in COPD and should be considered as providing substantial support to the exacerbation primary endpoint in the VA trial. Additionally, the exacerbation reduction can be explained physiologically by the effective bronchodilation throughout 24 hours with tiotropium HandiHaler®; an outcome that was maintained relative to the placebo control over 4 years of treatment.

Symptomatic efficacy was present over 4 years as demonstrated by the sustained improvements in the St. George's Respiratory Questionnaire scores compared to the placebo group.

Additionally, treatment with tiotropium was associated with a lower adverse event incidence rate of overall lower respiratory tract events and for respiratory failure. Evaluation of adverse events did not indicate an increased risk for death or cardiovascular morbidity (including myocardial infarction and stroke).

2.4 SUPPORTIVE DATA: POOLED ANALYSES OF CLINICAL TRIALS SUPPORTING REDUCTIONS IN EXACERBATIONS OF COPD

Twenty-six randomized, placebo-controlled, double-blind, placebo-controlled parallel-group trials of at least 4-weeks duration with tiotropium HandiHaler® 18 mcg daily have been conducted in patients with COPD. The COPD protocols generally incorporated similar inclusion and exclusion criteria. These 26 trials have been included in a pooled clinical trial safety database, recognizing that pooled data are subject to certain limitations and are considered supportive. The number of patients (patient-years of exposure) were 7,865 (10,578) for placebo and 9,149 (11,958) for tiotropium HandiHaler®. Of these 17,014 patients, there were 6,187 patients (36%) with at least one COPD exacerbation.

Incidence rates by treatment group and incidence rate differences (per 100 patient-years at risk) were calculated, whereby a rate difference (tiotropium – placebo) (RD) less than 0 indicates a decreased risk with tiotropium and an RD over 0 indicates a decreased risk with placebo.

Tiotropium was associated with a lower incidence rate (i.e. risk) for a COPD exacerbation whether considered within a narrower range of adverse event preferred terms denoting an exacerbation (RD (95% CI) = -8.90 (-11.0, -6.83) or broader range of terms (RD (95% CI) = -9.76 (-12.0, -7.50). Furthermore, there were reductions in risk for exacerbations reported as serious adverse events (RD (95% CI) = -1.58 (-2.37, -0.78). While relatively infrequent, a total of 136 fatal COPD exacerbations were reported among the trials. The rate difference for a fatal COPD exacerbation event was consistent with the other exacerbation findings (RD (95%CI) = -0.09 (-0.28, 0.10)). The reductions in risk for an exacerbation with tiotropium were observed regardless of sex, smoking behavior (i.e. continued and ex-smokers), age, concomitant respiratory medications and different severities of COPD.

With respect to other related outcomes, patients assigned to tiotropium HandiHaler® had lower incidence rates for adverse events of dyspnea and respiratory failure compared to placebo. Finally, the pooled analysis demonstrated that there was no increase in risk for all-cause mortality or cardiovascular morbidity (including myocardial infarction and stroke) in patients assigned to tiotropium HandiHaler®.

2.5 DATA FROM THE TIOTROPIUM RESPIMAT® DEVELOPMENT PROGRAM

Tiotropium Respimat® is comprised of an aqueous solution of tiotropium formulated with the excipients benzalkonium chloride and ethylenediaminetetraacetic acid, disodium salt (EDTA). A total of five trials involving tiotropium Respimat® 5 mcg met the same selection criteria for pooling of trials as described with the above 26 HandiHaler® trials (i.e. randomized, placebo-controlled, double-blind, parallel group studies with a treatment duration of at least 4 weeks). The trials demonstrated improvements in lung function over 24 hours with once daily dosing along with improvements in symptoms and a reduced risk for exacerbations of COPD.

In a pooled analysis of these five clinical trials (three of which were 1-year in duration), numerically more deaths were reported in the tiotropium Respimat® 5 mcg compared to the placebo group. The first two of the three 1-year trials included a tiotropium Respimat® 10 mcg group, which also showed a higher number of deaths relative to the placebo group. Subgroup analyses from the tiotropium Respimat® 5 mcg trials suggested that patients receiving tiotropium Respimat® who had known rhythm disorders at randomization, may be at an increased risk for a fatal event; however, a similar analyses performed in the tiotropium HandiHaler® pooled clinical trial safety database did not indicated an increased risk. An examination of the formulation properties indicates no known scientific rationale to expect a difference based on the pharmacology of the substance, the pharmacokinetics of the formulations or the excipients of each formulation. The mortality observations from the Respimat® database (5 trials, 6,448 patients, 5,487 patient-years at risk) are inconsistent with the larger tiotropium HandiHaler database (26 trials, 17,014 patients, 23,934 patient years at risk). In addition, the tiotropium HandiHaler® database includes a large study of 4-years duration, whereas the Respimat® database is limited to studies of up to 1-year in duration. Given the observations with the tiotropium Respimat® formulation, a large, long-term clinical trial will be initiated in 2010 examining the relative benefits and risks of tiotropium Respimat® (in two doses, 2.5 mcg and 5 mcg once daily) to tiotropium HandiHaler® 18 mcg once daily in patients with COPD. Note: the pooled analysis of the Respimat® database did not indicate an increased risk for stroke.

2.6 EPIDEMIOLOGIC STUDIES

Observation studies have been conducted utilizing databases from Denmark, the United Kingdom, and from the Netherlands. These studies examined mortality and cardiovascular events among tiotropium users compared to long-acting beta-agonist users or non-tiotropium use. The overall data did not indicate an excess risk of cardiovascular or fatal events with

tiotropium relative to the control group. Hazard ratios (tiotropium/control) for all three studies were below one for all-cause mortality.

2.7 CONCLUSION

COPD is a progressive disabling lung disease that is associated with significant morbidity and mortality. People with COPD have important limitations in daily function and quality of life. These patients often experience complications of respiratory disease and comorbid disease including premature mortality. Exacerbations contribute significantly to the morbidity and mortality associated with COPD which can be impacted with maintenance treatment with tiotropium HandiHaler®. The reductions in COPD exacerbations with tiotropium have been observed in individual trials with tiotropium HandiHaler®, including those of significant size and duration, and in an overall analysis of the clinical trial database. Additionally, the findings are consistent with the efficacy outcomes in tiotropium HandiHaler clinical trials and can be explained physiologically through effective bronchodilation throughout 24 hours.

The evaluation of safety with tiotropium HandiHaler® demonstrated no increased risk for fatal events or cardiovascular events including stroke. Regarding the higher rates of fatal event reporting with tiotropium Respimat®, a causal relationship has not been established as there is no known scientific rationale that would predict a difference based on the pharmacology of the substance, the pharmacokinetics of the formulations or the excipients of each formulation. Further data will be obtained through a large, long-term prospective clinical trial.

The exacerbation benefits observed in the VA trial and supported by the UPLIFT trial confirmed the observations documented from secondary endpoints in the Phase III registration trials and are the basis for the requested labeling revisions for tiotropium HandiHaler®. Specifically, Boehringer Ingelheim seeks to add reduction of COPD exacerbations to the Indication section and insert the applicable data from both trials into the Clinical Studies section. The key findings from the VA trial and the UPLIFT trial regarding exacerbations constitute important information that warrants inclusion in the label so that physicians can fully understand the longer term positive impact of tiotropium in the treatment of COPD.

3. INTRODUCTION

Tiotropium HandiHaler 18 mcg, a long-acting inhaled anticholinergic was approved by the FDA in the United States in 2004 for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD. Boehringer Ingelheim submitted a supplemental New Drug Application (sNDA) to request that the indication statement be expanded to include reductions in exacerbations.

The sNDA describes two large trials (Veterans Affairs (VA) trial and the UPLIFT trial) in which exacerbations were prospectively defined as an efficacy endpoint. In this supplement, the VA study is the pivotal trial supporting the exacerbation indication, with primary supportive evidence coming from the UPLIFT study. The sNDA also included supportive data derived from post hoc analysis of other phase III and IV clinical trials and epidemiological studies.

In both trials, all concomitant respiratory medications, other than inhaled anticholinergics, were permitted during the treatment period in order to provide data that would be representative of a patient population that is seen by health care practitioners in the community. These studies also demonstrated spirometric benefits similar to those demonstrated earlier, symptomatic improvement as measured by a validated scale, and reductions in reporting of respiratory failure.

This briefing document reviews the exacerbation data in the context of overall efficacy and safety. Relevant updated safety information is therefore being presented, including adverse event data from the UPLIFT trial, one of the largest COPD intervention trials performed along with data from observational studies, spontaneous reports and an alternative formulation of tiotropium not available in the United States (tiotropium Respimat inhalation spray).

In March 2008, the FDA posted an Early Communication based on information proactively forwarded by Boehringer Ingelheim in November 2007. The data were from a pooled analysis of adverse event data from 29 placebo-controlled clinical studies and an epidemiological study. In 25 of the clinical studies, patients were treated with tiotropium HandiHaler®. In the other 4 clinical studies, patients were treated with another formulation of tiotropium that has since been approved in Europe, tiotropium Respimat®. The 29 clinical studies included approximately 13,500 patients with COPD and the epidemiology study covered an additional 1,061 patients who had been prescribed tiotropium HandiHaler®. Based on data from these 29 clinical studies, the preliminary estimates of the risk of stroke were 0.8 patients per 100 patient-years at risk in the tiotropium group and 0.6 patients per 100 patient-years at risk with placebo. The FDA stated that it was important to interpret the preliminary results with caution and that the Early Communication was in keeping with the FDA's commitment to inform the public about its ongoing safety reviews of drugs. The FDA noted that the UPLIFT study data would provide additional long term safety data with tiotropium and additional insight into the risk of stroke or other safety findings with tiotropium HandiHaler®.

In October 2008, the information in the Early Communication was updated to state that preliminary data from UPLIFT, reported by Boehringer Ingelheim to the FDA, showed no increased risk of stroke with tiotropium compared to placebo. Additionally, the FDA identified two publications referring to retrospective analyses that described an increased risk for mortality and/or cardiovascular events in patients who inhaled anticholinergics, including tiotropium.

It is within the context of the Early Communication and the relevance to public health that the briefing document will summarize the tiotropium HandiHaler® safety information pertaining to mortality, cardiovascular events and stroke. The review of the UPLIFT trial, either alone or when combined into a pooled analysis of tiotropium HandiHaler® trials, and the overall totality of the safety data, does not show an increased risk for the aforementioned events with tiotropium HandiHaler® 18 mcg daily in patients with COPD.

3.1 EXACERBATIONS OF COPD – CLINICAL AND PUBLIC HEALTH BURDEN

COPD is a major cause of morbidity, disability and mortality disability. In the United States in the year 2000, COPD was responsible for 8 million outpatient office visits, 1.5 million emergency department visits, 726,000 hospitalizations, and 119,000 deaths (R04-1525).

Despite increased therapeutic options for COPD, an upward trend in emergency department visits for COPD was observed between 1992 and 2001 (from 1,095,000 to 1,549,000 emergency department visits per year, respectively) (R04-1525). Based on annual data from the National Hospital Discharge Survey in the United States, a decline in annual hospitalizations for COPD was observed between 1984 and 1989. This decrease was attributed to systematic changes in the US health care system such as diagnosis related groups (DRGs), pressure to decrease hospitalizations, etc., and not to a lower prevalence of COPD. Between 1990 and 1999 estimated hospitalization rates increased from 30.4/10,000 population to 44.9/10,000 population (or 463,000 to 787,000 hospitalizations/year, respectively). The largest increase in hospitalization rates were observed in older patients, with a 62% increase in hospitalization rates for 65-74 year olds and a 52% increase in those≥75 years of age (R04-1525).

Mortality data from the Mortality Component of the National Vital Statistics System indicates that between 1980 and 2000, there was a 67% increase in the overall death rate from COPD (R04-1525).

The Healthy People 2010 initiative has set forth two goals relative to COPD: 1) to reduce the proportion of adults≥45 years of age whose activity is limited secondary to chronic lung disease and breathing difficulties to 1.5% compared to 2.2% in 1997, and 2) to reduce deaths from COPD in adults≥45 years to 60 deaths/100,000 in 2010 compared to 119.4 deaths/100,000 in 1998 (R04-1525). Given the observed trends in COPD hospitalizations and mortality, this goal is unlikely to be accomplished in the absence of an intervention with the potential to reduce COPD morbidity and mortality .

One of the major clinical consequences of COPD is the periodic acute to subacute worsening of disease referred to as exacerbations. Exacerbations represent an enormous economic burden to health care systems. In 1993 in the United States, COPD was responsible for approximately 24 billion dollars in direct and indirect costs with approximately 15 billion dollars attributed to direct costs. In the United Kingdom in 1996 total costs were estimated at 4 billion dollars with 0.8 billion being direct cost (R04-1529). The major cost in treatment relates to exacerbations and in particular to exacerbation-related hospitalization (P99-00875).

Exacerbations can have a significant impact on the quality of life in patients with COPD. Seemungal and colleagues (R00-1350) performed multiple regression analyses on a closely followed cohort of COPD patients and documented that exacerbation frequency was strongly correlated with a disease-specific health-related quality of life instrument. Conners and colleagues evaluated quality of life outcomes in a study of patients hospitalized with acute exacerbations of COPD (R01-1223) and documented prolonged impacts of exacerbations on quality of life. Trade-off scores showed that 64% of patients were willing to trade a year of their current health status for less than a year (i.e. reduced quantity of life) of excellent health. In general, patients admitted to the hospital for acute exacerbations of COPD have an in-hospital mortality rate in the range of 10-14% depending on the patient population (R01-1223). One-year mortality following hospital admission for a COPD exacerbation is in the range of 22% to 43%, and higher for older subgroups and ICU admissions (R01-1223, R00-1373).

In summary, COPD results in physiologic limitations leading to impairment in performance of activities of daily living, significant morbidity, reduced quality of life and increased risk for premature mortality. The increased morbidity and mortality associated with COPD are multifactorial with the contribution of exacerbations being an important component. While meaningful physiologic (i.e. lung function) improvement is expected with an intervention that reduces exacerbations, it cannot be assumed that all interventions that improve lung function will impact exacerbations. Therefore, there is a need to directly demonstrate an effect of an intervention on exacerbations of COPD. Considering the complex nature and impact of COPD, therapeutic interventions are needed that can improve the physiologic abnormalities, reduce symptoms and reduce exacerbations. Such therapies may be expected to improve the well-documented morbidity of the disease and the lives of patients with COPD.

3.2 BACKGROUND: TIOTROPIUM HANDIHALER DEVELOPMENT FOR COPD

COPD is a disorder characterized by progressive and incompletely reversible expiratory airflow limitation. Breathlessness, a major reason for seeking medical care, develops over many years and eventually limits daily activities (European Respiratory Society [ERS], 1995/P95-3225). This airflow impairment is in large part responsible for the disability and associated handicaps in performing daily functions. In addition to smoking cessation, bronchodilator therapy is an important component of care. European (ERS, 1995/P95-3225), American (American Thoracic Society [ATS], 1995/P95-4381), and international (Global Initiative for Chronic Obstructive Lung Disease [GOLD], P06-12085) treatment guidelines

all place bronchodilators as the foundation of therapeutic management. Pharmacologic therapy for COPD begins with inhaled bronchodilators which relax airway smooth muscle. Two classes of inhaled drugs are currently utilized: beta-agonists and anticholinergics. Inhaled anticholinergic drugs such as ipratropium bromide and oxitropium bromide have had greater than two decades of use and have emerged as safe and effective agents in treating patients with COPD (P89-0446; P93-0916). The primary limitation of these agents is the need for frequent (i.e. four times daily) dosing.

The efficacy objective of the tiotropium clinical program was to demonstrate benefit in the treatment of COPD in terms of prolonged bronchodilation with once daily therapy. Therefore, sustained improvements in lung function approximately 24 hours after administration formed the basis of regulatory approval in the United States. Lung function is considered a surrogate for symptomatic improvement; however the relationship of lung function improvement to clinical benefits is variable. Accordingly, other endpoints such as symptom improvement (R00-1030), health-related quality of life (HRQoL) (R96-0686, R98-0966) and exacerbations were included in the phase III clinical trials.

The core of the clinical program was based on four replicate trials of one year duration in patients with COPD. Two trials conducted in Europe compared tiotropium (18 mcg daily) with ipratropium bromide (40 mcg QID) (205.126A/U00-3113; 205.126B/U00-3114) and two trials conducted in the United States compared tiotropium (18 mcg QD) with placebo (205.117/U99-3169; 205.128/U99-3170-01). In addition, two multi-national studies of six months duration compared tiotropium with salmeterol (50 mcg BID) and placebo (205.130/U01-1236-01; 205.137/U01-1231-01). A total of 1,456 COPD patients were randomized in the four one-year trials constituting the core program. An additional 1,207 patients were randomized in the two six-month trials comparing tiotropium to salmeterol and placebo. A total of 1,308 patients were exposed to tiotropium in these registration studies (906 patients in the four one-year trials and 402 patients in the two six-month trials).

The trials submitted in the original New Drug Application (NDA) provided consistent evidence of the therapeutic benefit of tiotropium HandiHaler® 18 mcg once daily for COPD as an effective bronchodilator that improves airflow and symptoms of COPD. Secondary endpoints investigated in the pivotal registration trials demonstrated improvements in HRQoL and reductions in COPD exacerbations.

United States marketing authorization for tiotropium was granted in January 2004. Tiotropium HandiHaler® is available in over 90 countries around the world.

Subsequently applications for additional labelling based on post-registration clinical trial results were submitted to regulatory agencies outside of the United States and approved based on additional clinical trials supporting reductions in COPD exacerbations (205.266/U03-3575-01, U05-1798), improvements in exercise endurance time during constant work cycle ergometry (205.131/U02-1202, 205.223/U04-3016, U05-1797) and improvements in health-related quality of life (205.256/U05-1961).

4. EXACERBATION ENDPOINT IN TWO RANDOMIZED TRIALS DESIGNED A PRIORI TO TEST THE HYPOTHESIS

Two large randomized trials, the Veterans Affairs (VA) Trial (205.266/U03-3575-01) and the Understanding Potential Long-Term Impacts in Function with Tiotropium (UPLIFT®) Trial (205.235/U08-3718-04) were designed a priori to test the hypothesis that tiotropium HandiHaler® reduces exacerbations of COPD. The VA trial (205.266) is a 6-month multi-center, randomized, double-blind, placebo-controlled, parallel group trial that was designed as a confirmatory study following observations of reductions in exacerbations in the registration trials. The VA trial pre-specified exacerbations of COPD as the primary endpoin with a separate case report form to collect the COPD exacerbation information versus adverse event reporting as was done in the registration trials. The UPLIFT® trial (205.235), a 4-year randomized, double-blind, placebo-controlled, parallel group international trial, documented this effect over a prolonged study period (4 years).

The definitions used to capture exacerbation information in tiotropium Phase III and IV clinical trials were generally similar and included the presence of a complex of respiratory symptoms (≥2) with a duration of≥3 days. The definitions differed primarily in the treatment required in order to be considered a COPD exacerbation. In the VA trial (205.266), patients were required either to be hospitalized (i.e. at least 24 hours stay within a hospital setting) or to be treated with antibiotics or steroids. In the UPLIFT trial (205.235), treatment with antibiotics or steroids was required whether or not the patient was hospitalized. A specific exacerbation case report form was used in each trial to collect exacerbation information.

Table 4: 1 Definition of exacerbation used in the VA and UPLIFT trials

Trial number	Exacerbation Outcome	Symptoms (all required ≥2 symptoms)	Duration (days)	Treatment Required
		Symptom Description		
205.266	Primary	Cough, sputum, sputum purulence, wheezing, dyspnea, chest tightness	≥3	Antibiotics and/or systemic steroids and/or hospitalization.
205.235	Secondary	Cough, sputum, sputum purulences, wheezing, dyspnea	≥3	Antibiotics and/or systemic steroids

Source data: see U03-3575-01, U08-3718-04

The advantage of the definition in the VA trial and UPLIFT is the requirement for three components: more than one respiratory symptom, a minimal time duration to minimize the likelihood of the symptoms simply representing day to day variability, and an intervention from a health care provider (indicating that the event is clinically important).

The definitions performed similarly in the VA and UPLIFT trials. The specific symptoms that were part of the definition of an exacerbation in the VA trial were captured on a case report form. The symptoms of cough, sputum, sputum purulence, wheeze, and dyspnea were common to the definitions in the VA trial and UPLIFT. Ninety-eight percent of all

exacerbations (780/796) in the VA trial would have met the UPLIFT definition (based on experiencing at least two of cough, sputum, sputum purulence, wheeze, and dyspnea) (data on file, Table 15.3.6:14). Of the hospitalized exacerbations, 98% (180/183) in the VA trial were prescribed antibiotics or steroids (data on file, Table 15.3.6: 17). Furthermore, 99% (543/551) of patients with exacerbations in the VA trial would have met the UPLIFT definition (data on file, Table 15.3.6: 13). Of the patients hospitalized for an exacerbation in the VA trial, 99% (149/151) were prescribed antibiotics or steroids (data on file, Table 15.3.6: 16). Therefore, while the definitions in the trials differed slightly, the definitions appeared to function almost identically.

5. VETERANS AFFAIRS TRIAL (205.266/U03-3575-01)

5.1 OBJECTIVES

The primary objectives of the Veterans Affairs (VA) Trial (205.266/U03-3575-01) were to determine whether tiotropium 18 mcg once daily via the HandiHaler® reduces the proportion of patients experiencing exacerbation and the proportion of patients hospitalized due to exacerbation in patients with COPD. The secondary efficacy endpoints included:

- The time to first COPD exacerbation
- The time to first hospitalization associated with a COPD exacerbation
- Number of exacerbations and exacerbation days
- Number of hospitalizations and hospitalization days due to an exacerbation
- Number of days on corticosteroids for exacerbations
- Number of days on antibiotics for exacerbation
- Number of unscheduled out-patient visits for exacerbation

5.2 STUDY DESIGN

The VA Trial (205.266/U03-3575-01) was a 6-month randomized, double-blind, placebo-controlled, parallel group trial with tiotropium 18 mcg HandiHaler® once daily in patients with COPD who received their medical care in the Veterans Affairs Medical System.

The study began in September 2001; the last patient was randomized in August 2002 and completed the study in February 2003. The randomization period covered approximately a full year and was not restricted to a specific season. A total of 1,829 patients were randomized and treated.

Patients were seen in clinic at 3 and 6 months following randomization. Telephone contacts occurred monthly between clinic visits to obtain information regarding exacerbations of COPD. All patients were encouraged to complete the study even if they had discontinued study medication. Exacerbations were also collected after last drug intake until the planned end of the trial. The data from patients who discontinued study drug and continued in the study were assigned to their treatment arm at randomization.

An exacerbation was defined as:

- a complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, sputum purulence, wheezing, dyspnea, or chest tightness
- with a duration of at least three days
- requiring treatment with antibiotics and/or systemic steroids and/or hospitalization admission.

Events were considered as an exacerbation-related hospital admission if the patient was held and treated for an acute respiratory condition in an urgent-care department or in an observation unit for greater than twenty-four hours.

5.3 STUDY POPULATION

All men and women receiving medical care at participating VA medical centers were potential study subjects. The inclusion criteria were similar to those in the original NDA registration trials and included age ≥40 years, a diagnosis of COPD with a screening $FEV_1 \leq 60\%$ of predicted normal with an $FEV_1/FVC \leq 70\%$, and a smoking history>10 pack-years (a pack-year being defined as 20 cigarettes per day for one year or equivalent). A previous history of an exacerbation was not required. Exclusion criteria were, in general, similar to those of the registration trials, and they excluded patients with asthma, known moderate to severe renal impairment, narrow-angle glaucoma, and moderate to severe symptomatic prostatic hypertrophy or bladder-neck obstruction. However, cardiac exclusion criteria were liberalized compared to the registration trials (i.e. myocardial infarction within the prior six months (compared to 1 year in the registration trials), a serious cardiac arrhythmia (compared to any drug treated arrhythmia in the registration trials) or hospitalization for heart failure within the prior year (compared to 3 years in the registration trials)). In addition, patients requiring continuous supplemental oxygen or inhaled long-acting inhaled beta-agonists were not excluded (stated as exclusion criteria in the registration trials). While this was a placebo-controlled trial, patients were allowed to use all classes of respiratory medications other than inhaled anticholinergics. In this respect, patient treatment in the study was approximating "usual care".

5.4 STATISTICAL METHODS

Exacerbation data was collected on a separate case report form. The information on the case report form included the reported term, onset and end dates, occurrence of cough, sputum, sputum purulence, wheezing, dyspnea, and chest tightness (yes/no), associated emergency room/urgent care/unscheduled visit (yes/no), associated hospitalization (yes/no), number of days on antibiotics and number of days on systemic steroids. The reported terms were coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA) and in accordance with the Boehringer Ingelheim Data Management & Statistics Manual guideline, Rules for Coding Medical Data. In addition, each exacerbation entry was electronically checked to ensure that it was of three or more day's duration and that there was more than one symptom associated with the exacerbation, per the protocol definition given above. Also, an electronic check was made to see if either: 1) antibiotics or steroids were prescribed as countermeasure or 2) the patient was hospitalized. Exacerbations were reported both as efficacy endpoints and as part of adverse event reporting.

The two primary endpoints were compared across the two treatment groups in a stepwise manner. In the first step, the percentage of patients with a COPD exacerbation was compared between tiotropium and placebo using the Cochran-Mantel-Haenszel test. If there were significantly fewer patients on tiotropium with exacerbation, the percentage of patients with a hospitalization due to COPD exacerbation were compared across the treatment groups, The stepwise procedure was used to protect the probability of type I error (0.05) using two-sided tests.

Time to first COPD exacerbation and time to exacerbation-associated hospitalization were compared between treatment groups using log-rank tests. Cox regression was used to derive hazard ratios (HR). Kaplan-Meier curves of the probability of no exacerbation and related hospitalization were displayed. The number of events and event days were compared between treatment groups using Poisson regression adjusted for treatment and center effects and corrected for treatment exposure. In a later analysis, corrections were made for overdispersion based on recommendations by Suissa (R07-0024). For time to event endpoints, the effects of treatment within each level of a given subgroup were obtained using Cox regression with treatment, separately for each level of a given subgroup. To assess the interaction effect, a separate Cox model with treatment, subgroup, and treatment by subgroup interaction was fitted.

5.5 PATIENT DEMOGRAPHICS

A total of 1,829 patients were randomized, 915 to placebo and 914 to tiotropium. A total of 73.2% of placebo treated and 83.7% of tiotropium treated patients completed trial medication and 87.9% of placebo treated and 91.5% of tiotropium treated patients completed the study (including those patients who consented to be followed despite discontinuation of study medication) (U03-3575-01, Tables 10.1:1 and 10.1:2). Of the randomized patients, 245 (27%) from the placebo arm and 149 (16%) from the tiotropium arm discontinued study medication prematurely. The most commonly cited reason was worsening of COPD. Discharge summaries were available for review from 94% of all hospitalizations.

As documented in the table, the two treatment arms were well matched for all baseline characteristics, including current medications and prior health care events related to COPD. The gender and racial compositions (98% male, 91% white) of the study subjects is representative of patients who receive medical care at VA medical facilities. The baseline FEV_1 was 1.04 L (36% of predicted) (U03-3575-01, Table 14.1.2:1).

Table 5.5: 1 Baseline characteristics of placebo and tiotropium patients in the VA trial

	Placebo (n = 915)	**Tiotropium (n = 914)**
Male	904 (99)	898 (98)
Age – years (mean±SD)	68.1 ± 8.5	67.6 ± 8.7
Caucasian race	823 (90)	847 (93)
Smoking status		
Current smoker	272 (30)	263 (29)
Pack-year history (mean±SD)	69.4 ± 36.6	67.4 ± 35.4
Duration of COPD – year (mean±SD)	11.9 ± 10.5	12.2 ± 10.4
Baseline spirometry (mean±SD)		
FEV_1 (liters)	1.04 ± 0.40	1.04 ± 0.40
FEV_1 (% predicted)	35.6 ± 12.6	35.6 ± 12.6
FEV_1/FVC (%)	47.7 ± 11.1	47.9 ± 11.5
Medications for COPD – N (% of patients)		
Inhaled beta-agonist (total)	864 (94)	851 (93)
Long-acting beta-agonists	351 (38)	346 (38)
Ipratropium bromide	728 (80)	735 (80)
Inhaled corticosteroids	531 (58)	559 (61)
Oral corticosteroids	97 (11)	94 (10)
Theophylline	118 (13)	141 (15)
Leukotriene antagonist	53 (6)	59 (6)
Home oxygen	272 (30)	259 (28)

Data displayed as n (%) unless otherwise specified. Values represent data obtained at screening.
Source data: P05-09172

5.6 EFFICACY RESULTS

5.6.1 Exacerbation

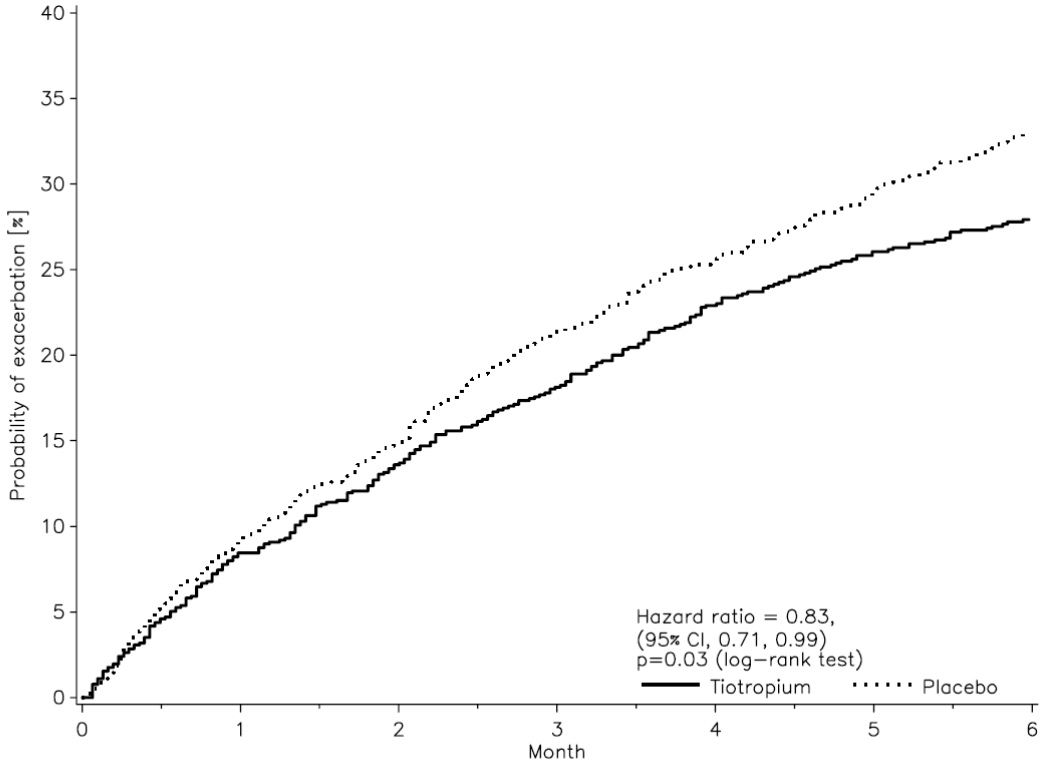
As compared with placebo, tiotropium significantly reduced the percentage of patients who experienced at least one COPD exacerbation during the six-month treatment period (28% vs. 32%, respectively, p= 0.037). Tiotropium also reduced the percentage of patients who experienced one or more hospitalizations due to COPD exacerbation during the same period; however, the difference was not statistically significant (7.0% vs. 9.5%, respectively, p = 0.056). Therefore all subsequent p-values should be considered as nominal.

Table 5.6.1: 1 Co-primary exacerbation outcomes from the VA trial

	Placebo (N=915)	**Tiotropium (N=914**	Odds ratio (95% CI)	p-value
Number (%) of patients with exacerbations[1]	296 (32.3)	255 (27.9)	0.81 (0.66, 0.99)	0.037
Number (%) of patients with hospitalizations for COPD[1]	87 (9.5)	64 (7.0)	0.72 (0.51, 1.01)	0.056

Results are expressed as number (%) of subjects with one or more event.[1]
[1]Cochran-Mantel-Haenszel test.
Source data: see U03-3575-01, Table 14.2.1: 1

As shown in the cumulative incidence rate (Kaplan-Meier) plots (Figures 5.6.1: 1 and 5.6.1:2), tiotropium, compared to placebo, delayed the time to first exacerbation (p=0.03) and the time to first hospitalization due to an exacerbation of COPD (p=0.05) with hazard ratios (95%CI) of 0.83 (0.71, 0.99) and 0.72 (0.52, 1.00), respectively.



No. of patients:

Tiotropium	914	836	786	739	689	655	328
Placebo	915	829	770	706	661	610	300

Figure 5.6.1: 1 Cumulative incidence rate (Kaplan-Meier) of the probability of a COPD exacerbation – VA trial.

No. of patients = number of patients at risk.
Source data: data on file, Figure 1.

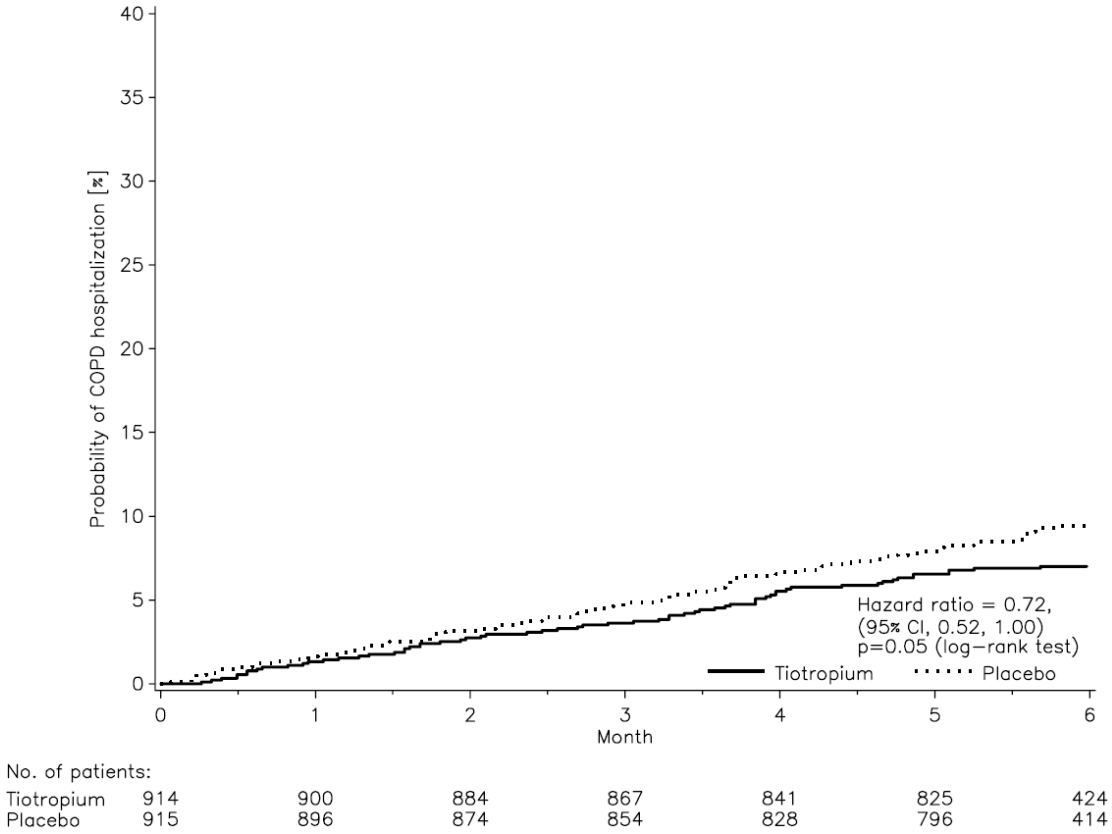


Figure 5.6.1: 2 Cumulative incidence rate (Kaplan-Meier) of the probability of COPD exacerbation leading to a hospitalization – VA trial.

No. of patients = number of patients at risk.
Source data: data on file, Figure 2.

Tiotropium reduced the number of exacerbations and improved other exacerbation variables (p-values ranged from 0.037 to 0.471, Table 5.6.1: 2). The relative decrease, depending on the variable, was between 15% and 30%.

Table 5.6.1: 2 Secondary exacerbation endpoints in the VA trial. Number of events and event days are expressed per patient-year.

	Placebo (N = 915)	Tiotropium (N = 914)	Rate ratio (95% CI)	p-value
Number of exacerbations	0.88	0.71	0.81 (0.67, 0.99)	0.037
Exacerbation days	12.6	9.96	0.79 (0.62, 1.01)	0.056
Antibiotic days for COPD exacerbations	7.86	6.51	0.83 (0.66, 1.04)	0.105
Systemic corticosteroid days for COPD exacerbations	5.26	4.44	0.85 (0.59, 1.22)	0.375
Unscheduled visits for COPD exacerbations	0.38	0.30	0.78 (0.61, 1.01)	0.056
Number of hospitalizations for COPD exacerbations	0.21	0.15	0.70 (0.48, 1.01)	0.054
Hospital days for COPD exacerbations	1.27	1.07	0.84 (0.53, 1.34)	0.471

Rate ratio from Poisson regression adjusted for treatment and center effects and corrected for treatment exposure
Source data: data on file, Tables 5.1 and 5.2

5.6.2 Subgroup analysis

Subgroup analyses were performed according to each of these pre-specified entry variables: age, current cigarette smoking, baseline FEV_1, hospitalization for COPD in the past year, one or more courses of systemic corticosteroids for COPD in the past year, one or more courses of antibiotics for COPD in the past year, and baseline use of inhaled corticosteroids, long-acting inhaled beta-agonists, combination of inhaled corticosteroids + long-acting beta-agonists, theophyllines or anticholinergics (discontinued at randomization). It is recognized that subgroup analyses need to be interpreted with caution given the reduced power in individual subgroups and reduced precision of the estimates as well as due to multiplicity.

As shown in the figure displayed below, tiotropium produced a fairly uniform reduction in exacerbations for all subsets included in the analyses. At the time of the study, the American Thoracic Society (ATS) criteria for severity of disease were being used and not GOLD staging (P01-01995); however, the stages are similar. Data on FEV_1 severity is based on pre-bronchodilator FEV_1 (spirometry following inhalation of short-acting bronchodilators was not performed) and suggested that the effect on exacerbations was most prominent in those with more severe disease, although the number of subjects with pre-bronchodilator $FEV_1 \geq$ 50% was low (287 patients in total). A test for interaction for each of these variables indicated no significant interactions with treatment assignment, although such tests are underpowered.

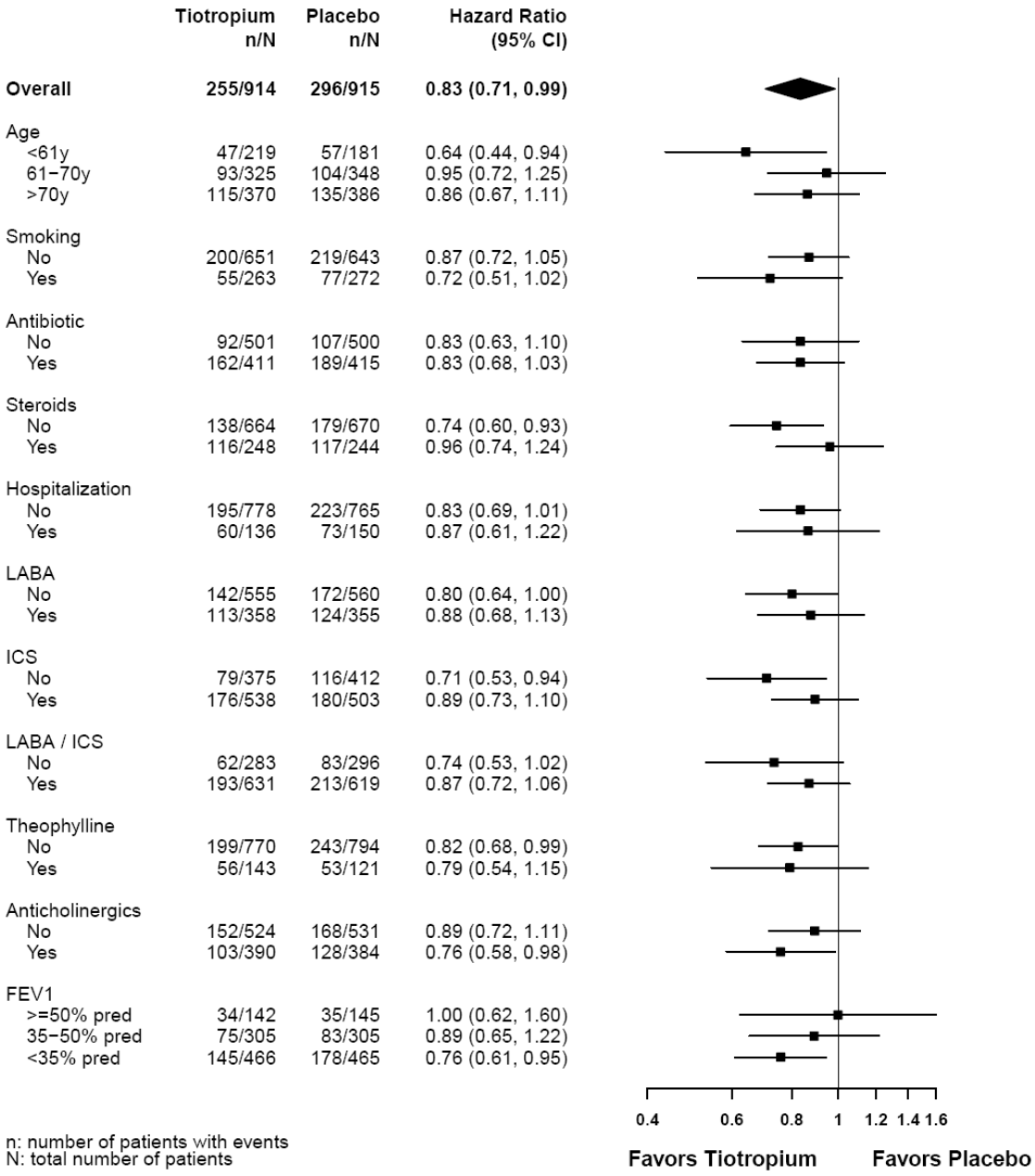


Figure: 5.6.2: 1 Hazards ratios and 95% confidence intervals (tiotropium/placebo) for reduction in risk for a COPD exacerbation with tiotropium according to selected baseline characteristics – VA trial.

Source data: data on file, Table 3 and P05-09172. Values represent data obtained at randomization.

5.6.3 Other relevant outcomes

Compared with placebo, tiotropium increased the FEV_1 response at 90 minutes after administration of study medication at study days 0, 90, and 180 by 0.13 L, 0.16 L, and 0.17 L, respectively ($p < 0.0001$ for all comparisons). Additionally, the morning trough FEV_1 prior to administration of study drug was higher in tiotropium treated patients than in placebo treated patients at study days 90 and 180 (0.10 L and 0.09 L, respectively; $p < 0.0001$ for both comparisons).

5.7 SUMMARY OF SERIOUS ADVERSE EVENTS

Only serious adverse events were documented in the VA trial. Non-serious adverse events were not requested. The following summary of adverse events from this 6 month trial is presented as number of events and/or crude frequencies. The overall adverse event reporting (until 30 days following the last dose of study medication) does not indicate a relevant imbalance between treatment groups (Table 5.7: 1).

Table 5.7: 1 Summary of adverse event reporting in the VA trial during treatment (up to 30 days following the last dose of study drug)

	Placebo N (%)	**Tiotropium N (%)**
Total Treated	915 (100)	914 (100)
Serious Adverse Events	156 (17.0)	162 (17.7)
Deaths	19 (2.1)	22 (2.4)

Source data: see U03-3575-01, Appendix 16.1.9. 2, Table 7.2: 1, Appendix 16.2 Listing 7.2.1

With the exception of a lower frequency of lower respiratory events in the tiotropium group, the overall safety profile of tiotropium observed in this trial is similar to that of placebo. The most frequently reported serious adverse events were lower respiratory system disorders. Fewer serious lower respiratory events occurred in the tiotropium group compared to placebo (7.9 vs. 9.8%, respectively). COPD exacerbation was the most commonly reported serious adverse event, and was reported in a smaller proportion of patients in the tiotropium group compared to placebo (4.2 vs.6.7%, respectively) (data on file, Table 10.21). Of note, there were fewer fatal lower respiratory events reported in the tiotropium group compared to placebo (2 vs. 7 deaths, respectively).

A table of the most common serious adverse events ($\geq$2 cases in either treatment group) is provided in Table 5.7: 2 (refer to Section 6.4.4 for a description of the coding system used). Cardiac disorders were the next most frequently occurring group of events. Serious adverse events of cardiac etiology were reported less frequently in the tiotropium group compared to placebo (3.6% vs. 5.2% of patients, respectively). Congestive heart failure was the most commonly reported cardiac serious adverse event, and occurred with similar frequency in the two treatment groups. Atrial fibrillation/atrial flutter occurred in fewer patients in the tiotropium group compared to the placebo group (3 vs. 10 patients, respectively). There were no clinically relevant imbalances between the two treatment groups with regard to other cardiac events. Fatal cardiac events were reported in 3 patients in the tiotropium group

compared to 6 patients in the placebo group. A total of 5 fatal events were reported as death of unexplained cause (4 in the tiotropium group and 1 in the placebo group). If these deaths are added to the events already attributed to a cardiac etiology, the incidence of fatal cardiac events is the same in the both treatment groups (U03-3575-01, Tables 14.3.1:2 and 14.3.1:4).

Table 5.7: 2 Serious adverse events occurring in more than two patients in either treatment group (205.266)

	Treatment at Onset		
MedDRA System Organ Class MedDRA Preferred Term	**Placebo N (%)**	**Tiotropium N (%)**	**Total N (%)**
Total Treated	915 (100)	914 (100)	1829 (100)
Total Treated with any Events	156 (17.0)	162 (17.7)	318 (17.4)
Cardiac Disorders	**48 (5.2)**	**33 (3.6)**	**81 (4.4)**
Angina	7 (0.8)	6 (0.7)	13 (0.7)
Atrial Fibrillation/ Atrial flutter	10 (1.1)	3 (0.3)	13 (0.7)
Cardiac arrest	3 (0.3)	2 (0.2)	5 (0.3)
Cardiac failure congestive	10 (1.1)	10 (1.1)	20 (1.1)
Coronary artery disease	6 (0.7)	4 (0.4)	10 (0.5)
Myocardial Infarction	7 (0.8)	9 (1.0)	16 (0.9)
Ventricular tachycardia	4 (0.4)	5 (0.5)	9 (0.5)
Gastrointestinal disorders	**16 (1.7)**	**20 (2.2)**	**36 (2.0)**
Gastritis	3 (0.3)	0 (0.0)	3 (0.2)
General disorders and administration site conditions	**5 (0.5)**	**12 (1.3)**	**17 (0.9)**
Chest pain	2 (0.2)	4 (0.4)	6 (0.3)
Death	1 (0.1)	4 (0.4)	5 (0.3)
Infections and infestations	**9 (1.0)**	**10 (1.1)**	**19 (1.0)**
Cellulitis	2 (0.2)	3 (0.3)	5 (0.3)
Sepsis	1 (0.1)	4 (0.4)	5 (0.3)
Injury, poisoning and procedural complications	**8 (0.9)**	**10 (1.1)**	**18 (1.0)**
Road traffic accident	3 (0.3)	1 (0.1)	4 (0.2)
Nervous system disorders	**15 (1.6)**	**16 (1.8)**	**31 (1.7)**
Presyncope	3 (0.3)	2 (0.2)	5 (0.3)
Syncope	1 (0.1)	3 (0.3)	4 (0.2)
Transient Ischemic attack	3 (0.3)	3 (0.3)	6 (0.3)
Psychiatric disorders	**3 (0.3)**	**2 (0.2)**	**5 (0.3)**
Depression	3 (0.3)	1 (0.1)	4 (0.2)
Renal and urinary disorders	**4 (0.4)**	**6 (0.7)**	**10 (0.5)**
Renal failure acute	1 (0.1)	4 (0.4)	5 (0.3)
Respiratory system disorders (lower)	**90 (9.8)**	**72 (7.9)**	**162 (8.9)**
Acute respiratory failure	2 (0.2)	3 (0.3)	5 (0.3)
Bronchitis	5 (0.5)	10 (1.1)	15 (0.8)
COPD Exacerbation	61 (6.7)	38 (4.2)	99 (5.4)
Dyspnea	2 (0.2)	3 (0.3)	5 (0.3)
Pneumonia	40 (4.4)	26 (2.8)	66 (3.6)
Pulmonary edema	0 (0.0)	3 (0.3)	3 (0.3)
Respiratory failure	5 (0.5)	1 (0.1)	6 (0.7)
Vascular disorders	**6 (0.7)**	**11 (1.2)**	**17 (0.9)**
Hypotension	2 (0.2)	3 (0.3)	5 (0.3)

Source data: data on file, Table 10.21
MedDRA Version 11.1 used for reporting
All primary system organ classes are defined by MedDRA with the exception of 'Respiratory, thoracic and mediastinal disorders' which has been divided into separate classes of Respiratory system disorders, lower, upper and other. Several of the terms represent combined preferred terms.

There were a total of 67 deaths reported for this trial. This number of fatal events is not unexpected considering the age, severity of COPD and the prevalence of serious comorbid conditions in the study population. Five deaths reported during the screening period, prior to any administration of trial medication; 21 deaths were reported during the post-treatment period. The number deaths reported during the treatment period (onset of fatal adverse event between first and last drug intake + 30 days) in the tiotropium group (22 deaths) was similar to the placebo group (19 deaths). Of the 62 deaths during the trial (i.e. including information collected from prematurely discontinued patients), 31 occurred in each of the treatment groups. Most deaths were due to respiratory or cardiac events. As noted above, deaths from lower respiratory tract events occurred with lower frequency in patients in the tiotropium group compared to placebo. Fatal cardiac events, including unexplained deaths, were balanced between the two treatment groups (U03-3575-01, Table 14.3.1:4).

In summary the results of this study are consistent with the established safety profile of tiotropium in patients with COPD.

6. UPLIFT TRIAL (205.235/U08-3718-04)

6.1 OBJECTIVES

The co-primary endpoints of the UPLIFT trial (205.235) were the rate of decline in pre- and post-bronchodilator FEV_1. The secondary endpoints include other spirometry variables, exacerbations of COPD (and exacerbation-associated hospitalization), health-related quality of life (as measured by the St. George's Respiratory Questionnaire (SGRQ), R96-0686, R98-0966) and mortality.

The co-primary outcomes were specified as follows:

– Yearly rate of decline in trough FEV_1 from Day 30 (steady state) until completion of double blind treatment. Trough FEV_1 is the pre-dose value measured approximately 24 hours after the previous dose of study drug.

– Yearly rate of decline in FEV_1 90 minutes after study drug and ipratropium administration (including 30 minutes post-albuterol) from Day 30 (steady state) until completion of double-blind treatment.

There were two key secondary endpoints that were specified in the statistical analysis plan prior to database lock and unblinding:

a) Time to first exacerbation.
b) Time to exacerbation leading to hospitalization.

The remainder of the specified secondary efficacy endpoints included:

- Mean yearly rate of decline in morning pre-dose (trough) forced vital capacity (FVC) and slow vital capacity (SVC) from Day 30 until completion of double-blind treatment.
- Mean yearly rate of decline in FVC and SVC measured 90 minutes after inhalation of study drug and ipratropium (and 30 minutes after albuterol) from Day 30 until completion of double-blind treatment.
- Mean yearly rate of decline in morning pre-dose (trough) and post-bronchodilator FEV_1, FVC, and SVC from Day 1 until completion of the trial (30 days post-study drug treatment).
- Pre and post bronchodilator FEV_1, FVC, and SVC at each visit
- Yearly rate of decline in St. George's Respiratory Questionnaire (SGRQ) total score, from 6 months until completion of double-blind treatment.
- SGRQ total, impact, symptom, and activity scores at each visit

The additional endpoints for COPD exacerbations and hospitalizations due to COPD exacerbations included:

- Number of COPD exacerbations
- Number of patients with at least one COPD exacerbation
- Number of COPD exacerbation days

- Time to first COPD exacerbation treated with steroids*
- Number of COPD exacerbations treated with steroids*
- Time to first COPD exacerbation treated with antibiotics*
- Number of COPD exacerbations treated with antibiotics*
- Number of patients with at least one COPD exacerbation leading to hospitalization
- Number of hospitalizations for COPD exacerbations
- Number of days hospitalized due to COPD exacerbations

*Analyses not in the protocol but defined in the trial statistical analysis plan prior to unblinding.

6.2 STUDY DESIGN

The UPLIFT Trial (205.235) was a 4 year, multi-centre, randomized, double-blind, placebo-controlled trial of tiotropium HandiHaler® 18 mcg once daily involving 5,993 patients with COPD that was conducted in Europe, Asia, North America, South America, South Africa, Australia and New Zealand.

The study began in January 2003, with the last patient completed in February 2008. A total of 5,993 patients were randomized. The UPLIFT trial was conducted in accordance with Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH).

After obtaining written informed consent, study personnel advised active smokers to discontinue smoking and these patients were offered a smoking cessation program (e.g., counselling sessions, patient education and supportive literature). The first session was followed by a contact at two weeks (via phone or clinic visit) and a final session at or before randomization. Patients could decline participation in the smoking cessation program. Following this initial screening period, patients meeting inclusion and exclusion criteria were randomized to tiotropium or placebo. Patients were seen after one month on treatment, at three months and then every three months until study drug termination (four years). At study drug termination, all patients were to receive open-label ipratropium for 30 days. The final visit occurred 30 days post-treatment. Self-reported smoking status was recorded at each visit.

A COPD exacerbation was defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular or intravenous) steroids.

An independent Data and Safety Monitoring Board (DSMB) monitored all accruing safety data at least annually. The DSMB was composed of independent pulmonologists, a cardiologist, and a biostatistician. During the trial, amendments to the protocol established procedures for collection of vital status information (i.e. whether the patient was dead (with cause of death) or alive) for up to 4 years post-randomization on patients who prematurely discontinued the trial, and established a mortality adjudication committee, separate frin te DSMB and independent, evaluating the primary cause of death from blinded data (U08-3718-04, Section 16.1.1). The mortality adjudication committee was established in order to have a

standardized independent approach to assigning the primary cause of death. The last clinic visit of the 34 patients remaining in the trial after January 31, 2008 was accelerated as recommended by the DSMB upon observing a lower mortality rate in the tiotropium group. The reason for the recommendation was not communicated to the trial team until after unblinding.

Four years treatment in a randomized, double-blind clinical trial was considered as sufficient to evaluate the long-term efficacy and safety of tiotropium, including the rate of decline in FEV_1 as well as impacts on infrequent adverse events such as all-cause mortality.

Spirometry measurements (FEV_1, FVC, and SVC) were obtained using calibrated spirometers, commencing in the morning at approximately the same time of day at all visits throughout the study. With the exception of the first test set, which was only performed post-bronchodilator, spirometry was performed pre- and post-bronchodilator at all visit dates. After pre-bronchodilator spirometry was performed, four inhalations of ipratropium bromide (80 mcg via metered dose inhaler) were administered, followed by four inhalations of albuterol (400 mcg via metered dose inhaler) 60 minutes later. The post-bronchodilator spirometry was performed 90 minutes after ipratropium bromide inhalation (30 minutes after albuterol inhalation). After randomization, study drug was administered immediately prior to ipratropium bromide at clinic visits where spirometry was performed. SVC by slow exhalation maneuver was performed first, followed by the FVC maneuver. Both maneuvers were performed in triplicate, although up to five forced expiratory maneuvers were obtained in an effort to achieve three acceptable efforts. The highest acceptable FEV_1 and the highest FVC each obtained on any of three blows (even if not from the same curve) meeting the American Thoracic Society (ATS) criteria constituted the data for that test set (R96-1186). The highest SVC value was recorded for the test set.

To standardize spirometry, all sites were provided with identical spirometry systems (KoKo Spirometer, nSpire Health, Inc., Louisville, CO, USA) with customized, study-specific software. All study staff responsible for performing pulmonary function testing received identical, detailed training at the investigators meetings. All technicians were required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable pulmonary function tests (ATS criteria, R96-1186) prior to performing testing on study patients. After each test was performed, the spirometry software provided immediate feedback to the technician indicating whether the effort met ATS acceptability and reproducibility standards. All efforts were stored electronically. After completion of testing, the study staff electronically transmitted the spirometric measurements for centralized quality assurance review (Quantum Research, Inc., Louisville, CO, USA). Feedback on the quality of the measurements was then provided to the investigational site and to Boehringer Ingelheim for central data management.

The analysis plan for the primary and for the key secondary efficacy endpoints are summarized in Section 6.4.

6.3 STUDY POPULATION

Patients were recruited from 487 investigational centres in 37 regions including countries in Asia, Europe, North America, and South America, as well as South Africa, Australia and New Zealand. Criteria for participation in the present trial included a diagnosis of COPD (P95-4381), age $\geq$ 40 years, $\geq$ 10 pack-years of cigarette smoking, an FEV_1 $\leq$ 70% of the predicted normal according to ECCS criteria (R98-0814) and an FEV_1 $\leq$70% of FVC following bronchodilator inhalation. Screening criteria excluded patients with asthma, known moderate to severe renal impairment, significant uncontrolled symptomatic prostatic hyperplasia or bladder-neck obstruction, and narrow-angle glaucoma. Cardiac exclusion criteria were a history of a myocardial infarction within the prior six months, any unstable or life threatening cardiac arrhythmia requiring intervention or change in drug therapy in the past year, or a hospitalization for heart failure (New York Heart Association Class III or IV) within the past year. Other exclusion criteria were regular use of daytime supplemental oxygen for >12 hours per day, cancer requiring treatment in the preceding five years, thoracotomy with pulmonary resection and recent respiratory tract infection. Overall, the inclusion and exclusion criteria were similar to that used in other Phase IIIb/IV clinical studies with tiotropium, with some liberalization of the cardiac exclusion criteria.

Of note, concomitant respiratory therapies (i.e. short-acting beta-agonists, long-acting beta-agonists, inhaled steroids, theophyllines), other than inhaled anticholinergics were permitted upon entry and during the clinical trial. Respiratory medication could be adjusted during the trial as necessary by the patient's health care practitioner.

6.4 STATISTICAL METHODS

6.4.1 Statistical analysis of the primary endpoints

As noted previously, the two co-primary endpoints of UPLIFT were the rates of decline in pre- and post-bronchodilator FEV_1 from Day 30 to the last day of treatment. For these end points the yearly decline for each treatment group was computed from a normal random-effects model in which the mean FEV_1 changed linearly after day 30 for each patient, the intercepts and slopes among patients were assumed to be random with an arbitrary covariance matrix, and the treatment effect was fixed (R07-1385). For the two endpoints, treated patients with at least 3 acceptable morning pre-drug (i.e. trough) FEV_1 and FEV_1 90 minutes after study drug and ipratropium (including 30 minutes after albuterol), respectively, from Day 30 were included in the analysis.

6.4.2 Statistical analysis of the secondary endpoints

The two key secondary endpoints, time to first COPD exacerbation and time to first exacerbation leading to a hospitalization, were compared between treatment groups using log-rank tests. Cox regression was used to derive hazard ratios (HR). Kaplan-Meier curves of the probability of no exacerbation and related hospitalization were displayed. The proportions of patients with events were compared using Fisher's exact test. The number of events and event days were compared between treatment groups using Poisson regression

with correction for treatment exposure and overdispersion.For time to event endpoints, the effects of treatment within each level of a given subgroup were obtained by using Cox regression with treatment, separately for each level of a given subgroup. To assess the interaction effect, a separate Cox model with treatment, subgroup, and treatment*subgroup interaction was then fit.

For other spirometry related rate of decline analyses (i.e., trough and peak FVC and SVC) as well as for SGRQ scores, the yearly rate of decline was the regression slope from the random-effects model. The mean effects at various visits were compared in the two study groups with the use of repeated-measures analysis of covariance without imputation of missing values. Baseline was used as a covariate. All patients who had at least three post-randomization data points (at least two for the SGRQ) were included in the analyses.

Analyses were performed using SAS software version 8.2 (SAS Institute, Inc., Cary, NC, United States).

6.4.3 Multiplicity

In consideration of multiplicity in hypothesis testing, the following strategy was used in accordance with the DSMB Charter and protocol.

- For the primary analysis, a hierarchical testing was performed first for the pre-bronchodilator FEV_1, and if significance was achieved a second test was to be performed for the post-bronchodilator FEV_1. The significance level was set at 0.049.

- In parallel to the testing of the protocol defined co-primary endpoints, the number of hospitalizations per patient year was tested at 0.001 significance level at the request of the DSMB prior to review of unblinded data.

- If the significance of the co-primary endpoints was achieved, two key secondary endpoints, time to the first exacerbation and time to the first COPD exacerbation leading to hospitalization were to be tested using log-rank test in hierarchical order. Time to first exacerbation was to be tested first at 0.049 significance level. If the significance was achieved, time to the first COPD exacerbation leading to hospitalization would be tested at a level of 0.049.

All reported p values are two-sided and were not adjusted for multiple testing.

6.4.4 Safety analyses

All 5,992 patients in the UPLIFT trial who were randomized and received at least one dose of the study medication were included in the safety analyses.

Time to event analyses were conducted using the log-rank test, and hazard ratios (HR) were calculated using Cox regression. The effects of treatment within each level of a given subgroup were obtained by using Cox regression with treatment, separately for each level of

a given subgroup. To assess the interaction effect, a separate Cox model with treatment, subgroup, and treatment*subgroup interaction was then fit.

Fatal events are presented as:

(a) on-treatment + vital status information from prematurely discontinued patients (i.e. intention to treat) until 1440 days (4 years) following the initiation of study medication,
(b) on-treatment + vital status information from prematurely discontinued patients until 1470 days following the initiation of the study medication (4 years plus the 30-day washout)
(c) on-treatment only

In addition, the fatal event analysis was examined based on (a) the mortality adjudication committee evaluation and (b) as determined by the investigator.

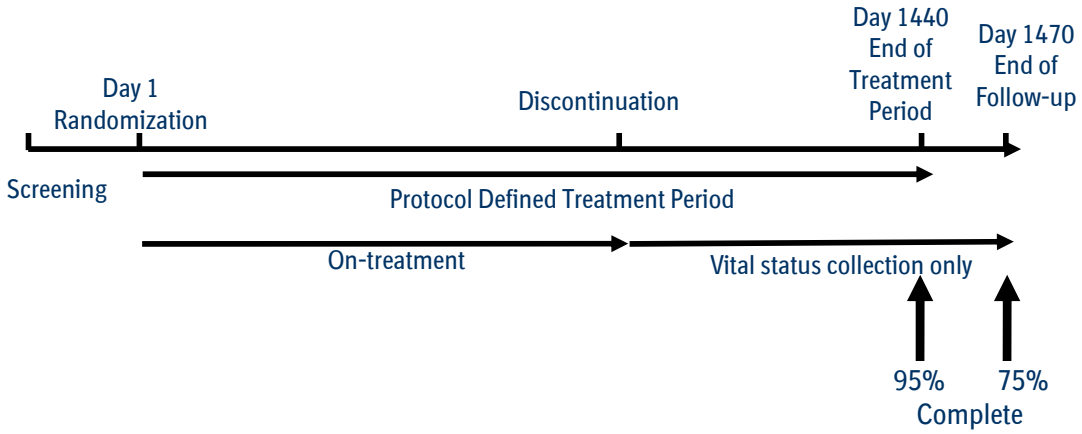


Figure 6.4.4: 1 Time points indicating fatal event analyses in the UPLIFT trial.

The following methods were applied to the analysis of safety in UPLIFT and to the pooled analyses of trials.

Incidence rates of adverse events were computed as the number of patients experiencing an event divided by the person-years at risk. For on-treatment analyses, time at risk was the time of exposure + 30 days for subjects who did not experience a specific event, and time from start of treatment to onset of a specific event for subjects who experienced this event. For all-death (including vital status) analyses, time at risk was the total time known to be alive for subjects who did not die and time from start of treatment to onset of a fatal event for subjects who died. Incidence rate differences were estimated based on the method described by Greenland and Robins (R09-1299) with trial as stratum. The 95% confidence interval was

calculated for each rate difference in order to describe the precision of the effect estimate. A rate difference (RD) < 0 indicates a decreased risk with tiotropium and a RD > 0 indicates a decreased risk with placebo. A p-value less than 0.05 is indicated when the width of the confidence interval excludes the value 0.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 11.1. The dictionary provided individual terms, referred to as preferred terms (PT), and combined terms into organ classes, referred to as system organ classes (SOC). As several preferred terms in the dictionary were considered clinically similar, they were combined (i.e. pooled) to capture clinical endpoints of interest more comprehensively under the SOC of interest, and to improve the precision of rate estimates. In subsequent tables preferred terms or combined (pooled) preferred terms have been listed under their specific SOC. An individual patient may be represented in several preferred terms or pooled preferred terms but will only be represented once when the data have been displayed according to the SOC (total).

Additionally, preferred terms with a primary or secondary relationship to *Respiratory, thoracic and mediastinal disorders* system organ class (SOC) were divided into three categories of respiratory system disorders: *Lower, Upper*, and *Other* that represent Spiriva® SOCs. Non-neoplastic disorders of the upper respiratory tract and the lung parenchyma have been categorized according to anatomic location (*Upper* or *Lower* respiratory tract). Respiratory tract disorders *Other* includes neoplastic and vascular disorders coding to *Respiratory, thoracic and mediastinal disorders* as a primary or secondary MedDRA SOC. Respiratory signs, symptoms, and disorders that could not be clearly attributed to either the upper or lower respiratory tract or those attributed to congenital disorders have been included in this category, as were procedures involving the respiratory system. Preferred terms with a secondary relationship to MedDRA SOC *Respiratory, thoracic and mediastinal disorders* were not included in their primary SOC.

A composite endpoint of major cardiovascular events was included in the analysis following unblinding. The composite endpoint represents fatal events in the SOC cardiac disorders and SOC vascular disorders combined with myocardial infarction (fatal and non-fatal), stroke (fatal and non-fatal) and the preferred terms sudden death, sudden cardiac death and cardiac death. The latter three preferred terms are not coded to the cardiac or vascular SOCs by the MedDRA dictionary as a primary path and appear under a different SOC. For the composite endpoint of fatal major cardiovascular events, non-fatal myocardial infarction and non-fatal stroke were removed.

There is no single preferred term for the clinical endpoint of "stroke". An endpoint consisting of pooled preferred terms was created prior to unblinding based on multiple preferred terms that can be found in several SOCs. The list of preferred terms included in the endpoint of stroke can be found in Appendix 17.1. Adverse event data pertaining to exacerbations will be discussed in Section 8, whereas mortality and cardiovascular safety data will be discussed in Section 9.

6.5 PATIENT DEMOGRAPHICS

A total of 5,993 COPD patients were randomized from 8,020 patients recruited. One patient discontinued prematurely and was subsequently re-enrolled in the study. The patient was counted twice and all patient-time data from both randomizations were included. One patient did not receive randomized treatment, which reduced the randomized and treated patient numbers to 5,992. In total, there were 9,222 person-years of exposure to tiotropium (2,986 patients) and 8,499 person-years of exposure to placebo (3,006 patients), which included the 30 day follow-up period (no study drug taken). The exposure excluding the 30 day follow-up period was 9,468 person-years of exposure to tiotropium and 8,746 person-years of exposure to placebo. Of patients randomized, 4,383 (73%) completed 2 years, 3,891 (65%) completed 3 years, and 3,569 (60%) completed ≥ 45 months (U08-3718-04, Table 12.1: 1). A higher proportion of patients failed to complete ≥ 45 months of treatment in the placebo group (44.6%) compared with the tiotropium group (36.2%, $p<0.001$) (U08-3718-04, Tables 15.3.1.1: 1 and 15.3.1.1: 3). The majority of discontinuations were due to adverse events (U08-3718-04, Table 10.1: 1).

As documented in the Table 6.5:1, the two treatment arms were well matched for all baseline characteristics, including age, gender, and baseline respiratory medications. The mean age was 65±8 years (range 40 – 88 years), 75% were men, and approximately 30% were current smokers (U08-3718-04, Table 15.1.4.1: 1). Mean pre-bronchodilator FEV_1 was approximately 1.10±0.40 L (39% predicted) and post-bronchodilator FEV_1 was approximately 1.32±0.44 L (48% predicted). Mean increase in FEV_1 following maximal bronchodilation was 23±18% (U08-3718-04, Table 15.1.4.1: 2). Patients classified as GOLD Stages II, III and IV comprised approximately 46, 44, and 9%, respectively. Three patients had the protocol violation of being in GOLD Stage I (tiotropium 2, placebo 1) but were allowed to continue in the study. Mean baseline pre-bronchodilator FEV_1 was lower in patients who discontinued study medication (37% predicted vs. 41% predicted in those who continued, $p<0.001$) (U08-3718-04, Table 15.3.1.1: 4). Over 90% of patients were receiving respiratory medications at baseline, including 60% who were receiving long-acting beta-agonists and 62% who were receiving inhaled corticosteroids. Inhaled anticholinergics, other than study medication, were discontinued at randomization.

Table 6.5: 1 Baseline characteristics of patients in the placebo and tiotropium groups - UPLIFT

Characteristic	**Placebo (n = 3,006)**	**Tiotropium (n = 2,986)**
Male (%)	73.9	75.4
Age (years)[1]	64.5 ± 8.5	64.5 ± 8.4
Body mass index[1]	25.9 ± 5.1	26.0 ± 5.1
Smoking status		
Current smoker (%)	29.9	29.3
Smoking history (pack-years)[1]	48.4 ± 27.9	49.0 ± 28.0
Duration of COPD (years)[1]	9.7 ± 7.4	9.9 ± 7.6
Baseline spirometry[1]		
Pre-BD FEV_1 (L)	1.09 ± 0.40	1.10 ± 0.40
Pre-BD FEV_1 (% predicted)	39.3 ± 11.9	39.5 ± 12.0
Pre-BD FVC (L)	2.63 ± 0.83	2.63 ± 0.81
Pre-BD FEV_1/FVC (%)	42.1 ± 10.5	42.4 ± 10.5
Post-BD FEV_1 (L)	1.32 ± 0.44	1.33 ± 0.44
Post-BD FEV_1 (% predicted)	47.4 ± 12.6	47.7 ± 12.7
Post-BD FVC (L)	3.09 ± 0.90	3.09 ± 0.86
Post-BD FEV_1/FVC (%)	43.3 ± 10.7	43.6 ± 10.8
GOLD Stage II/III/IV (%)[2]	45/44/9	46/44/8
SGRQ total score (units)[1,3]	46.0 ± 17.2	45.7 ± 17.0
Respiratory medications (% of patients)		
Any respiratory medication	93.1	93.4
Short-acting inhaled anticholinergics[4]	44.1	44.9
Long-acting inhaled anticholinergics	1.6	2.0
Short-acting inhaled β_2-agonists[4]	68.1	68.5
Long-acting inhaled β_2-agonists[4]	60.1	60.1
Inhaled corticosteroids[4]	61.9	61.6
Oral steroids	8.3	8.4
Theophylline compounds	28.5	28.4
Mucolytics	6.9	7.4
Leukotriene receptor antagonists	3.1	3.3
Supplemental oxygen	1.9	2.3

Source data: see U08-3718-04, Tables 11.2:1, 11.2:2, 11.2:3, 11.2:4, 15.1.4.1:1 (for GOLD stage)
[1]Mean ± SD; [2]Missing data in 2% of patients; [3]placebo n=2,909; tiotropium n=2,888
[4]Used alone or as a fixed combination

During the study period, 26% of patients changed smoking behavior (U08-3718-04, Table 15.2.1:8). On at least one clinic visit, 74% of patients reported having received inhaled corticosteroids, and 72% reported long-acting beta-agonists, and 48% reported a fixed combination of the two (U08-3718-04, Table 15.1.6.1: 1).

6.6 EFFICACY RESULTS

Although the focus of this document is to describe the data supporting an indication for reductions in exacerbations of COPD, lung function is described first, as the rates of decline in pre- and post-bronchodilator FEV_1 were the co-primary endpoints.

6.6.1 Spirometry

There were no significant differences between treatment groups in the mean annual rate of decline (i.e., slopes) for either pre-bronchodilator or post-bronchodilator FEV_1 and FVC from day 30 to the end of treatment at Visit 19 (Table 6.6.1: 1). Therefore, all subsequent p-value should be considered as descriptive and nominal. However, given the size and duration of the UPLIFT trial, as well as the association of the spirometry data to both both the present indication and the proposed revision to the label, the data may be considered as important and relevant supportive information. Details of the spirometric outcomes are found in Sections 15.2.1, 15.2.2 and 15.2.3 of the clinical trial report for 205.235 (U08-3718-04).

Table 6.6.1: 1 Mean±SE rate of decline in FEV_1 and FVC from day 30 until end of treatment in the tiotropium and placebo groups - UPLIFT

	Placebo (n= 3,006)		**Tiotropium (n = 2,986)**			
	N	Mean±SE	N	Mean±SE	Δ Tio – Pla	p-value
Pre-bronchodilator FEV_1	2413	-30±1	2557	-30±1	0±2	0.95
Post-bronchodilator FEV_1	2410	-42±1	2554	-40±1	2±2	0.21
Pre-bronchodilator FVC	2413	-39±3	2557	-43±3	-4±4	0.30
Post-bronchodilator FVC	2410	-61±3	2554	-61±3	-1±4	0.84

p−values are from the random−effects model. Patients with at least 3 measurements after (including) day 30 are included in the analysis
Source data: see U08-3718-04, Tables 11.4.1.1: 1 and 11.4.1.2.2: 2

In a post-hoc analysis, between-treatment differences in the mean annual rate of decline in post-bronchodilator FEV_1 were observed in favour of tiotropium (7±4 mL/year, p=0.046) in the subgroup of patients who were not receiving inhaled steroids or long-acting beta-agonists at baseline (n=1,551) (U08-3718-04, Table 15.2.7:4). The mean annual rate of decline in post-bronchodilator FEV_1 in those who prematurely discontinued (55±4 mL/year in the tiotropium group and 57±4 mL/year in the placebo group) was higher than those who completed the treatment period (38±1 mL/year in the tiotropium group and 40±1 mL/year in the placebo group).

Mean pre-bronchodilator and post-bronchodilator FEV_1 values showed improvements with tiotropium that were maintained at all time points following randomization vs. placebo ($p<0.001$) (Figures 6.6.1: 1 to 6.6.1: 2). Improvements in pre-bronchodilator FVC ($p<0.001$ for all time-points) and post-bronchodilator FVC ($p<0.001$ until month 36, p=0.002 at month 42 and p=0.0038 at month 48) were also observed compared to placebo). Mean values at each time point are displayed in Appendix 17.2. Results of all subgroup analyses for the co-primary endpoints are provided in the Clinical Trial Report (U08-3718-04, Section 15.2.1: 4).

Figures 6.6.1: 1 to 6.6.1: 4 display estimated means at each time point for pre-bronchodilator FEV_1 (Figure 6.6.1: 1), post-bronchodilator FEV_1 (Figure 6.6.1: 2), pre-bronchodilator FVC (Figure 6.6.1: 3), and post-bronchodilator FVC (Figure 6.6.1: 4) from Day 30 to end of treatment. Repeated measure ANOVA was used to estimate means. Means were adjusted for baseline measurements. Patients with ≥3 acceptable PFTs after day 30 and non-missing baseline value were included in the analysis. All p-values were <0.001 except post-bronchodilator FVC at 30, 42 and 48 months ($p<0.05$) (U08-3718-04, Table 15.2.1: 12 and

15.2.2: 5). However, it must be considered that for the post-bronchodilator values both treatment groups received 4 actuations of ipratropium and 4 actuations of albuterol in addition to study drug.

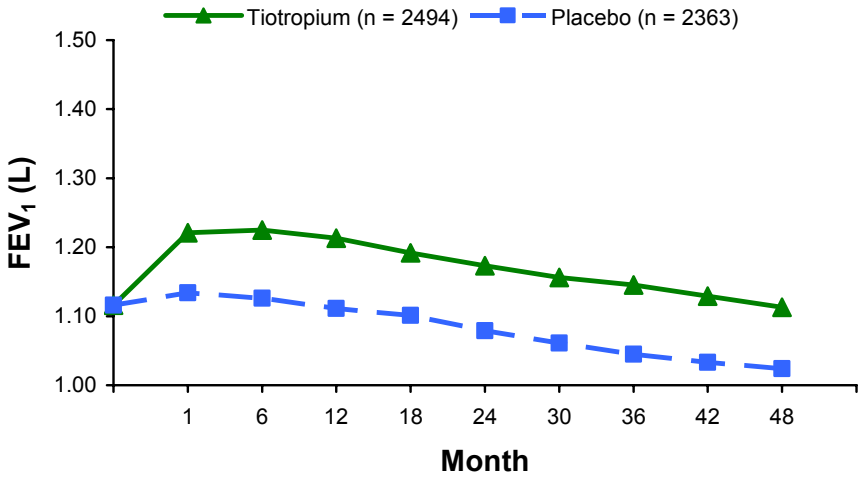


Figure 6.6.1: 1 Pre-bronchodilator FEV_1 in the tiotropium and placebo groups over time - UPLIFT

Source data: see U08-3718-04, Figure 15.2.1: 1

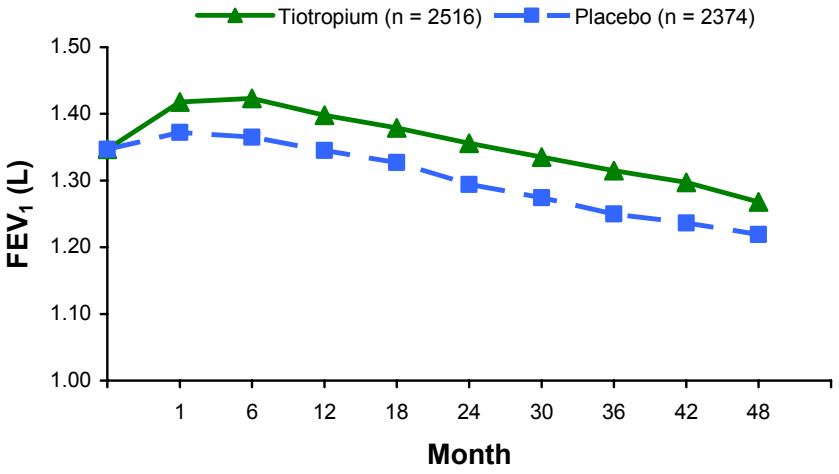


Figure 6.6.1: 2 Post-bronchodilator FEV_1 in the tiotropium and placebo groups over time - UPLIFT

Source data: see U08-3718-04, Figure 15.2.1:2

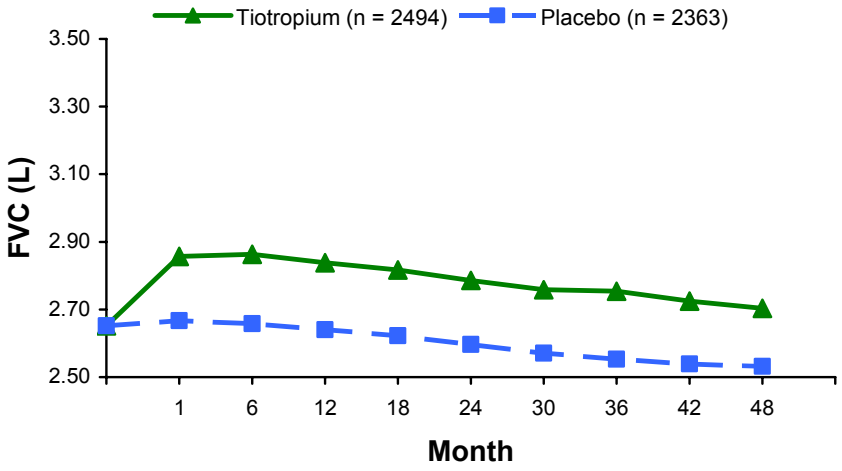


Figure 6.6.1: 3 Pre-bronchodilator FVC in the tiotropium and placebo groups over time - UPLIFT

Source data: see U08-3718-04, Figure 15.2.2:1

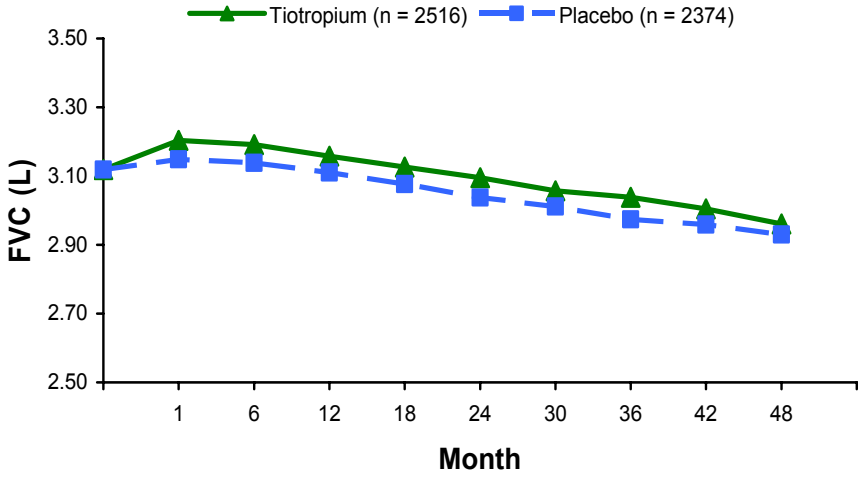


Figure 6.6.1: 4 Post-bronchodilator FVC in the tiotropium and placebo groups over time - UPLIFT

Source data: see U08-3718-04, Figure 15.2.2:2

6.6.2 Exacerbations

Tiotropium delayed the time to the first exacerbation (Figure 6.6.2: 1) and the time to first hospitalization for an exacerbation (Figure 6.6.2: 2). The hazard ratios (HRs) (95% confidence intervals [CI]) for an exacerbation or exacerbation leading to hospitalization were 0.86 (0.81, 0.91) and 0.86 (0.78, 0.95), respectively.

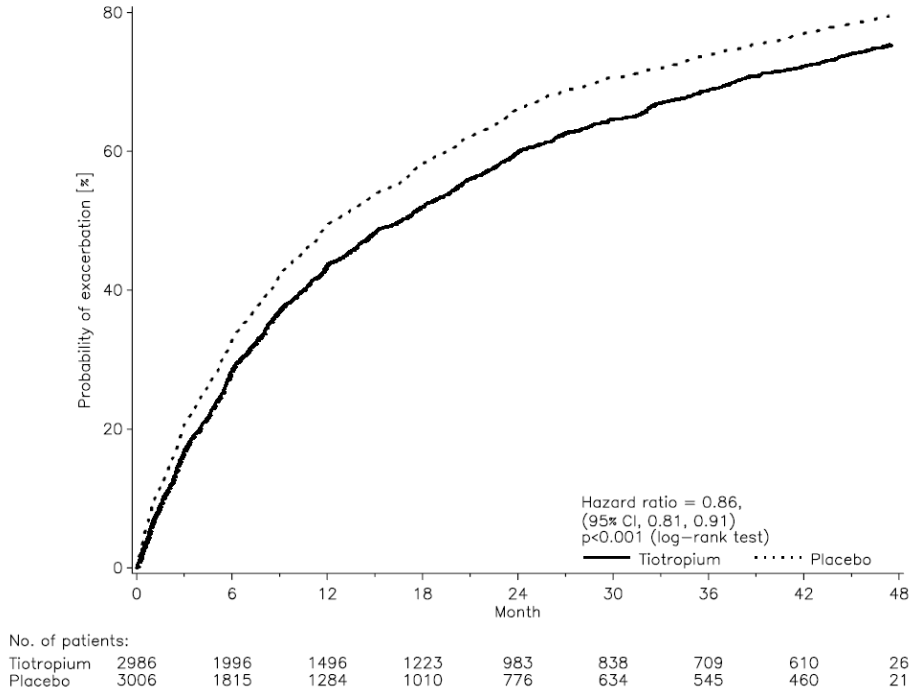


Figure 6.6.2: 1 Cumulative incidence rate (Kaplan-Meier) of the probability of a COPD exacerbation - UPLIFT

No. of patients =number of patients at risk.
Source data: data on file, Figure 4a.

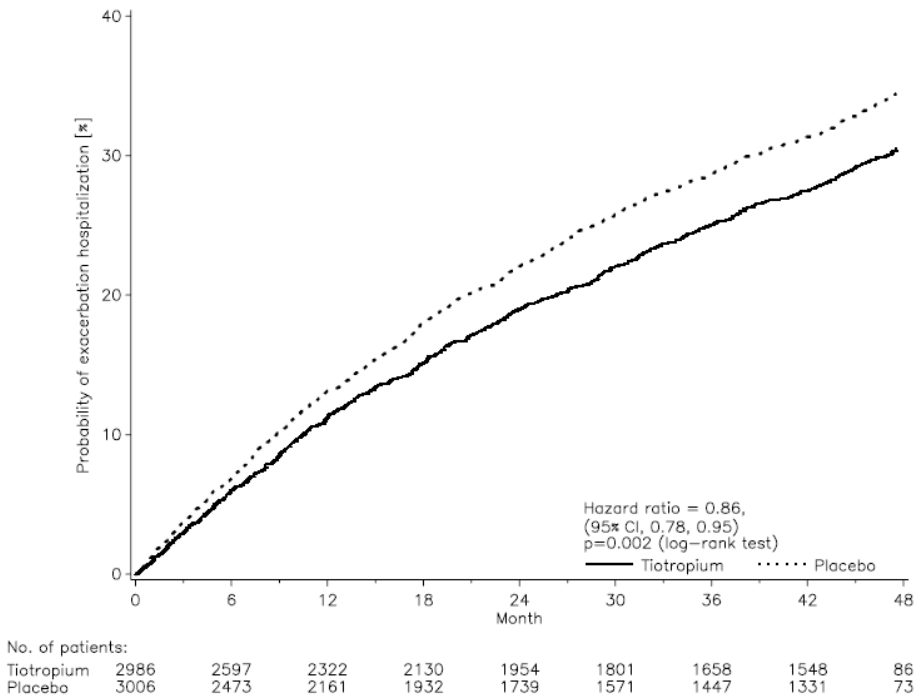


Figure 6.6.2: 2 Cumulative incidence rate (Kaplan-Meier) of the probability of a COPD exacerbation leading to hospitalization - UPLIFT

No. of patients =number of patients at risk.
Source data: data on file, Figure 4b.

The mean number of exacerbations as well as exacerbation days was significantly less for the tiotropium group. The mean number of exacerbations leading to hospitalizations was low and not significantly different between treatment arms (Table 6.6.2: 1). During the four year study, 68% of the placebo patients and 67% of the tiotropium patients had at least one COPD exacerbation

Table 6.6.2: 1 COPD exacerbations and exacerbations leading to hospitalizations in the tiotropium and placebo groups - UPLIFT

	Placebo	Tiotropium	Rate Ratio (95% CI) (tiotropium/placebo)	p-value
Number (%) of patients with exacerbations[1]	2049 (68.2)	2001 (67.0)	–	0.35
Number (%) of patients with exacerbations leading to hospitalizations[1]	811 (27.0)	759 (25.4)	–	0.18
Mean (SE) number of exacerbations per patient-year[2]	0.85 (0.02)	0.73 (0.02)	0.86 (0.81, 0.91)	<0.001
Mean (SE) number of exacerbations leading to hospitalizations per patient-year[2]	0.16 (0.01)	0.15 (0.01)	0.94 (0.82, 1.07)	0.34
Mean (SE) number of exacerbation days per patient-year[2]	13.64 (0.35)	12.11 (0.32)	0.89 (0.83, 0.95)	0.001
Mean (SE) number of exacerbation hospitalization days per patient-year[2]	3.13 (0.17)	3.17 (0.17)	1.01 (0.87, 1.18)	0.86

[1] Fisher's exact test

[2] Rate ratio from Poisson regression corrected for treatment exposure and overdispersion

Abbreviations: CI = confidence interval; SE = standard error

Source data: see U08-3718-04, Tables 15.2.5.2: 4, 15.2.6.2: 3, 15.2.5.2: 2, 15.2.6.2: 1, 15.2.5.2: 8, 15.2.6.2: 5

Exacerbations treated with steroids or antibiotics were similarly reduced with tiotropium relative to placebo (Table 6.6.2: 2).

Table 6.6.2: 2 Exacerbations according to treatment with steroids or antibiotics - UPLIFT

	Placebo (n = 3,006)	Tiotropium (n = 2,986)	Tiotropium/placebo*
			Hazard Ratio (95%CI)
Time to 1st exacerbation treated with steroids[1]	-	-	0.84. (0.78, 0.90)
Time to 1st exacerbation treated with antibiotics[1]	-	-	0.87 (0.81, 0.93)
			Rate Ratio (95%CI)
Mean (SE) number of exacerbation treated with steroids per patient-year[2]	0.52 (0.02)	0.44 (0.01)	0.84 (0.78, 0.91)
Mean (SE) number of exacerbation treated with antibiotics per patient-year[2]	0.71 (0.02)	0.62 (0.01)	0.87 (0.82, 0.93)

*All p-values <0.001 ; [1] Cox regression; [2] Rate ratio from Poisson regression corrected for treatment exposure and overdispersion; Abbreviations: CI = confidence interval; SE = standard error.

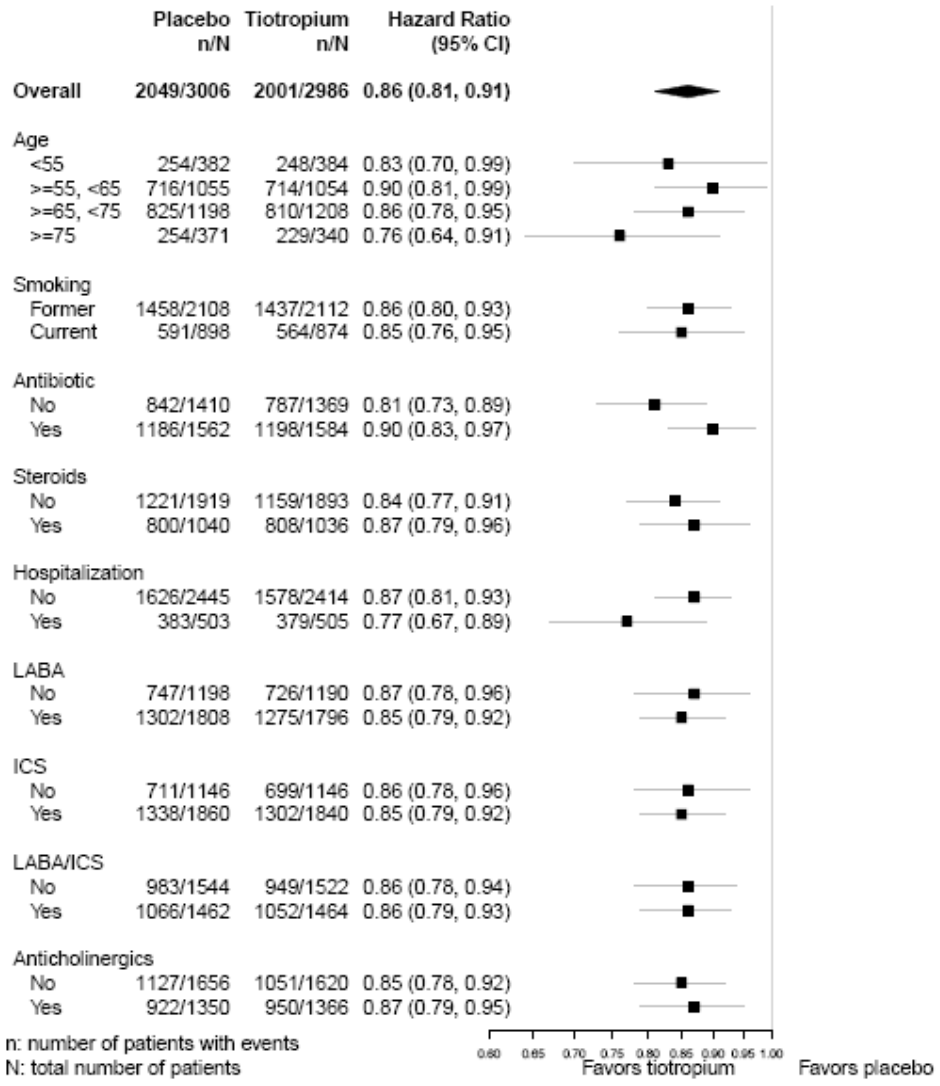
Source data: U08-3718-04, Tables 15.2.5.1: 3, 15.2.5.1: 4, 15.2.5.2: 6, 15.2.5.2: 7

6.6.2.1 Subgroup analyses

Subgroup analyses were performed according to each of the following variables: age, current cigarette smoking, prescription for antibiotics and steroids for COPD in the preceding year, hospitalization for COPD in the preceding year, baseline use of maintenance respiratory medications (inhaled corticosteroids, long-acting inhaled beta-agonists, combination inhaled corticosteroids + long-acting inhaled beta-agonists, and inhaled anticholinergics), post-bronchodilator FEV_1 severity (GOLD stage), region and gender. As always, subgroup analyses need to be interpreted with caution given the reduced power in individual subgroups and reduced precision of the estimates as well as due to multiplicity.

As shown in the figures displayed below, tiotropium produced a fairly uniform reduction in exacerbations for all subsets included in the analyses. There were no significant interactions between the subgroup and treatment assignment for all the subgroups (U08-3718-04); however, these tests for interactions were underpowered.

(a)



Source data: data on file, Table 5a

(b)

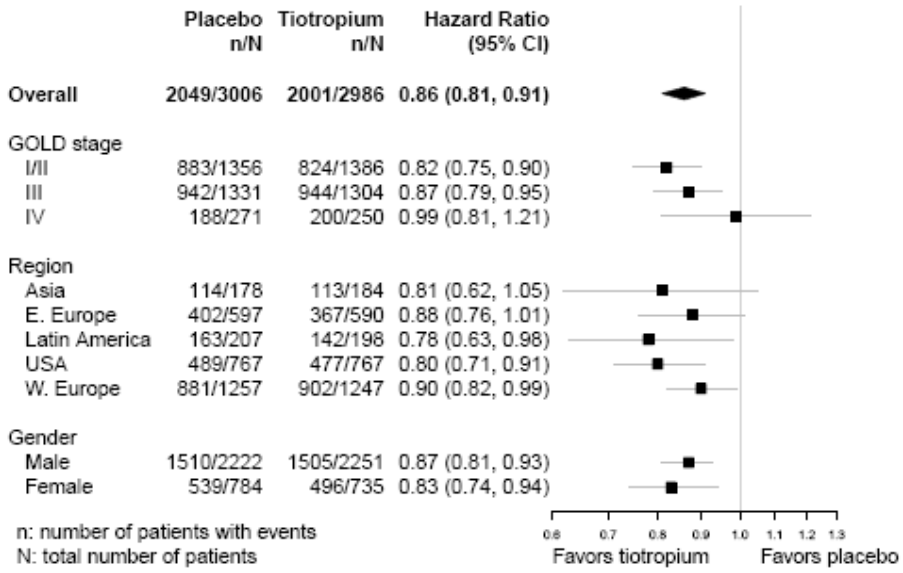
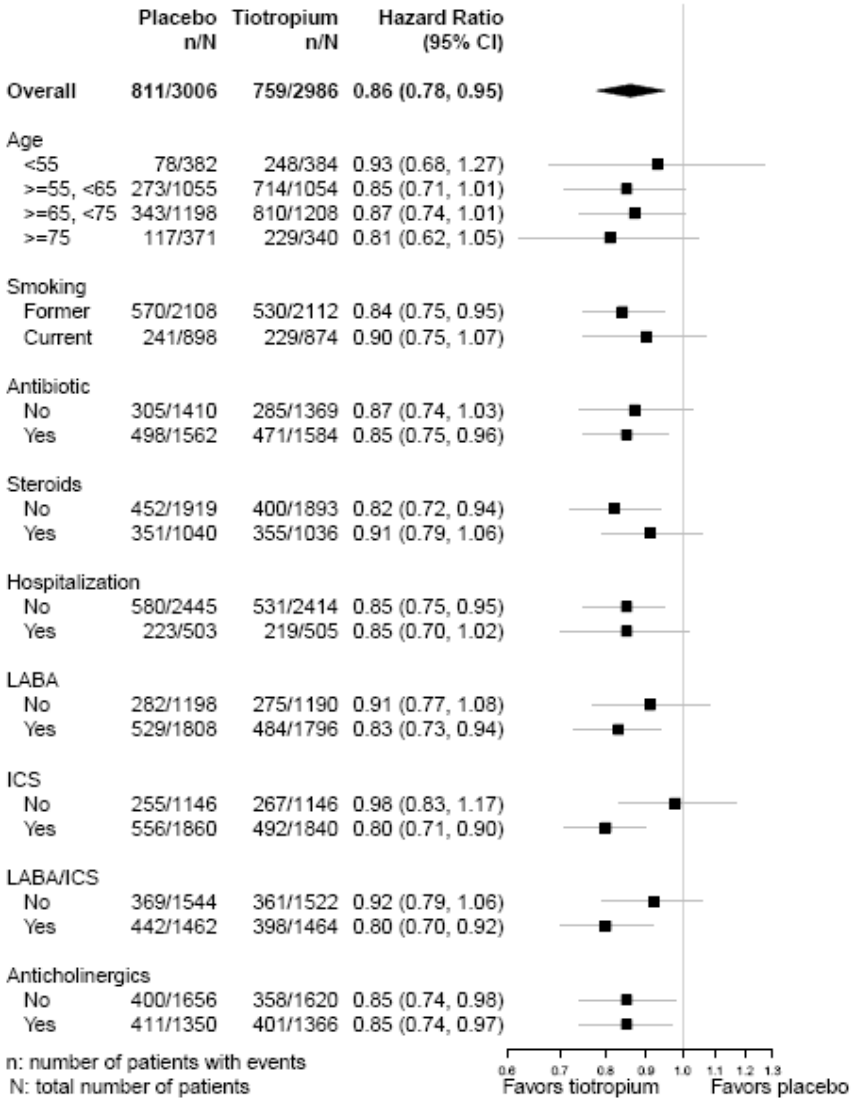


Figure 6.6.2.1: 1 Hazard ratios and 95% confidence intervals (tiotropium/placebo) for reduction in risk for a COPD exacerbation according to (a) selected baseline characteristics and concomitant respiratory medications and (b) GOLD Stage* and region - UPLIFT

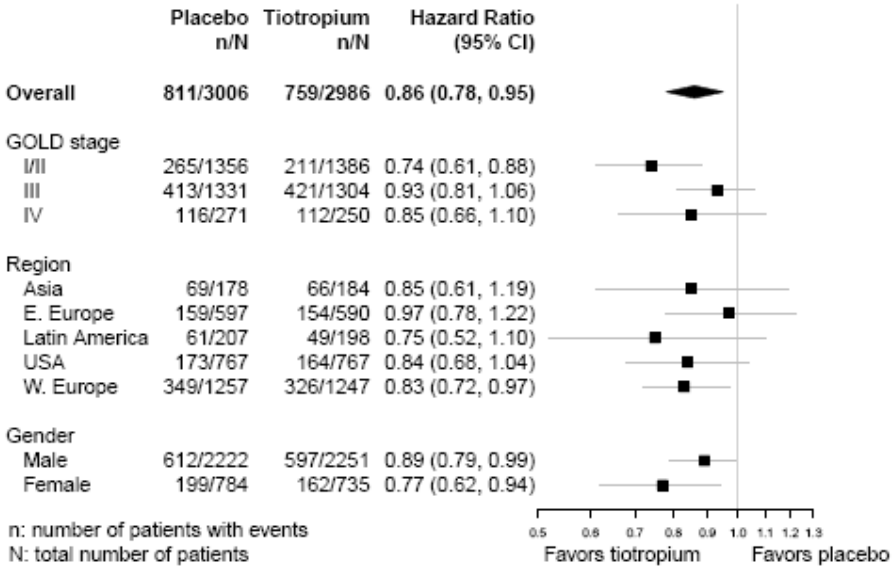
*Including 3 patients with GOLD stage I disease.
Source data: data on file, Table 5b

(a)



Source data: data on file, Table 6a

(b)



*Including 3 patients with GOLD stage I disease.
Source data: data on file, Table 6b

Figure 6.6.2.1: 2 Hazard ratios and 95% confidence intervals (tiotropium/placebo) for reduction in risk for a COPD exacerbation leading to a hospitalization according to (a) selected baseline characteristics and concomitant respiratory medications and (b) GOLD Stage* and region - UPLIFT

The results for the United States patients were similar to the overall results of the study. The hazard ratios (HRs) (95%CI) for an exacerbation or an exacerbation-related hospitalization were 0.80 (0.71, 0.91) and 0.84 (0.68, 1.04), respectively. The ratio (tiotropium/placebo) for the number of exacerbations per patient year was 0.86 (0.81, 0.91).

Source data: data on file, Figure 4a

6.6.3 Health-related quality of life

The St. George's Respiratory Questionnaire (SGRQ) total score represents disease specific health-related quality of life (HRQoL) and incorporates three domains (Activity, Impacts, and Symptoms). The total score ranges from 0 to 100, where 0 indicates perfect HRQoL and 100 indicates the worst possible HRQoL (i.e. a lower score indicates better HRQoL). A 4-unit change is reported to be a minimal clinically important difference. Symptomatic status in COPD can be measured with the SGRQ.

In UPLIFT, SGRQ scores were obtained at baseline and every 6 months thereafter. Repeated measure ANCOVA was used to estimate means, which were adjusted for baseline measurements. Patients with ≥2 acceptable SGRQ total scores after month 6 and non-missing baseline values were included in the analysis. Estimated means at each time point for SGRQ total score from month 6 to end of treatment are displayed in Figure 6.6.3: 1

After improvement at the first on-treatment measurement, SGRQ scores worsened at a similar rate in the two treatment groups. The early improvement in the tiotropium group was significantly greater, and this advantage was maintained for the duration of the trial ($p < 0.001$ at all time points). A higher proportion of patients in the tiotropium compared to placebo groups achieved ≥4 unit improvements in the SGRQ total scores from baseline at years 1 (49.1% vs. 41.2%), 2 (47.5% vs. 39.0%), 3 (46.2% vs. 36.5%), and 4 (44.9% vs. 36.3%) ($p<0.001$ for all). Details of the SGRQ outcomes are found in Section 15.2.4 of the clinical trial report for 205.235 (U08-3718-04).

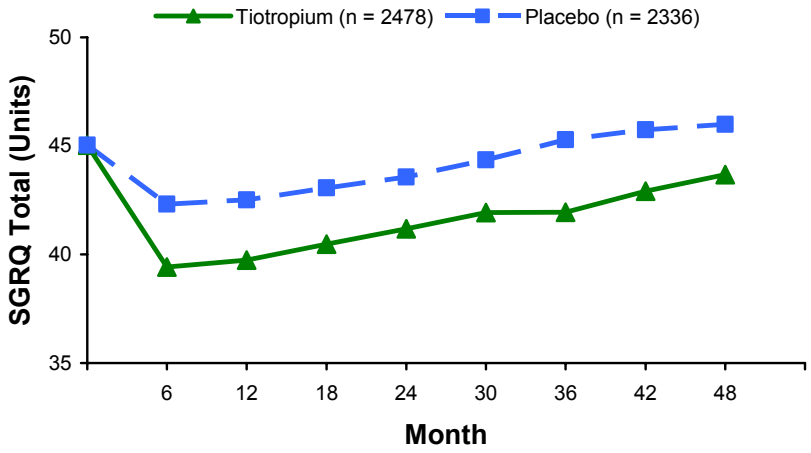


Figure 6.6.3: 1 Mean SGRQ total score from month 6 to end of treatment in the tiotropium and placebo groups ($p<0.001$ at all time points) - UPLIFT

Source data: see U08-3718, Figure 15.2.4:4

Significant improvements with tiotropium HandiHaler® relative to placebo were present in all domains, including the symptom domain (Table 6.6.3: 1). The data from the SGRQ indicated that patients receiving tiotropium experienced symptomatic improvement for up to 4 years of treatment.

Table 6.6.3: 1 Estimated overall mean (SE) SGRQ scores - UPLIFT.

	Placebo (n = 3,006[2])	Tiotropium (n = 2,986[3])	Difference (95%CI)	p-value
Activity	61.1 (0.3)	58.1 (0.3)	-3.0 (-3.8,-2.2)	<0.0001
Impact	33.8 (0.3)	31.4 (0.3)	-2.4 (-3.1,-1.7)	<0.0001
Symptom	45.8 (0.3)	42.8 (0.3)	-3.0 (-3.9,-2.2)	<0.0001
Total	44.1 (0.2)	41.4 (0.2)	-2.7 (-3.3,-2.0)	<0.0001

The mean, standard error and 95% confidence interval are estimated using repeated measure ANCOVA model adjusted for baseline. Patients with at least 2 SGRQ measurements after month 6 were included in the analysis.
Source data: see U08-3718-04, Table 15.2.4:3

7. SUPPORTIVE EXACERBATION DATA: EFFICACY OUTCOMES FROM ADDITIONAL TRIALS

While the claim for a reduction in exacerbations of COPD is based on data from the VA and UPLIFT trials, data from other phase III and IV tiotropium HandiHaler trials is documented in this section to demonstrate an overall consistency of efficacy that is supportive of the findings in the VA and UPLIFT trials. The phase III registration trials are primarily discussed as they were the trials where data was first generated regarding exacerbation benefits.

7.1 REGISTRATION TRIALS

Three pairs of replicate studies were submitted to the FDA as part of the original New Drug Application for tiotropium HandiHaler®. All were randomized and double-blind (with double-dummy as appropriate). Two one-year studies compared tiotropium to placebo (205.114/117 U99-3169, 205.115/128 U99-3170-01) and two one-year studies compared tiotropium to ipratropium (205.126A/U00-3113, 205.126B/U00-3114). The two six-month studies compared tiotropium to placebo and to salmeterol (205.130/U01-1236-01, 205.137/U01-1231-01). In all of these studies, exacerbations were noted as secondary outcomes. The individual studies do not have sufficient power to detect differences in exacerbations. Pooling of the one-year studies was not pre-specified for exacerbations, but pooling was pre-specified in the six-month studies. These studies provide supportive information that tiotropium reduces the frequency of exacerbations and associated hospitalizations (U00-3253). The pooled results of the pairs of studies are presented in detail below. The analysis method when these studies were unblinded differed somewhat from the approaches currently applied but is consistent with the methods used for the VA and UPLIFT trials.

7.1.1 Description of analyses of exacerbation endpoints

A COPD exacerbation was defined in the protocols as a complex of new or worsened COPD-related symptoms (i.e., cough, wheeze, dyspnea, or sputum production) lasting longer than three days. Exacerbation information was taken from the adverse event data. Such events were generally acute worsening of the underlying disease, usually associated with infection and requiring antibiotic and/or oral steroid therapy. In the case of an exacerbation that appeared to last three days or less based on review of adverse event reporting, the investigator was queried to determine if it was truly an exacerbation. If not, the appropriate preferred term code was assigned based on the World Health Organization (WHO) dictionary (used at the time of the trials). Concurrent events which, taken together, met the definition of a COPD exacerbation were combined into one event and coded as an exacerbation.

In each of the one-year individual clinical trial reports, some patients having only pneumonia were not included as having a COPD exacerbation in the original analysis in spite of meeting the criterion for a COPD exacerbation. Since it was difficult to distinguish pneumonia from a COPD exacerbation and these patients met the criteria for exacerbation, they were included

as having a COPD exacerbation in the analysis presented in this document. For the six-month trials a protocol amendment was made to include pneumonia events as COPD exacerbations prospectively prior to unblinding. Only those adverse events that occurred after patients were randomized and before they stopped their treatment were included in all analyses. The day on which patients took their last dose was included.

Time to first COPD exacerbation and time to first COPD-associated hospitalization, were compared between treatment groups using log-rank tests. Cox regression was used to derive hazard ratios (HR). The proportion of patients with events was compared using Fisher's exact test. The number of events and event days were compared between treatment groups using Poisson regression with correction for treatment exposure and overdispersion.

Table 7.1.1: 1 Number of exacerbation and exacerbation days in the tiotropium HandiHaler® registration trials

	Placebo	Tiotropium	Rate ratio (95%CI) (tiotropium/placebo	p-value
1 year placebo-controlled trials	N=371	N=550		
Number (%) of patients with exacerbations[1]	155 (41.8%)	197 (35.8)	-	0.068
Mean (SE) number of exacerbations per patient-year[2]	0.93 (0.07)	0.74 (0.05)	0.79 (0.65, 0.96)	0.019
Mean (SE) number of exacerbation days per patient-year[2]	15.0 (1.31)	14.8 (1.0)	0.98 (0.79, 1.22)	0.875
1 year ipratropium-controlled trials	N=179	N=356		
Number (%) of patients with exacerbations[1]	83 (46.4)	126 (35.4)	-	0.014
Mean (SE) number of exacerbations per patient-year[2]	0.94 (0.10)	0.70 (0.06)	0.75 (0.58, 0.97)	0.031
Mean (SE) number of exacerbation days per patient-year[2]	17.8 (1.9)	10.9 (1.0)	0.61 (0.46, 0.81)	0.001
6-month placebo-controlled trials	N=400	N=402		
Number (%) of patients with exacerbations[1]	156 (39.0)	130 (32.3)	-	0.049
Mean (SE) number of exacerbations per patient-year[2]	1.42 (0.11)	1.06 (0.09)	0.74 (0.60, 0.93)	0.008
Mean (SE) number of exacerbation days per patient-year[2]	25.3 (2.0)	17.3 (1.6)	0.69 (0.54, 0.87)	0.002

[1]Fisher's exact test; [2]rate ratio from Poisson regression corrected for treatment exposure and overdispersion
Abbreviations: CI = confidence interval, SE = standard error
Source data: data on file, Tables 15.3.7.1.1: 1, 15.3.7.2.1: 1, 15.3.7.2.1: 2, 15.3.7.3.1: 1, 15.3.7.1.1: 2, 15.3.7.3.1: 2, 15.3.7.4:1-3

In each pair of these trials, tiotropium increased the time to first exacerbation (log-rank test), whether the comparator was placebo in the six-month trials (HR (95%CI) = 0.72 (0.57, 0.90), p = 0.005), placebo in the one-year trials (HR (95%CI) = 0.76 (0.62, 0.94), p = 0.011), or ipratropium in the one-year trials (HR (95%CI) = 0.69 (0.52, 0.91), p = 0.009).

Table 7.1.1: 2 Number of hospitalization due to exacerbations and hospitalization days in the tiotropium HandiHaler® registration trials.

	Placebo	Tiotropium	Rate ratio (95%CI) (tiotropium/placebo	p-value
1 yr placebo controlled trials	N=371	N=550		
Number (%) of patients with exacerbations[1]	35 (9.4)	30 (5.5)	-	0.022
Mean (SE) number of exacerbations per patient-year[2]	0.16 (0.02)	0.09 (0.01)	0.53 (0.39, 0.72)	<0.001
Mean (SE) number of exacerbation days per patient-year[2]	1.2 (0.1)	0.6 (0.1)	0.51 (0.37, 0.70)	<0.001
1 yr ipratropium controlled trials	N=179	N=356	-	
Number (%) of patients with exacerbations[1]	21 (11.7)	26 (7.3)		0.089
Mean (SE) number of exacerbations per patient-year[2]	0.16 (0.03)	0.10 (0.01)	0.62 (0.42, 0.91)	0.016
Mean (SE) number of exacerbation days per patient-year[2]	2.1 (0.3)	1.4 (0.2)	0.67 (0.45, 1.0)	0.053
6-month placebo controlled trials	N=400	N=402		
Number (%) of patients with exacerbations[1]	21 (5.3)	14 (3.5)	-	0.223
Mean (SE) number of exacerbations per patient-year[2]	0.15 (0.02)	0.10 (0.01)	0.67 (0.47, 0.97)	0.031
Mean (SE) number of exacerbation days per patient-year[2]	1.9 (0.2)	1.0 (0.2)	0.52 (0.35, 0.78)	0.001

[1]Fisher's exact test; [2]rate ratio from Poisson regression corrected for treatment exposure and overdispersion
Abbreviations: CI = confidence interval, SE = standard error
Source data: data on file; Tables 15.3.7.1.2: 1, 15.3.7.2.2: 1, 15.3.7.3.2: 1, 15.3.7.1.2: 2, 15.3.7.3.2: 2, 15.3.7.4:1-3

In each pair of these trials, tiotropium was associated with an increase in the time to first exacerbation-related hospitalization (log-rank test). The difference was statistically significant in the placebo-controlled one-year trials (HR (95%CI) = 0.52 (0.32, 0.85), p = 0.009) and in the ipratropium-controlled one-year trials (HR (95%CI) = 0.58 (0.33, 1.04), p = 0.067), but not in the placebo-controlled six-month trials (HR (95%CI) = 0.60 (0.31, 1.19), p=0.143).

7.2 OTHER TRIALS

Collection of exacerbation information either through specific case report forms or as part of adverse event reporting has been incorporated in all tiotropium trials. National trials of at least six-month duration in which such data were collected were trials 205.214 (1-year), 205.270 (1-year), 205.259 (1-year), 205.256 (9-months) and 205.230 (6-months). Outcomes consistent with a positive exacerbation effect with tiotropium were observed in trials 205.214, 205.270, 205.256. A summary of each of the trials with the exacerbation outcomes are detailed in Appendix 17.3.

8. SUPPORTIVE EXACERBATION DATA: SAFETY OUTCOMES

The following section describes lower respiratory tract events including COPD exacerbations, pneumonia and respiratory failure obtained through adverse event reporting in the UPLIFT trial and in an integrated database of placebo-controlled, randomized, double-blind clinical trials of at least 4-weeks duration with tiotropium HandiHaler® 18 mcg daily. The purpose of the analysis is to demonstrate a consistency in findings that provide additional evidence supporting the beneficial effect of tiotropium on exacerbations of COPD. UPLIFT is analyzed separately and as part of the integrated database due to the size and duration of the study.

8.1 METHODOLOGY

The methodology described in this section applies to subsequent sections regarding other relevant safety endpoints (i.e. mortality, cardiovascular events).

8.1.1 Study population

The safety data will be displayed from the UPLIFT trial alone and a pooled database consisting of 26 completed clinical trials with tiotropium HandiHaler® 18 mcg daily as of March 2009 (including UPLIFT). For inclusion into the pooled database, all trials were required to have used a randomized placebo-controlled, double-blind and parallel-group study design. Trials were restricted to COPD as an indication and were required to be at least 4 weeks in duration.

Table 8.1.1: 1 Source studies included in the pooled tiotropium analysis

BI Trial Number	Country	Duration (Weeks)	Placebo (# treated patients)	Tiotropium (# treated patients)
205.114/117	US	48	191	279
205.115/128	US	48	180	271
205.123	Multinational	6	40	81
205.124	UK	4	30	65
205.130	Multinational	24	201	209
205.137	Multinational	24	199	193
205.131	Multinational	6	100	98
205.214	France	48	510	500
205.215	France	12	54	46
205.218	US	4	41	40
205.223	Multinational	6	130	131
205.230	US	25	53	55
205.235	Multinational	210	3006	2986
205.247	Italy	25	117	117
205.256	France	36	288	266
205.257	Germany	12	403	1236
205.259	Canada	48	305	608
205.266	US	24	915	914
206.269	Spain	16	127	123
205.270	UK	52	73	69
205.276	UK	12	195	200
205.281	Sweden	12	117	107
205.282	Portugal	12	164	147
205.284	US	12	96	100
205.294	US	8	86	80
205.301	Germany	12	244	228

Publications or clinical trial reports according to trial: 205.114/117 (P02-01290), 205.115/128 (P02-01290), 205.123 (P03-08088), 205.124 (P04-05941), 205.130 (P03-04061) , 205.131 (P04-05869), 205.137 (P03-04061), 205.214 (P06-02670), 205.215 (P06-08536), 205.218 (P03-10426), 205.223 (P05-09483), 205.230 (P05-02413), 205.235 (P08-12524), 205.247 (P08-15644), 205.256 (P08-04366), 205.257 (P06-06969), 205.259 (P07-14136), 205.266(P05-09172), 205.269 (U07-1983), 205.270 (P07-10504), 205.276 (P07-08572), 205.281 (P08-08332), 205.282 (P08-03061), 205.284 (P05-13005), 205.294 (P08-08937), 205.301 (P08-08937).

The protocol inclusion and exclusion criteria for all trials were similar. Men and women who were at least 40 years of age, had a diagnosis of COPD, $\geq$ 10 pack-years of smoking, and spirometric confirmation of airflow limitation including an FEV_1 $\leq$70% of FVC were eligible for participation. Exclusion criteria included a diagnosis of asthma, symptomatic prostatic hypertrophy or bladder neck obstruction, and narrow-angle glaucoma. Patients with significant disease other than COPD which could preclude participation or significantly confound the study results were excluded. Hospitalization for heart failure in the previous 3 years, cardiac arrhythmia requiring drug therapy, or myocardial infarction within the previous year were excluded from earlier protocols; however, other than those specific criteria, patients with ischemic heart disease or heart failure were not specifically excluded. More recent trials changed the exclusion criteria as follows: hospitalization for heart failure in the previous year, myocardial infarction within the previous 6 months, life-threatening cardiac

arrhythmia or arrhythmia requiring a change in medication within the last year. All protocols were approved by ethics committees and written informed consent was obtained from all patients.

All trials permitted concomitant use of short-acting beta-agonists, theophyllines and inhaled corticosteroids. The larger and more recent trials such as the 4-year UPLIFT trial (5,992 treated patients) and trial 205.266 (1,829 patients) permitted use of inhaled long-acting beta-agonists as prescribed. Long-acting beta-agonists were also permitted in trials 205.259, 205.270, 205.282 and 205.284.

8.1.2 Study variables

All studies included spirometry that conformed to American Thoracic Society standards (R96-1186). Different studies involved a variety of evaluations including exercise testing, questionnaire-based assessments of dyspnea and health-related quality of life, and collection of exacerbation data. All trials collected information on COPD exacerbations on adverse event case report forms. Several trials additionally collected exacerbation information on COPD specific case report forms. Adverse events were collected at all study visits in all trials.

8.1.3 Adverse event reporting

All adverse events occurring during the conduct of the trial were reported by the investigational sites to Boehringer Ingelheim. An adverse event was defined as any untoward medical occurrence occurring during the trial; the event did not necessarily have to have a causal relationship with the treatment. A serious adverse event was defined as any adverse event that resulted in death, was immediately life-threatening, resulted in persistent or significant disability / incapacity, required or prolonged patient hospitalization, or was deemed serious for any other reason representing a significant hazard, which is comparable to the aforementioned criteria. In one trial (205.266) non-serious adverse events were, a priori, not to be recorded unless the investigator decided that another non-serious event was a contributing factor to the serious event reported (P05-09172). Analyses are presented separately for adverse events, serious adverse events, and fatal adverse events.

8.1.4 Categorization of adverse events

Categorization of adverse events is as described in Section 6.4.4. In addition, adverse events related to lower respiratory disorders and COPD exacerbations were grouped in several different ways for some of the tables that appear in this section:

- Entries headed “Lower Respiratory SOC” include all events coded to the lower respiratory system organ class (“SOC”);

- Entries headed “COPD exacerbation” include all events coded to any of the preferred terms “chronic obstructive pulmonary disease,” “infective exacerbation of chronic obstructive airways disease,” and “obstructive airways disorder.”

- Entries headed "COPD exacerbation (broad)" include the "COPD exacerbation" events and all events coded to any of about two dozen other preferred terms (listed in Appendix 17.1) suggestive of supervening infection without explicit pneumonia.

- Entries headed "COPD exacerbation + pneumonia" include the "COPD exacerbation (broad)" events and all events coded to any of 40 other preferred terms (listed in Appendix 17.1) describing pneumonia.

- Entries headed "Asthma" include all events coded to any of the preferred terms "analgesic asthma syndrome," "asthma," and "asthma late onset."

- Entries headed "Bronchitis" include all events coded to any of about a dozen preferred terms (listed in Appendix 17.1).

- Entries headed "Dyspnea" include all events coded to any of seven preferred terms (listed in Appendix 17.1).

- Entries headed "Lower respiratory tract infection" include all events coded to any of about ninety preferred terms (listed in Appendix 17.1).

- Entries headed "Pneumonia" include all events coded to any of about 40 preferred terms (listed in Appendix 17.1).

- Entries headed "Respiratory failure" include all events coded to any of seven preferred terms (listed in Appendix 17.1).

- Entries headed "Sputum purulent" include all events coded to either of the preferred terms "sputum discoloured," or "sputum purulent."

8.1.5 Statistical methods

The statistical methods used to compare adverse events across treatment groups focused on the differences in incidence rates based on patient-time at risk rather than hazard ratios. Hazard ratios were used for specific pre-sprecified endpoints such as efficacy outcomes (i.e. exacerbations) and for mortality. The main reason for using incidence rate differences for adverse events was that for rare adverse events hazard ratios are not sufficiently informative. In particular, the hazard ratio can not be computed when a treatment group has no events. The comparison of crude rates based on patient as a unit had somewhat limited utility as it is was likely to be biased given that most tiotropium trials have significantly greater number of patients in the placebo group discontinuing the trial early compared to tiotropium treated patients.

Total exposure time to study drug included all days from the first dose to the last dose of study drug. Time at risk was determined from first intake of drug until 30 days post-treatment (tiotropium, placebo) or until the onset of the specific adverse event analyzed,

whichever came first. For each event, an incidence rate (IR) was calculated from the number of patients with an event divided by the cumulative time at risk within a treatment group and expressed as patient-years. Incidence rate differences were estimated based on the method described by Greenland and Robins (R09-1299) with trial as stratum. The 95% confidence interval was calculated for each rate difference in order to describe the precision of the effect estimate. A rate difference (RD) < 0 indicated a decreased risk with tiotropium and a RD > 0 indicated a decreased risk with placebo. Potential heterogeneity among trials for adverse events, serious adverse events and fatal adverse events were explored prior to combining trials using Zelen's test (R09-0578). For the pooled trial analysis, incidence rates and rate differences were also derived by subgroup for severity stage (based on pre-bronchodilator FEV_1), gender, age groups, smoking status, and respiratory medication at study entry as well as for United States residency. The subanalyses based on LABA and LABA/ICS use were restricted to trials that allowed use of LABAs (205.235, 205.259, 205.266, 205.270, 205.282, and 205.284).

8.2 UPLIFT TRIAL

8.2.1 Lower respiratory disorders and COPD exacerbations

The following three tables display data from the system organ class (SOC) "lower respiratory disorders," including all adverse events (Table 8.2.1:1), only serious adverse events (Table 8.2.1:2), and only fatal events (Table 8.2.1:3).

Individual patients may be represented in multiple categories, but a patient was only represented once within a category at the SOC level (i.e. lower respiratory disorders). For example, if a patient had been described by the investigator as having had only bronchitis, then this patient would be counted in these tables in the rows headed "Lower Respiratory SOC," "COPD exacerbation (broad)," and "Bronchitis."

Compared to placebo, tiotropium was associated with a smaller incidence of adverse events in almost every tabulated category, whether one looked at all events, only serious events, or only fatal events. With respect to all of the most common events (including all three versions of "COPD exacerbation," serious or not), the differences occurred with a p-value <0.05.

Table 8.2.1: 1 Incidence rates and rate difference (tiotropium - placebo) per 100 patient years for lower respiratory adverse events in the UPLIFT trial

	Placebo (n= 3,006)		Tiotropium (n= 2,986)		Tiotropium – Placebo
	N	IR	N	IR	RD (95% CI)
Lower Respiratory SOC	2339	65.4	2262	52.8	-12.5 (-16.0, -9.09)*
COPD exacerbation	1986	45.5	1935	38.1	-7.41 (-10.0, -4.79)*
COPD exacerbation (broad)	2066	50.2	2019	41.6	-8.53 (-11.4, -5.71)*
COPD exacerbation + pneumonia	2144	54.2	2094	44.8	-9.35 (-12.3, -6.36)*
Asthma	2	0.02	2	0.02	-0.00 (-0.04, 0.04)
Bronchitis	239	2.89	235	2.61	-0.28 (-0.78, 0.21)
Dyspnea	443	5.49	364	4.09	-1.39 (-2.06, -0.73)*
Lower respiratory tract infection	670	8.87	703	8.57	-0.29 (-1.22, 0.63)
Pneumonia	418	5.14	436	4.98	-0.17 (-0.84, 0.51)
Respiratory failure	179	2.09	157	1.68	-0.40 (-0.81, -0.00)*
Sputum purulent	12	0.14	12	0.13	-0.01 (-0.12, 0.10)

Source data: data on file, Tables 3.17.1.4.1.1 and 3.17.1.6.1.1
n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; terms used are composed of multiple MedDRA preferred terms; *=p<0.05

Table 8.2.1: 2 Incidence rate, rate difference (tiotropium - placebo) per 100 patient years for lower respiratory serious adverse events in the UPLIFT trial.

	Placebo (n= 3,006)		Tiotropium (n= 2,986)		Tiotropium – Placebo
	N	IR	N	IR	RD (95% CI)
Lower Respiratory SOC	985	13.47	911	11.32	-2.16 (-3.27, -1.04)*
COPD exacerbation	742	9.70	688	8.19	-1.51 (-2.44, -0.58)*
COPD exacerbation (broad)	764	10.05	719	8.62	-1.43 (-2.38, -0.48)*
COPD exacerbation + pneumonia	901	12.17	844	10.38	-1.79 (-2.85, -0.73)*
Asthma	2	0.02	0	0.00	-0.02 (-0.05, 0.01)
Bronchitis	29	0.33	38	0.40	0.07 (-0.11, 0.25)
Dyspnea	54	0.62	36	0.38	-0.24 (-0.45, -0.03)*
Lower respiratory tract infection	336	4.04	352	3.94	-0.11 (-0.70, 0.49)
Pneumonia	290	3.46	299	3.31	-0.15 (-0.70, 0.40)
Respiratory failure	160	1.86	136	1.45	-0.41 (-0.79, -0.03)*

Source data: data on file, Tables 3.17.1.4.1.2 and 3.17.1.6.1.2
n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; terms used are composed of multiple MedDRA preferred terms; *=p<0.05

Table 8.2.1: 3 Incidence rate, rate difference (tiotropium - placebo) per 100 patient years for lower respiratory fatal adverse events in the UPLIFT trial.

	Placebo (N=3,006)		Tiotropium (N=2,986)		Tiotropium – Placebo
	N	IR	N	IR	RD (95% CI)
Lower Respiratory SOC	144	1.66	129	1.37	-0.29 (-0.65, 0.07)
COPD exacerbation	59	0.68	55	0.58	-0.09 (-0.33, 0.14)
COPD exacerbation (broad)	60	0.69	57	0.60	-0.08 (-0.32, 0.15)
COPD exacerbation + pneumonia	84	0.96	88	0.93	-0.03 (-0.32, 0.25)
Asthma	1	0.01	0	0.00	-0.01 (-0.03, 0.01)
Bronchitis	1	0.01	0	0.00	-0.01 (-0.03, 0.01)
Dyspnea	4	0.05	0	0.00	-0.05 (-0.09, -0.00)*
Lower respiratory tract infection	34	0.39	37	0.39	0.00 (-0.18, 0.18)
Pneumonia	31	0.36	32	0.34	-0.02 (-0.19, 0.15)
Respiratory failure	64	0.73	48	0.51	-0.23 (-0.46, 0.00)

Source data: data on file, Tables 3.17.1.4.1.3 and 3.17.1.6.1.3
n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; terms used are composed of multiple MedDRA preferred terms; *=p<0.05

8.2.2 Respiratory failure

The previous tables (Tables 8.2.1: 1 to 3) documented a lower incidence rate with tiotropium for events considered in a combined term (i.e. pooled from several preferred terms) for "respiratory failure" in the UPLIFT trial. Additionally, there were fewer patients with adverse event reports of the preferred term "respiratory failure" relative to the control group. The observation was noted for the categories of all adverse events, serious adverse events and for fatal adverse events (Tables 8.2.2: 1 to 3). There were 208 patients who were reported to have had an adverse event reported under the preferred term "respiratory failure" during the trial. There was a lower rate of respiratory failure in the tiotropium group (RD (95% CI) = -0.45 (-0.77, -0.14). Ninety-six percent of the events were considered serious (n=198). The associated RD (95% CI) for serious respiratory failure was -0.40 (-0.71, -0.09). Fatal events as reported by the investigator (n=77) were also significantly reduced with tiotropium (RD (95% CI) = -0.20 (-0.39, -0.01).

According to The Textbook of Respiratory Medicine (R08-4334), "… the term respiratory failure is used clinically to denote major abnormalities in the exchange of gases between the atmosphere and a person's arterial blood." For clinical purposes, respiratory failure can be considered as either ventilatory failure or as oxygenation failure. However, information regarding respiratory failure was captured in UPLIFT and the other clinical trials through adverse event reporting. There was no pre-specified trial protocol definition. Nevertheless, investigators with expertise in respiratory disease were preferentially reporting fewer patients with such events in the tiotropium group. Therefore, additional post-hoc analyses were conducted to further explore the observation.

Based on the above definitions several reported preferred terms under MedDRA (Version 11.1) were pooled under the clinical definition of "respiratory failure". These

preferred terms have been analyzed both individually and as the pooled term. The previous tables (Tables 8.2.1: 1, 8.2.1:2 and 8.2.1: 3) displayed the pooled term for respiratory failure.

The following tables represent the incidence rates and rate differences for adverse events (Table 8.2.2: 1), serious adverse events (Table 8.2.2: 2), and fatal events (Table 8.2.2: 3) according to the individual preferred terms that have been combined to form the pooled term for "respiratory failure".

Table 8.2.2: 1 Incidence rates and rate differences (tiotropium - placebo) per 100 patient years for adverse event reporting of preferred terms within the pooled term "respiratory failure" - UPLIFT

	Placebo (N = 3,006)		Tiotropium (N = 2,986)		Tiotropium - Placebo
	N	IR	N	IR	RD (95% CI)
Respiratory failure (total)	179	2.09	157	1.68	-0.40 (-0.81, 0.00)*
Acute respiratory failure	31	0.36	30	0.32	-0.04 (-0.21, 0.13)
Cardiopulmonary failure	12	0.14	10	0.11	-0.03 (-0.13, 0.07)
Chronic respiratory failure	9	0.10	10	0.11	0.00 (-0.09, 0.10)
Hypoxia	19	0.22	27	0.29	0.07 (-0.08, 0.21)
Respiratory acidosis	3	0.03	2	0.02	-0.01 (-0.06, 0.04)
Respiratory distress	1	0.01	1	0.01	0.00 (-0.03, 0.03)
Respiratory failure	120	1.39	88	0.94	-0.45 (-0.77, -0.14)*

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; *p<0.05
Source data: data on file, Table 3.17.1.5.1.1

Table 8.2.2: 2 Incidence rates and rate differences (tiotropium - placebo) per 100 patient years for serious adverse event reporting of preferred terms within the pooled term "respiratory failure" - UPLIFT

	Placebo (N = 3,006)		Tiotropium (N = 2,986)		Tiotropium - Placebo
	N	IR	N	IR	RD (95% CI)
Respiratory failure (total)	160	1.86	136	1.45	-0.41 (-0.79, -0.03)*
Acute respiratory failure	31	0.36	29	0.31	-0.05 (-0.22, 0.12)
Cardiopulmonary failure	12	0.14	10	0.11	-0.03 (-0.13, 0.07)
Chronic respiratory failure	5	0.06	7	0.07	0.02 (-0.06, 0.09)
Hypoxia	8	0.09	12	0.13	0.04 (-0.06, 0.13)
Respiratory acidosis	3	0.03	1	0.01	-0.02 (-0.07, 0.02)
Respiratory distress	1	0.01	0	0.00	-0.01 (-0.03, 0.01)
Respiratory failure	113	1.31	85	0.90	-0.40 (-0.71, -0.09)*

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; *p<0.05
Source data: data on file, Table 3.17.1.5.1.2

Table 8.2.2: 3 Incidence rates and rate differences (tiotropium - placebo) per 100 patient years for fatal adverse event reporting of preferred terms within the pooled term "respiratory failure" - UPLIFT

	Placebo (N = 3006)		Tiotropium (N = 2986)		Tiotropium - Placebo
	N	IR	N	IR	RD (95% CI)
Respiratory failure (total)	64	0.73	48	0.51	-0.23 (-0.46, 0.00)
Acute respiratory failure	8	0.09	8	0.08	-0.01 (-0.09, 0.08)
Cardiopulmonary failure	8	0.09	8	0.08	-0.01 (-0.09, 0.08)
Chronic respiratory failure	1	0.01	1	0.01	0.00 (-0.03, 0.03)
Hypoxia	0	0.00	1	0.01	0.01 (-0.01, 0.03)
Respiratory acidosis	1	0.01	0	0.00	-0.01 (-0.03, 0.01)
Respiratory failure	46	0.53	31	0.33	-0.20 (-0.39, -0.01)*

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; *p<0.05

Source data: data on file, Table 3.17.1.5.1.3

In summary, the adverse event database of the UPLIFT trial demonstrated that tiotropium HandiHaler® 18 mcg daily provided additional information supporting the exacerbation efficacy data. These rate difference estimates for COPD exacerbations and for the lower respiratory disorder SOC based on reported adverse events are below 0 and the upper boundary of the confidence intervals are less than 0 for all adverse events and serious adverse events. The rate difference for fatal COPD exacerbations has a confidence interval that includes 0, although there are numerically fewer fatal events in the tiotropium group. The consistency of the result was corroborated by parallel reductions in rate differences for dyspnea and reports of respiratory failure. The data regarding respiratory failure is novel information not previously identified as a potential benefit of treatment with pharmacotherapy and serves as corrobation of the effects of tiotropium HandiHaler® on exacerbations of COPD.

8.3 POOLED CLINICAL TRIAL DATA

Owing to the virtues of randomization in reducing bias due to confounding, placebo-controlled trials are generally considered to be the most informative means of assessing causal effects of medications. Clinical trials are generally limited in detecting rare effects due to the relatively small number of participants required to test the primary efficacy endpoints. By integrating information across multiple studies in a pooled analysis, the size of the study population is increased thereby enhancing the precision of effect estimates and improving detection of rare or infrequent events. The pooled analysis therefore may add additional value above what has been presented with UPLIFT alone.

8.3.1 Study population

For the 26 HandiHaler® trials the number of patients (patient years of exposure) was 7,865 (10,578) for placebo and 9,149 (11,958) for tiotropium (data on file, Table 3.17.1.2.4).

Baseline demographics (Table 8.3.1: 1) were balanced between treatment groups. The mean age of the population was 65 years and 76% were men. Mean baseline FEV_1 was 1.16 L (41% predicted), FVC was 2.48 L, and FEV_1/FVC was 0.47. Approximately 34% of patients were active smokers at randomization. There were a total of 4,508 prematurely discontinued patients with a higher discontinuation rate in the placebo-treated patients (30.9% vs. 22.7%) (data on file, Table 3.17.1.1.1.4). Zelen's test for adverse events, serious adverse events and fatal adverse events did not indicate heterogeneity among trials (p-values = 0.42, 1.00, 1.00 respectively) (data on file, Table 3.17.1.3.5)

Table 8.3.1: 1 Baseline characteristics of patients in the placebo and tiotropium groups in the pooled analysis of 26 tiotropium HandiHaler® trials

Characteristic	**Placebo (N = 7,865)**	**Tiotropium (N = 9,149)**
Age (years)*	64.7 (8.9)	64.5 (8.8)
Male (%)	76.0	76.0
Current smoker (%)	33.0	33.8
Baseline spirometry		
FEV_1 (L)*	1.15 (0.46)	1.17 (0.47)
FEV_1 (% predicted) *	40.8 (14.1)	41.3 (14.3)
FVC (L)*	2.50 (0.82)	2.47 (0.81)
FEV_1/FVC*	0.47 (0.12)	0.48 (0.13)
GOLD Stage I+II/III/IV (%)	25.9 / 49.5 / 23.5	27.4 / 48.3 / 23.2

*Mean (SD); FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity

Source data: data on file, Table: 3.17.1.1.1.4

Baseline (i.e. taken prior to study entry) concomitant respiratory medication use was generally balanced (Table 8.3.1: 2). Approximately 39% and 55% of patients had received long-acting beta-agonists and inhaled corticosteroids respectively at study entry. Short and long-acting inhaled anticholinergics were used by approximately 40% and 1% of patients respectively.

Table 8.3.1: 2 Baseline concomitant respiratory medications (% of patients) in the placebo and tiotropium groups in the pooled analysis of 26 tiotropium HandiHaler® trials

	Placebo (N = 7,865)	**Tiotropium (N = 9,149)**
Any respiratory medication	6776 (86.2)	7737 (84.6)
Short-acting inhaled anticholinergics[a]	3219 (40.9)	3627 (39.6)
Long-acting inhaled anticholinergics	91 (1.2)	94 (1.0)
Short-acting inhaled β_2-agonists[a]	2823 (35.9)	3396 (37.1)
Long-acting inhaled β_2-agonists[a]	3184 (40.5)	3369 (36.8)
Inhaled corticosteroids[a]	4407 (56.0)	5024 (54.9)
Oral corticosteroids	289 (3.7)	374 (4.1)
Theophylline compounds	1686 (21.4)	2076 (22.7)
Mucolytics	401 (5.1)	458 (5.0)
Leukotriene receptor antagonists	176 (2.2)	189 (2.1)
Supplemental oxygen	399 (5.1)	414 (4.5)

Baseline period for medications is defined as time before consent date and ending after or equal to consent date.
[a]alone or in combination

Source data: data on file, Table 5.3.4

8.3.2 Lower respiratory disorders and COPD exacerbations

The tables and descriptions are similar to that described in Section 8.2.1 for the UPLIFT trial. As in the corresponding UPLIFT section, the terms listed are pooled terms rather than preferred terms.

In the 26 tiotropium HandiHaler® trials, there were 7,364 patients with at least one lower respiratory adverse event. The rate difference (95% CI) for any lower respiratory event (tiotropium - placebo) was -14.2 (-17.0, -11.5). Tiotropium was associated with a significant decrease in the risk for a COPD exacerbation whether considered within the narrower term (RD (95% CI) = -8.90 (-11.0, -6.83) or broader term (RD (95% CI) = -9.76 (-12.0, -7.50), indicating a reduction of 8.9 to 9.8 cases per 100 patient years at risk. In addition, there was a consistency in the data in that there were reduced rate differences for dyspnea and respiratory failure in the pooled database.

Table 8.3.2: 1 Incidence rate, rate difference (tiotropium - placebo) per 100 patient years for exacerbation and other lower respiratory adverse events in the pooled analysis of 26 tiotropium HandiHaler® trials

	Placebo (N= 7,865)		Tiotropium (N= 9,149)		Tiotropium – Placebo
	N	IR	N	IR	RD (95% CI)
Lower Respiratory SOC	3648	65.0	3716	53.2	-14.2 (-17.0, -11.5)*
COPD exacerbation	2829	43.2	2793	34.9	-8.90 (-11.0, -6.83)*
COPD exacerbation (broad)	3070	49.2	3117	40.7	-9.76 (-12.0, -7.50)*
COPD exacerbation + pneumonia	3199	52.7	3253	43.5	-10.5 (-12.8, -8.08)*
Asthma	10	0.09	10	0.08	-0.01 (-0.08, 0.07)
Bronchitis	366	3.42	407	3.35	-0.39 (-0.87, 0.08)
Dyspnea	747	7.15	804	6.72	-1.88 (-2.57, -1.19)*
Lower respiratory tract infection	995	10.0	1157	10.3	-0.55 (-1.41, 0.31)
Pneumonia	525	4.96	572	4.78	-0.25 (-0.83, 0.33)
Respiratory failure	209	1.89	183	1.46	-0.38 (-0.71, -0.05)*
Sputum purulent	99	0.89	218	1.73	0.16 (-0.11, 0.44)

Source data: data on file, Table 3.17.1.4.4.1 and 3.17.1.6.4.1
n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; terms used are composed of multiple MedDRA preferred terms; *=p<0.05

Table 8.3.2: 2 Incidence rate, rate difference (tiotropium - placebo) per 100 patient years for exacerbation and other lower respiratory serious adverse events in the pooled analysis of 26 tiotropium HandiHaler® trials

	Placebo (N= 7,865)		Tiotropium (N= 9,149)		Tiotropium – Placebo
	N	IR	N	IR	RD (95% CI)
Lower Respiratory SOC	1301	13.4	1265	11.3	-2.23 (-3.20, -1.27)*
COPD exacerbation	951	9.44	921	7.95	-1.58 (-2.37, -0.78)*
COPD exacerbation (broad)	987	9.85	967	8.39	-1.53 (-2.34, -0.72)*
COPD exacerbation + pneumonia	1170	11.9	1145	10.1	-1.90 (-2.80, -0.99)*
Asthma	2	0.02	3	0.02	0.00 (-0.03, 0.03)
Bronchitis	40	0.36	53	0.42	0.07 (-0.09, 0.23)
Dyspnea	72	0.65	64	0.51	-0.20(-0.39, -0.01)*
Lower respiratory tract infection	437	4.06	476	3.92	-0.21 (-0.73, 0.31)
Pneumonia	370	3.41	390	3.18	-0.26 (-0.73, 0.22)
Respiratory failure	191	1.73	161	1.28	-0.40(-0.72, -0.08)*

Source data: data on file, Tables 3.17.1.4.4.2 and 3.17.1.6.4.2
n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; terms used are composed of multiple MedDRA preferred terms; *=p<0.05

Table 8.3.2: 3 Incidence rate, rate difference (tiotropium - placebo) per 100 patient years for exacerbation and other lower respiratory fatal adverse events in the pooled analysis of 26 tiotropium HandiHaler® trials

	Placebo (N=7,865)		Tiotropium (N=9,149)		Tiotropium – Placebo
	N	IR	N	IR	RD (95% CI)
Lower Respiratory SOC	165	1.48	147	1.16	-0.30 (-0.59, -0.00)*
COPD exacerbation	68	0.61	65	0.51	-0.09 (-0.28, 0.10)
COPD exacerbation (broad)	69	0.62	67	0.53	-0.08 (-0.27, 0.11)
COPD exacerbation + pneumonia	98	0.88	100	0.79	-0.07 (-0.31, 0.16)
Asthma	1	0.01	0	0.00	-0.01 (-0.03, 0.01)
Bronchitis	1	0.01	0	0.00	-0.01 (-0.03, 0.01)
Dyspnea	4	0.04	0	0.00	-0.04 (-0.07, -0.00)*
Lower respiratory tract infection	40	0.36	40	0.32	-0.03 (-0.18, 0.12)
Pneumonia	36	0.32	34	0.27	-0.04 (-0.18, 0.10)
Respiratory failure	71	0.63	51	0.40	-0.22 (-0.40, -0.03)*

Source data: data on file, Tables 3.17.1.4.4.3 and 3.17.1.6.4.3
n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk);
RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; terms used are composed of multiple MedDRA preferred terms; *=p<0.05

In summary, the pooled database of 26 randomized, double-blind, placebo-controlled clinical trials with a treatment duration of at least four weeks demonstrated that tiotropium HandiHaler® 18 mcg daily reduced COPD exacerbations. These rate difference estimates based on reported adverse events were below 0 and the upper boundary the confidence intervals were less than 0 for all adverse events and serious adverse events with a trend towards a reduction in fatal events. The consistency of the result was corroborated by parallel reductions in rate differences for dyspnea and reports of respiratory failure.

8.3.3 Exacerbation results (restricted data set using common definition)

While the clinical trials in the pooled analysis indicated a robust effect, several minor limitations can be identified. Although definitions for exacerbations were commonly pre-specified in the clinical trial protocols, the above analyses were based on adverse event reporting. Not all trials used exactly the same definition and the results of the large UPLIFT trial (205.235) could potentially mask inconsistencies in the overall database.

8.3.3.1 Methods

As a sensitivity analysis, all randomized, double-blind, placebo-controlled, parallel-group studies with tiotropium 18 mcg once daily delivered via the HandiHaler® in COPD with an observation period of 6 to 12 months completed by December 2008 were included in a separate pooled analysis (n=9) (P02-01290, P03-04061, P06-02670, P08-04366, P05-09483, P07-10504). This analysis was conducted prior to completion on UPLIFT and does not include data from the UPLIFT trial.

In this analysis, an exacerbation was defined as ≥2 (increased or new-onset) respiratory symptoms such as cough, sputum, wheezing, dyspnea, or chest tightness, lasting ≥3 days and requiring treatment with antibiotics and/or systemic steroids and/or hospitalization. This definition was retrospectively applied to all trials and was the definition used originally in the VA trial where an exacerbation of COPD was the primary endpoint 205.266 (P05-09483). Exacerbations were determined from records of adverse events or via case report form. All hospitalizations that included COPD exacerbation were considered as exacerbation-related hospitalizations.

8.3.3.2 Data analysis

All treated patients from the trials were included in the pooled analysis. Endpoints were (1) proportion of patients with COPD exacerbation, (2) proportion of patients with hospitalization associated with COPD exacerbation, (3) time to first COPD exacerbation, and (4) time to first hospitalization associated with COPD exacerbation.

Although trial 205.230 (P05-02413) had a 24-week observation period, it was decided not to include this study in the pooled analysis as patients underwent pulmonary rehabilitation alongside tiotropium or placebo treatment.

Stratified Cox regression was used to compute hazard ratios of tiotropium compared with placebo using trial as a stratum. By trial Cox regression analysis was also conducted and 95% confidence intervals (CIs) provided for the hazard ratios.

As sensitivity analyses, crude incidence rates and exposure-adjusted incidence rates (since studies were subject to different durations and rate of premature withdrawal) were also provided. Exposure was defined as the cumulative time that patients were in the study from randomization until either the onset of an event or the discontinuation of treatment. The Cochran-Mantel-Haenszel procedure, using study as stratum, was used to compare the two treatment groups.

Time to COPD exacerbation and hospitalization associated with exacerbation are displayed using cumulative incidence rates based on Kaplan-Meier estimates of probability of no event. Plots were truncated to 46 weeks, at which time a substantial number of patients still received study drug, though the analyses were conducted using the entire dataset.

8.3.3.3 Results

A total of 6,171 patients were included (3,309 tiotropium and 2,862 placebo). Of these, 1,403 (22.7%) discontinued early (626 (18.9%) in the tiotropium group and 777 (27.1%) in the placebo group). The main reported reasons for early withdrawal were worsening of COPD/lack of efficacy (9.9% in the tiotropium group and 16.1% in the placebo group). The mean age of the patients was 66 years, 81% were male and 68% had stopped smoking prior to randomization. The mean smoking history was 54.7 pack-years. The mean percentage predicted FEV_1 was 39.5% and FEV_1/FVC was 48.6%. Patients were balanced with respect to demographics and other baseline characteristics across the two treatment groups.

Stratified Cox regression showed that tiotropium significantly reduced the risk of COPD exacerbation by 21% (HR (95%CI) = 0.79 (0.73, 0.86)) compared with placebo (p<0.0001). Figure 8.3.3.3: 1 shows that the reduction in hazard ratio with tiotropium compared with placebo was consistent in 8/9 studies, which had a range of hazard ratio from 0.52 to 0.86. In trial 205.259, the hazard ratio was 1.03.

Source	Tiotropium n/N	Placebo n/N	Hazard ratio (95% CI)
205.117	104/279	89/191	0.699 (0.527,0.928)
205.128	78/271	55/180	0.858 (0.608,1.212)
205.130	65/209	71/201	0.733 (0.523,1.026)
205.137	51/193	62/199	0.792 (0.547,1.147)
205.214	204/500	256/510	0.717 (0.596,0.861)
205.256	93/266	120/288	0.709 (0.540,0.929)
205.259	268/608	125/305	1.031 (0.834,1.275)
205.266	255/914	296/915	0.833 (0.705,0.985)
205.270	24/69	41/73	0.520 (0.314,0.862)
Combined study	**1142/3309**	**1115/2862**	**0.793 (0.729,0.862)**

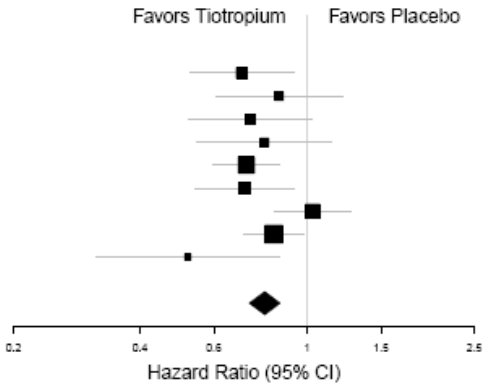


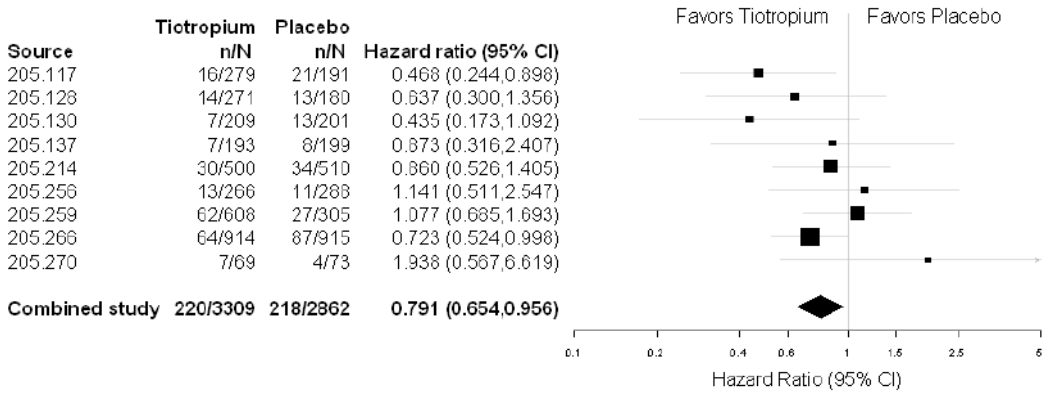
Figure 8.3.3.3: 1 Hazard ratios for an exacerbation of COPD in the tiotropium group compared with the placebo group in trials of at least six-month duration (excluding UPLIFT)

Source data: P09-08969

Analysis of crude rates of exacerbations between tiotropium and placebo groups showed a rate ratio of 0.87 (95% CI = 0.82, 0.93). Using an exposure-adjusted approach, the rate ratio for exacerbation incidence was 0.78 (95% CI = 0.72, 0.85).

There were very few fatal exacerbations (<0.5%). The number of fatal exacerbations was 17 (6 in the tiotropium group and 11 in the placebo group). The stratified Cox regression for fatal exacerbations resulted in a HR of 0.45 (95% CI = 0.16, 1.22).

Stratified Cox regression showed that tiotropium significantly reduced the risk of hospitalization associated with COPD exacerbation compared with placebo (Figure 2; p=0.015). The hazard ratio was 0.79 (95% CI = 0.65, 0.96). Figure 8.3.3.3: 2 shows that the hazard ratio for hospitalization associated with COPD exacerbation of tiotropium with placebo was <1 in 6/9 studies.



Source	Tiotropium n/N	Placebo n/N	Hazard ratio (95% CI)
205.117	16/279	21/191	0.468 (0.244,0.898)
205.128	14/271	13/180	0.637 (0.300,1.356)
205.130	7/209	13/201	0.435 (0.173,1.092)
205.137	7/193	8/199	0.873 (0.316,2.407)
205.214	30/500	34/510	0.860 (0.526,1.405)
205.256	13/266	11/268	1.141 (0.511,2.547)
205.259	62/608	27/305	1.077 (0.685,1.693)
205.266	64/914	87/915	0.723 (0.524,0.998)
205.270	7/69	4/73	1.938 (0.567,6.619)
Combined study	**220/3309**	**218/2862**	**0.791 (0.654,0.956)**

Figure 8.3.3.3: 2 Hazard ratios for an exacerbation-associated hospitalization of COPD in the tiotropium group compared with the placebo group in trials of at least six-month duration.

Source data: P09-08969

Figure 8.3.3.3: 3 displays the cumulative frequency for COPD exacerbation over time based on the Kaplan-Meier procedure. It showed a separation between tiotropium and placebo ($p<0.001$). The cumulative incidence rate of COPD exacerbation at 46 weeks was 42.1% for tiotropium compared with 50.8% for placebo. A separation between tiotropium and placebo was similarly shown in Figure 8.3.3.3: 3b for the cumulative incidence rates for hospitalization associated with COPD exacerbation over time based on Kaplan-Meier procedure ($p=0.015$). The cumulative incidence rate of hospitalizations associated with COPD exacerbation at 46 weeks (322 days) was 8.5% for tiotropium compared with 10.8% for placebo.

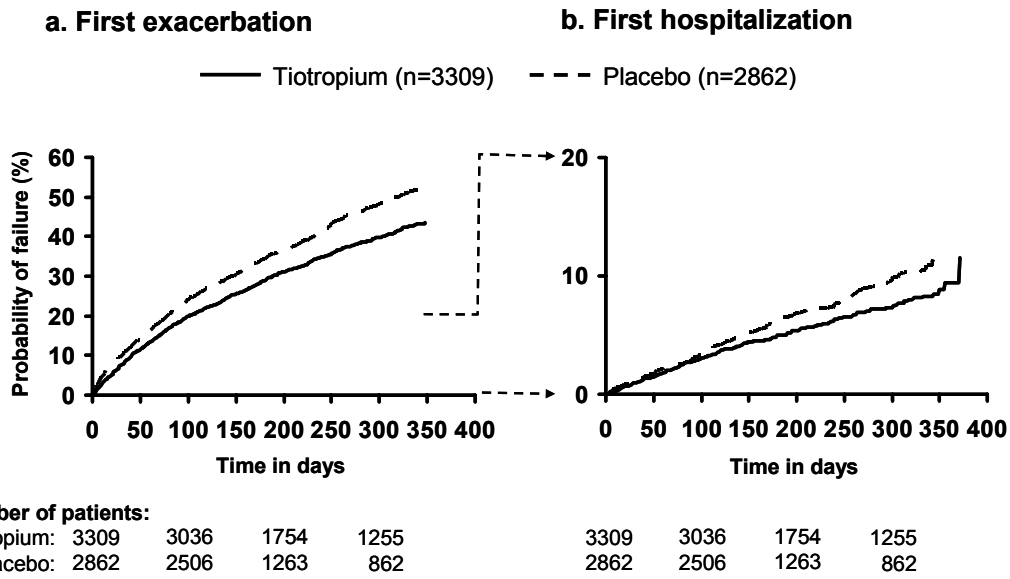


Figure 8.3.3.3: 3 Cumulative incidence rate (Kaplan-Meier) for the probability for (a) exacerbation and (b) exacerbation-associated hospitalization

Number of patients = number of patients at risk.
Source data: P09-08969.

In summary, the above sensitivity analysis supports the consistency of the data demonstrating a reduction in exacerbations of COPD with tiotropium. Although the design of the individual trials were similar with regard to inclusion/exclusion criteria, there were some differences in the data acquisition modalities, time between visits, trial durations, follow-up of withdrawn patients, original definitions of exacerbations and the populations studied. In this analysis, the definition of exacerbation was standardized, with one definition (P05-09483) applied to all studies. This definition was similar to that used in other COPD studies evaluating alternative treatment options (P03-01576, P04-00793, P03-01593). Tiotropium reduced the proportion of patients with exacerbations in 8/9 studies, with effect sizes ranging from a 48% reduction (P07-10504) to a 3% excess (P07-14136). The reasons for the 3% excess in trial 205.259 remain unclear. This trial had longer (18-week) intervals between visits without interim phone calls or patient record cards; therefore, there may have been underreporting of exacerbations in this trial, which recruited a large number of patients with advanced COPD, which may have been numerically magnified by the unequal randomization used (2:1, tiotropium:placebo). At the other extreme, the most positive study (205.270, P07-10504) was conducted at a single centre specializing in COPD exacerbations, and used sophisticated patient record cards for documentation.

8.3.4 Related Respiratory events

It is reasonable to surmise that an intervention that reduces exacerbations of COPD based on sustained improvements in airflow and hyperinflation should also have no detrimental effects on other lower respiratory events and perhaps indicate a further benefit. The aforementioned analyses indicated that tiotropium was not associated with an increased risk for pneumonia and was associated with a decreased risk for reports of respiratory failure. None of the clinical trials pre-specified a definition for either pneumonia or respiratory failure. There were no requirements for either performing or collecting data from chest imaging or arterial blood gases. Nevertheless, there is no inherent trial bias that would preferentially distinguish tiotropium from placebo in terms of reporting pneumonia or respiratory failure, other than that associated with the pharmacologic properties of the study drug. The previous tables from the full pooled analysis described the pooled terms for pneumonia and respiratory failure.

8.3.4.1 Pneumonia

The combined (i.e. pooled) term "pneumonia" is composed of several preferred terms (Appendix 17.1). The most common preferred terms within the combined term are displayed in Table 8.3.4.1: 1. The number of cases under the preferred term "pneumonia" represented 83% of the entire cohort for the pooled term "pneumonia" (i.e. 911/1097 cases). There was no evidence of an increased risk for pneumonia with tiotropium.

Table 8.3.4.1: 1 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for the pooled term pneumonia and the three most common preferred terms within the pooled term of pneumonia in the pooled analysis of 26 tiotropium HandiHaler® trials

	Placebo (N=7,865)		Tiotropium (N= 9,149)		Tiotropium – Placebo
	N	IR	N	IR	RD (95% CI)
Adverse Events					
Pneumonia (pooled term)	525	4.96	572	4.78	-0.30 (-0.88, 0.28)
Pneumonia	438	4.10	473	3.92	-0.21 (-0.74, 0.31)
Lobar pneumonia	49	0.44	62	0.49	0.02 (-0.15, 0.19)
Bronchopneumonia	47	0.42	41	0.32	-0.10 (-0.26, 0.05)
Serious Adverse Events					
Pneumonia (pooled term)	370	3.41	390	3.18	-0.30 (-0.77, 0.17)
Pneumonia	301	2.76	305	2.47	-0.29 (-0.71, 0.14)
Lobar pneumonia	40	0.36	55	0.43	0.05 (-0.11, 0.21)
Bronchopneumonia	36	0.32	30	0.24	-0.08 (-0.22, 0.05)
Fatal Adverse Events					
Pneumonia (pooled term)	36	0.32	34	0.27	-0.05 (-0.19, 0.09)
Pneumonia	26	0.23	25	0.20	-0.03 (-0.15, 0.09)
Lobar pneumonia	2	0.02	6	0.05	0.03 (-0.01, 0.08)
Bronchopneumonia	7	0.06	2	0.02	-0.05 (-0.10, 0.01)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk; RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk
Source data: data on file, Tables 3.17.1.4.4.1, 3.17.1.4.4.2, 3.17.1.4.4.3, 3.17.1.5.4.1, 3.17.1.5.4.2 and 3.17.1.5.4.3

8.3.4.2 Respiratory failure

In the pooled analysis of 26 trials, there were 233 patients who were reported to have had an adverse event reported under the preferred term "respiratory failure" during the trial (Table 8.3.4.2: 1). There was a lower risk of respiratory failure (based on the preferred term) in the tiotropium group (RD (95%CI) = -0.42 (-0.68, -0.17). The events were considered serious in 95% of the patients (i.e. 222/233) (Table 8.3.4.2: 2). The associated rate difference (95%CI) for serious respiratory failure (preferred term) was -0.38 (-0.63, -0.13). Fatal events as reported by the investigator (n=84) were also significantly reduced with tiotropium (RD (95%CI) = -0.19 (-0.32, -0.03) (Table 8.3.4.2: 3).

As described in Section 8.2.2, there are several reported preferred terms under MedDRA (version 11.1) that could be considered as clinically indicative of "respiratory failure". As with the UPLIFT safety database, these terms have been analyzed both individually and as a pooled term for respiratory failure. The following tables represent the incidence rates and rate differences for adverse events (Table 8.3.4.2: 1), serious adverse events (Table 8.3.4.2: 2), and fatal events (Table 8.3.4.2: 3) according to the individual preferred terms and the pooled term "respiratory failure". For all adverse events (Table 8.3.4.2: 1), there was a reduction in the risk for reporting "respiratory failure" in the tiotropium group relative to the placebo group (0.37 cases per 100 patient-years at risk). There was a reduced

risk for reporting of serious and fatal events (0.40 and 0.22 cases per 100 patient-years at risk respectively) under the pooled term respiratory failure respectively with tiotropium.

Table 8.3.4.2: 1 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for adverse event reporting of the pooled term "respiratory failure" in the 26 tiotropium HandiHaler® trials

	Placebo N =7,865		**Tiotropium N =9,149**		**Tiotropium – Placebo**
	N	**IR**	**N**	**IR**	**RD (95% CI)**
Respiratory failure (pooled)	212	1.92	188	1.50	-0.37 (-0.70, -0.03)*
Acute respiratory failure	43	0.38	39	0.31	-0.06 (-0.22, 0.09)
Cardiopulmonary failure	12	0.11	13	0.10	-0.00 (-0.08, 0.08)
Chronic respiratory failure	10	0.09	10	0.08	-0.01 (-0.08, 0.07)
Hypoxia	22	0.20	33	0.26	0.07 (-0.05, 0.19)
Respiratory acidosis	4	0.04	2	0.02	-0.02 (-0.06, 0.02)
Respiratory distress	3	0.03	5	0.04	0.01 (-0.03, 0.06)
Respiratory failure	136	1.22	97	0.77	-0.42 (-0.68, -0.17)*

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; *=p<0.05
Source data: data on file, Table 3.17.1.5.4.1 Respiratory failure (broad)

Table 8.3.4.2: 2 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for serious adverse event reporting of pooled term "respiratory failure" in the 26 tiotropium HandiHaler® trials

	Placebo (N = 7,685)		**Tiotropium (N = 9,149)**		**Tiotropium – Placebo**
	N	**IR**	**N**	**IR**	**RD (95% CI)**
Respiratory failure (pooled)	191	1.73	161	1.28	-0.40 (-0.71, -0.08)*
Acute respiratory failure	43	0.38	38	0.30	-0.07 (-0.22, 0.08)
Cardiopulmonary failure	12	0.11	12	0.09	-0.01 (-0.09, 0.07)
Chronic respiratory failure	6	0.05	7	0.06	0.00 (-0.06, 0.06)
Hypoxia	11	0.10	14	0.11	0.02 (-0.06, 0.10)
Respiratory acidosis	4	0.04	1	0.01	-0.03 (-0.07, 0.01)
Respiratory distress	2	0.02	3	0.02	0.00 (-0.03, 0.04)
Respiratory failure	128	1.15	94	0.74	-0.38 (-0.63, -0.13)*

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; *=p<0.05
Source data: data on file, Table 3.17.1.5.4.2 Respiratory failure (broad)

Table 8.3.4.2: 3 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for fatal adverse event reporting of pooled term "respiratory failure" in the 26 tiotropium HandiHaler® trials

	Placebo (N = 7,865)		Tiotropium (N = 9,149)		Tiotropium – Placebo
	N	IR	N	IR	RD (95% CI)
Respiratory failure (pooled)	71	0.63	51	0.40	-0.22 (-0.40, -0.03)*
Acute respiratory failure	8	0.07	8	0.06	-0.01 (-0.07, 0.06)
Cardiopulmonary failure	8	0.07	9	0.07	0.00 (-0.07, 0.07)
Chronic respiratory failure	1	0.01	1	0.01	-0.00 (-0.02, 0.02)
Hypoxia	1	0.01	1	0.01	-0.00 (-0.02, 0.02)
Respiratory acidosis	1	0.01	0	0.00	-0.01 (-0.03, 0.01)
Respiratory distress	1	0.01	0	0.00	-0.01 (-0.03, 0.01)
Respiratory failure	51	0.46	33	0.26	-0.19 (-0.34, -0.03)*

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; *=p<0.05
Source data: data on file, Table 3.17.1.5.4.3 Respiratory failure (broad) #PV

In summary, the results from the pooled term of respiratory failure were consistent with the individual preferred term and indicated a reduction in the risk for reporting of respiratory failure associated with tiotropium. The limitations of the data included: (a) no trial specific definition for respiratory failure, and (b) absence of a systematic collection of information that would provide objective laboratory confirmation of respiratory failure (i.e. arterial blood gases). However, the findings were consistent and there was no trial design issue that would create a bias leading to unbalanced reporting, other than trial drug allocation. The data provided additional support for the beneficial effects of tiotropium HandiHaler® in reducing exacerbations of COPD.

8.3.5 Subgroup analyses of interest

Subgroup analyses were conducted to examine for consistency of results. The rate difference (95% CI) for an exacerbation (tiotropium - placebo) was calculated according to GOLD stage of FEV_1 severity, age groups, gender, smoking behavior, concomitant respiratory medication and for patients residing in the United States. The exacerbation analysis was based on adverse event reporting as previously described for the 26 HandiHaler® trials.

Table 8.3.5: 1 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for COPD exacerbation adverse events in the 26 tiotropium HandiHaler® trials

	Placebo (N =7,865)		Tiotropium (N =9,149)		Tiotropium – Placebo
	N	**IR**	**N**	**IR**	**RD (95% CI)**
GOLD stage					
II	555	30.0	502	22.8	-7.13 (-10.4, -3.89)*
III	1441	42.5	1437	34.9	-8.61 (-11.5, -5.74)*
IV	781	64.3	808	52.2	-11.75 (-17.6, -5.94)*
Gender					
Male	2060	40.7	2056	33.3	-8.00 (-10.3, -5.71)*
Female	768	51.5	736	40.1	-11.9 (-16.6, -7.20)*
Age					
< 60	794	41.7	764	33.6	-7.97 (-11.8, -4.18)*
60 to 70	1126	42.4	1150	34.5	-8.88 (-12.1, -5.66)*
>70	908	45.6	878	36.6	-9.85 (-13.7, -6.00)*
Smoking					
Current	866	42.3	852	33.9	-8.63 (-12.3, -4.95)*
Ex-smoker	1961	43.6	1939	35.3	-9.04 (-11.6, -6.54)*
Respiratory Meds[a]					
LABA[b,d] (yes)	1393	51.5	1386	42.3	−9.30 (−12.8, −5.79)*
LABA[b,d] (no)	808	33.4	793	27.8	−5.94 (−8.97, −2.92)*
ICS[b] (yes)	1814	50.7	1786	40.7	-10.7 (-13.7, -7.66)*
ICS[b] (no)	1014	34.1	1006	27.8	-6.90 (-9.64, -4.16)
LABA/ICS[c,d] (yes)	1147	53.7	1155	44.0	−9.77 (−13.79, −5.74)*
LABA/ICS[c,d] (no)	1054	35.3	1024	29.3	−6.30 (−9.09, −3.51)*
Anticholiner (yes)	1294	49.5	1342	40.1	-10.9 (-14.4, -7.45)*
Anticholiner (no)	1534	39.0	1450	31.1	-8.00 (-10.6, -5.45)
United States residency	718	38.7	717	31.2	-9.08 (-12.7, -5.44)*

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk;
[a]respiratory medications at baseline, [b]alone or in combination; [c]fixed combination or combination of two monoproducts;
[d]analysis restricted to clinical trials where concomitant use of LABAs was permited (205.235 (UPLIFT®), 205.259, 205.266 (VA), 205.270, 205.282 and 205.284); *p<0.05
Source data: data on file, Gender:Tables 3.17.1.11.2.2.1.1, 3.17.1.11.2.3.1.1,
Age: Tables 3.17.1.11.1.2.1.1, 3.17.11.1.3.1.1, 3.17.1.11.1.4.1.1
Severity stage: I/II-Table 3.17.1.11.3.2.1.1, III- Table 3.17.1.11.3.3.1.1, IV - Table 3.17.1.11.3.4.1.1
Smoking: Current - Table 3.17.1.11.4.3.1.1; Ex-smoker – 3.17.1.11.4.2.1.1
Repiratory Medications: LABA - Table –Used Table 3.17.1.11.7.1.3.1.1 and 3.17.1.11.7.1.2.1.1, ICS - Table – 3.17.1.11.8.3.1.1 and 3.17.1.11.8.2.1.1, LABA/ICS - Table –3.17.1.11.9.1.3.1.1 Table 3.17.1.11.9.1.2.1.1, Anticholinergics - Table – 3.17.1.11.6.3.1.1 and 3.17.1.11.6.2.1.1
United States Residency - Table 3.17.1.11.5.2.1.1

The table showed that the overall results were not due to skewing of data due to any individual subgroup. The results showed a consistency of effects across relevant subgroups.

8.4 SUMMARY

In summary, the pooled trial analysis included 6,187 patients with at least one COPD exacerbation and permitted numerous different approaches to examining the effect of

tiotropium on exacerbations. Tiotropium was associated with a significant decrease in the risk for a COPD exacerbation (calculated as rate differences (RD) of the tiotropium incidence rate minus the placebo incidence rate per 100 patient years) whether considered within a narrower range of preferred terms denoting an exacerbation (RD (95% CI) = -8.90 (-11.0, -6.83) or a broader range of terms (RD (95% CI) = -9.76 (-12.0, -7.50)). There was no increase in the risk for pneumonia as seen by the RD (95% CI) = -0.25 (-0.83, 0.33). Furthermore, there were reductions in risk for exacerbations reported as serious adverse events (RD (95% CI) = -1.58 (-2.37, -0.78)). While relatively infrequent, a total of 136 fatal COPD exacerbations were reported among the trials (RD (95%CI) = -0.09 (-0.28, 0.10)).

The results are consistent with adverse reporting of other associated respiratory terms. The risk for reporting of dyspnea and respiratory failure was lower in the tiotropium group.

The pooled analysis provides appropriate power to examine several important subgroups. Reductions in risk for an exacerbation with tiotropium were observed regardless of gender, smoking behaviour (i.e. continued and ex-smokers), categories of age, concomitant respiratory medications and different lung function severities of COPD.

9. SAFETY OVERVIEW FROM UPLIFT: FATAL AND CARDIOVASCULAR ADVERSE EVENTS

The data from adverse event reporting in the UPLIFT trial provided substantial evidence to illustrate the favorable benefit-risk of tiotropium HandiHaler®, particularly in the context of requesting an indication for reduction of exacerbations of COPD. This section will begin with a detailed analysis of fatal events. An overview of all safety with a detailed analysis of cardiovascular safety including stroke will subsequently be described. Further support will be presented from the pooled analysis of tiotropium HandiHaler® trials in Section 10. It should be noted that an individual patient can be represented in more than one preferred term, but will only be represented once within a combined term or an SOC.

9.1 UPLIFT: FATAL EVENTS

9.1.1 Fatal event summary

During the trial, two amendments associated with mortality data were implemented. As originally written in the protocol, follow-up of patients ceased 30 days after treatment discontinuation. The first amendment established procedures for the collection of vital status information (i.e. whether the patient was alive or dead, cause of death and date of death) on patients who prematurely discontinued from the trial extending to the protocol defined 4-year treatment period post-randomization (listed as day 1440 in the protocol) + the 30 day follow-up period (listed as day 1470 in the protocol). The second amendment established procedures for the adjudication of the primary cause of death by an independent committee.

Time to death was defined as time to the end date of the fatal adverse event. All patients were censored at 1470 days for the Kaplan-Meier estimates and Cox regression. In addition, as the protocol defined end-of-treatment protocol was day 1440, an analysis was performed using the cut-off of day 1440. The mortality endpoints for these analyses included all cause, lower respiratory, cardiac disorders, stroke, and any fatal adverse events that occurred in more than 1% (or 60 cases) of the patients. The analyses for all-cause mortality at the SOC level are presented as hazard ratios (HR). The data on the preferred term level are presented as incidence rate differences (using time to onset of event to derive time at risk).

Fatal events are presented in two ways: (1) all deaths including post-discontinuation vital status collection (referred to as "vital status") and (2) deaths on-treatment. Both (1) and (2) were analyzed with a cut-off of 1440 days (4 years), 1470 days (4 years and 30 days) and with no cut-off date.

The protocol for study 205.235 (UPLIFT) was amended to include the collection of vital status information during the conduct of the trial. This amendment was implemented at a point (15 November 2005) when approximately 1,000 of the 5,992 patients in the study were known to have prematurely discontinued from the trial. The amendment defined "vital status" information as whether the patient was alive or dead and cause of death, if known.

Vital status information (at least 45 months of follow-up, including discontinued patients) was known for 98% of tiotropium-treated patients and 97% of placebo-treated patients (U08-3718-04, Table 15.1.1: 3). For the period until day 1440, full vital status information was known for approximately 95% of patients. For the period until day 1470, full vital status information was known for approximately 75% of patients. The difference in the ascertainment of complete vital status information reflects the procedures from which the vital status information was obtained. The major reason for the difference relates to the definition of a completed patient for the purpose of the mortality analysis. If the investigator indicated on the case report form that the patient had completed treatment, then no further vital status information was sought. There were 971 patients where the patient had completed treatment and the last clinic visit occurred prior to day 1470 and only 17 patients where this occurred prior to day 1440. A second but less prevalent reason was some ambiguity in the wording of the protocol amendment which led to variability of understanding of what constituted full completion of vital status (i.e. day 1440, 4-years calculation of days (day 1460) or day 1470). Hence, the most complete and reliable data for an intention-to-treat approach should be considered as the analysis until the end of the protocol-defined treatment period (day 1440).

A tabulated summary of all cause mortality is provided in Table 9.1.1: 1 below. The category of "all" considers all data without censoring after a specific date. An additional 40 deaths were reported beyond day 1470 for a total of 981 deaths (noted in category "vital status (all)").

Table 9.1.1: 1 Number (%) of patients with fatal adverse events and hazard ratios (95%CI) - UPLIFT

	Placebo N = 3,006	**Tiotropium N = 2,986**	Δ	**Tiotropium/Placebo**	
	N (%)	N (%)		HR (95% CI)	p-value
Vital Status (day 1440)	491 (16.3)	430 (14.4)	1.9%	0.87 (0.76, 0.99)	0.034
Vital Status (day 1470)	495 (16.5)	446 (14.9)	1.6%	0.89 (0.79, 1.02)	0.086
Vital Status (all)	514 (17.1)	467 (15.6)	1.5%	0.89 (0.78, 1.00)	0.058
On-Treatment (day 1440)	400 (13.3)	361 (12.1)	1.2%	0.83 (0.72, 0.95)	0.010
On Treatment (day 1470)	402 (13.4)	374 (12.5)	0.9%	0.85 (0.74, 0.98)	0.024
On-Treatment (all)	411 (13.7)	381 (12.8)	0.9%	0.84 (0.73, 0.97)	0.016

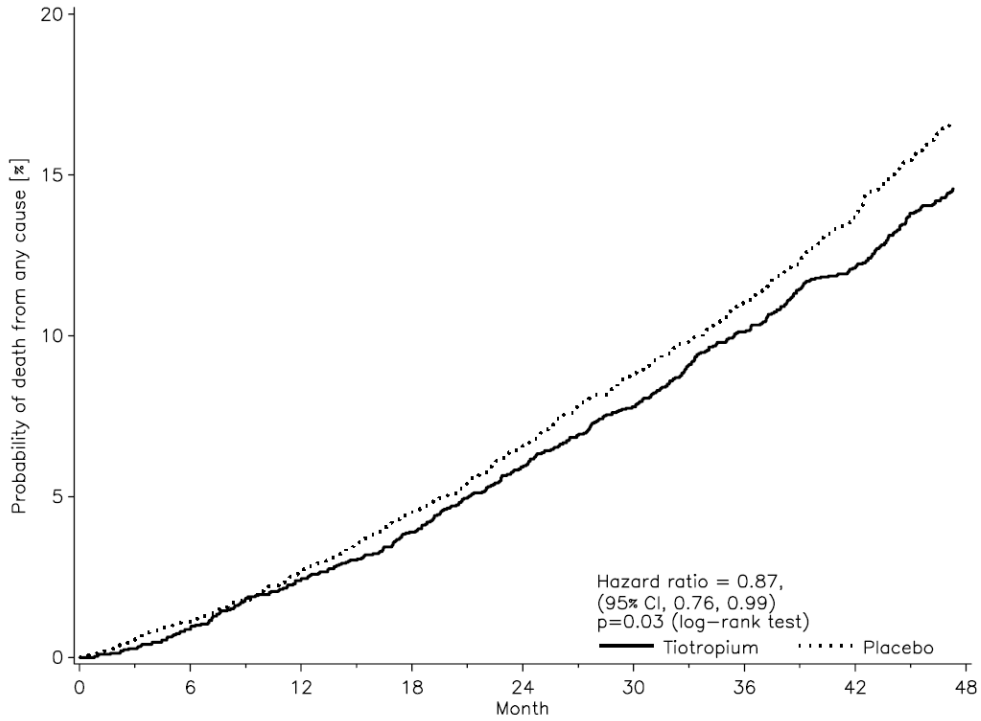
Hazard ratio is calculated using Cox regression with treatment as covariate; * P−value is calculated using log−rank test
Source data: see U08-3718-04, Tables 12.3:1

In the primary analyses, the cause of death assessed by the adjudicated committee was utilized; however, the investigator-reported cause and a shift table summarizing the differences in the reporting of the primary cause are presented in Table 15.3.2.2.1.1:4 in the clinical trial report (U08-3718-04).

9.1.2 Vital status

As previously stated, the analysis referred to as "vital status" includes data from the on-treatment period plus vital status information on patients who prematurely discontinued study medication (i.e. intention-to-treat approach).

A total of 921 deaths were reported for the full 4 year (1440 days) including vital status with a lower risk of death in the tiotropium group (HR=0.87, 95% CI 0.76, 0.99). For the period of 4 years plus 30 days (1470 days) there were 941 deaths with a HR of 0.89 (0.79, 1.02) (Table 9.1.1: 1). The cumulative frequency (Kaplan-Meier) estimates for all cause death for the period of 1440 and 1470 days are displayed below in Figure 9.1.2: 1 and 2. The two treatment curves begin to separate at approximately one-year and indicated no evidence of an increased risk for a fatal event with tiotropium HandiHaler®.

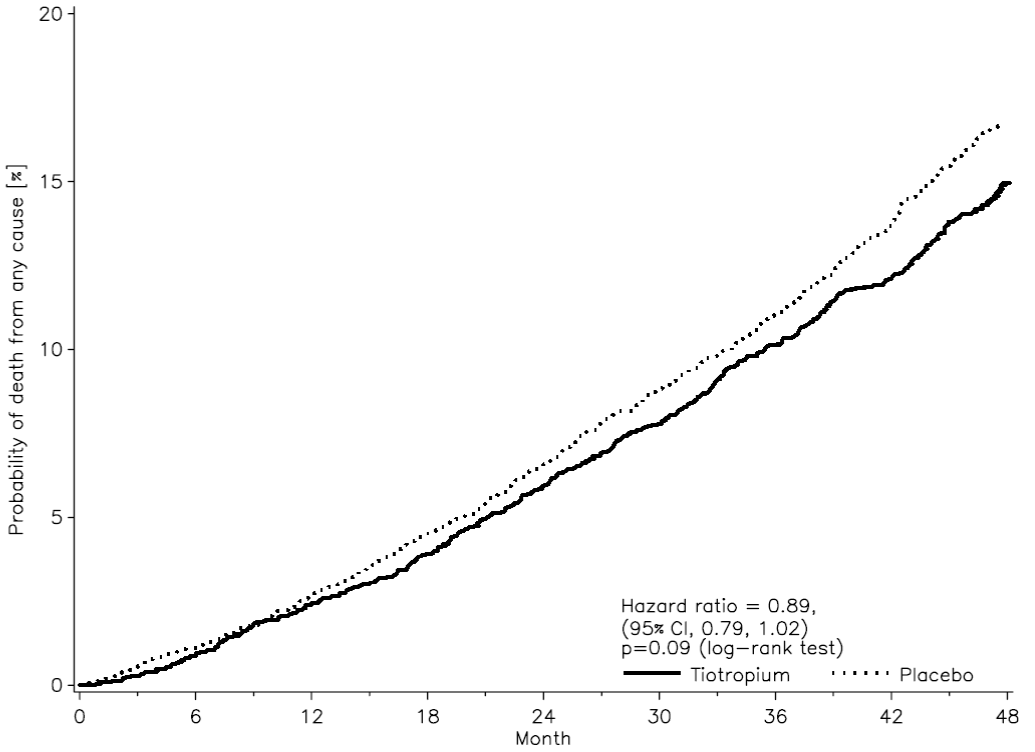


No. of patients:

Tiotropium	2986	2948	2899	2851	2785	2721	2646	2574
Placebo	3006	2961	2903	2836	2772	2696	2624	2523

Figure 9.1.2: 1 Cumulative incidence rate (Kaplan Meier) of the probability of all cause mortality (all deaths including vital status censored at day 1440) – UPLIFT

Number of patients at Day 1440: placebo 2351, tiotropium 2421. Number of patients =number of patients at risk
Source data: see U08-3718-04, Section 16.1.9.2



No. of patients:

Tiotropium	2986	2948	2899	2851	2785	2721	2646	2574	2306
Placebo	3006	2961	2903	2836	2772	2696	2624	2523	2249

Figure 9.1.2: 2 Cumulative incidence rate (Kaplan Meier) of the probability of all cause mortality (all deaths including vital status censored at day 1470) - UPLIFT

Number of patients = number of patients at risk.
Source data: see U08-3718-04, Figure 15.3.2.2.3.

Between days 1440 and 1470, there were 4 deaths in the placebo group and 16 deaths in the tiotropium group (Table 9.1.1: 1). The 4 deaths in the placebo group occurred over 200 days following termination of study drug and none had completed the study according to protocol. However, 6/16 deaths in the tiotropium group had completed the full study treatment period (i.e. completed the trial according to protocol) and had died between 9 and 33 days following termination of tiotropium. A possible explanation for the minor differences in the hazard ratio and the confidence intervals for the endpoint of all-cause mortality (day 1440 compared to day 1470) is loss of the beneficial effects on airflow limitation and hyperinflation upon withdrawal of tiotropium. However, this may not be the case based on the total number of patients who died between 1 and 30 days of discontinuing study drug at any time during the trial (n=307), which indicates numerically more cases in the placebo group (placebo = 160, tiotropium = 147). Consideration of the additional 40 deaths (19 in the placebo group and 21 in the tiotropium group) reported beyond day 1470 yields a HR (95% CI) = 0.89 0.78, 1.00

(Table 9.1.1: 1) and provides further data indicating an absence of increased risk of a fatal event with tiotropium.

The most common causes of death by preferred term (including on-treatment and vital status from prematurely discontinued until day 1470) as adjudicated were: COPD exacerbation (150 on placebo, 120 on tiotropium), lung neoplasm malignant (70 on placebo, 78 on tiotropium), death (59 on placebo, 56 on tiotropium), and pneumonia (21 on placebo, 32 on tiotropium) (U08-3718-04, Table 15.3.2.2.1.1: 1). The associated rate differences (tiotropium – placebo) (95%CI) per 100 patient years were -0.28 (-0.57, 0.01), 0.07 (-0.15, 0.29), -0.03 (-0.22, 0.16) and 0.10 (-0.03, 0.23) respectively (data on file, Tables 3.20.28, 3.20.29, 3.20.30, 3.20.31).

The hazard ratios for deaths reported in >1% of patients by system organ class (SOC) are displayed in Table 9.1.2: 1. The proportion of patients reporting events was less in the tiotropium group in 4 of the 5 SOCs where an adjudicated cause of death was reported. For the SOC Respiratory Systems Disorders Other, which is primarily the SOC where lung cancers are reported, there were 82 deaths in the tiotropium group and 72 in the placebo group. The preferred terms used under the SOC General Disorders were death (referring to unknown cause), sudden cardiac death and sudden death.

Table 9.1.2: 1 Deaths reported in >1% of patients by SOC (adjudicated; on treatment mortality, including vital status until day 1470) - UPLIFT

System Organ Class	Placebo N = 3,006	Tiotropium N = 2,986	Tiotropium/Placebo	
	N (%)	N (%)	HR (95% CI)	p-value*
Respiratory disorders (lower)	140 (4.7)	131 (4.4)	0.85 (0.67, 1.08)	0.19
General disorders	70 (2.3)	57 (1.9)	0.75 (0.53, 1.06)	0.11
Respiratory disorders (other)**	72 (2.4)	82 (2.7)	1.04 (0.76, 1.42)	0.82
Neoplasms	41 (1.4)	36 (1.2)	0.80 (0.51, 1.25)	0.32
Cardiac disorders	25 (0.8)	24 (0.8)	0.88 (0.50, 1.55)	0.66

Hazard ratio is calculated using Cox regression with treatment as covariate; * p−value is calculated using log−rank test;
**predominantly lung cancer
Source data: see U08-3718-04, Table 15.3.2.2.2:7

9.1.3 On-treatment mortality

The total number of deaths from any cause during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tiotropium group. The hazard ratio (HR) for death from any cause (tiotropium/placebo) was 0.84 (95% CI = 0.73, 0.97) (Table 9.1.1: 1).

The cumulative frequency (Kaplan-Meier) estimate for death on-treatment by day 1470 is displayed in Figure 9.1.3: 1. It is evident from the figure that the two curves separate after 12 months with the separation being maintained until month 48. The figure and the hazard ratio indicated a lower incidence rate for death during treatment with tiotropium relative to the placebo group (U08-3718-04, Table 15.3.3: 2).

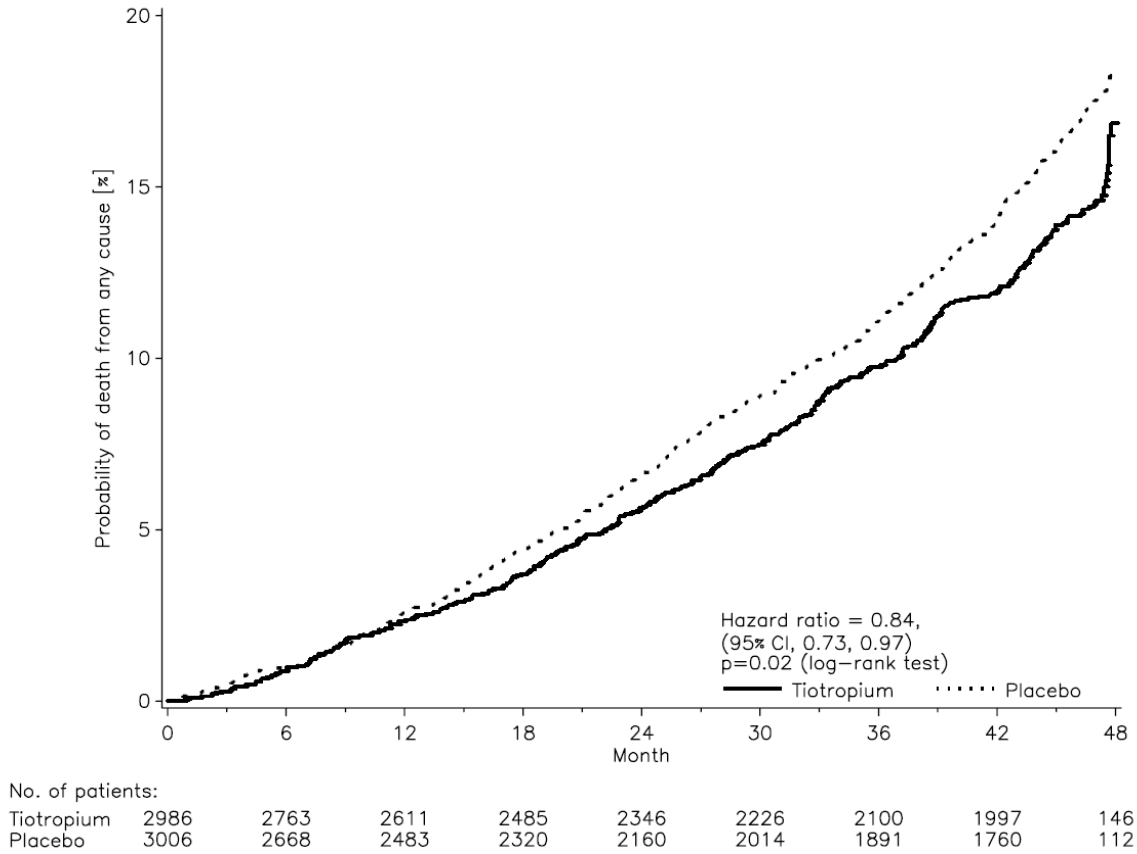


Figure 9.1.3: 1 Cumulative incidence rate (Kaplan-Meier) of the probability of all-cause mortality on-treatment (data censored at day 1470) - UPLIFT

Number of patients = number of patients at risk.
Source data: see U08-3718-04, Figure 15.3.2.2.2: 1.

The most common causes of death by preferred term (reported in >1% of patients in either treatment group) during study drug treatment as assessed by the adjudication committee were COPD exacerbation (121 on placebo, 103 on tiotropium), lung neoplasm malignant (66 on placebo, 73 on tiotropium) and death of unknown cause (36 on placebo, 29 on tiotropium) (U08-3718-04, Table 15.3.2.2.1.2:2). The associated rate differences (tiotropium – placebo) (95% CI) per 100 patient years were: -0.30 (-0.62, 0.03), 0.02 (-0.24, 0.27) and -0.11 (-0.28, 0.07), respectively (data on file, Tables 3.20.32, 3.20.33 and 3.20.34).

The HR (95% CI) for deaths in the SOC respiratory disorders (lower) (272 cases) was 0.85 (0.67, 1.08). The HR (95% CI) for deaths in the SOC cardiac disorders (50 cases) at day 1470 was 0.85 (0.49, 1.48).

Table 9.1.3: 1 Deaths reported in >1% of patients by SOC (adjudicated; on-treatment mortality) - UPLIFT

System Organ Class	Placebo N = 3,006	Tiotropium N = 2,986	Tiotropium/Placebo	
	N (%)	N (%)	HR (95% CI)	p-value*
Respiratory system disorders (lower)	141 (4.7)	131 (4.4)	0.85 (0.67, 1.08)	0.18
General disorders	71 (2.4)	58 (1.9)	0.75 (0.53, 1.06)	0.10
Respiratory system disorders (other)	73 (2.4)	83 (2.8)	1.03 (0.75, 1.41)	0.85
Neoplasms	45 (1.5)	37 (1.2)	0.72 (0.47, 1.12)	0.15
Cardiac disorders	26 (0.9)	24 (0.8)	0.85 (0.49, 1.48)	0.56

Hazard ratio is calculated using Cox regression with treatment as covariate; * P−value is calculated using log−rank test

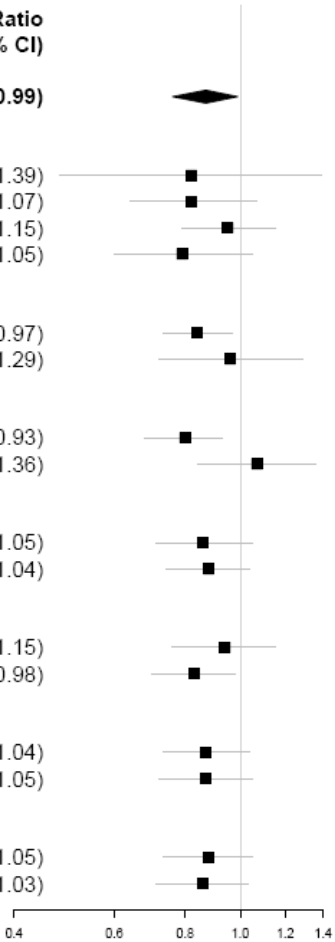
Source data: see U08-3718-04, Table 15.3.3: 10

9.1.4 Subgroup analysis – mortality

The mortality data with tiotropium versus placebo indicated no increased risk with tiotropium. In the UPLIFT study, subgroup analyses were conducted to further explore the risk for a fatal event and whether a specific population could be at either an increased or decreased risk. It is recognized that subgroup analyses need to be interpreted with caution given the reduced power in individual subgroups and reduced precision of the estimates as well as due to multiplicity. Subgroups according to basic demographics are displayed (age, gender, smoking status at baseline, baseline use of inhaled steroids, long-acting beta-agonists, inhaled steroids and long-acting beta-agonists, anticholinergics, GOLD stage and region). Figures 9.1.4: 1, 2 and 3 display the hazard ratios and 95% confidence intervals for all-cause mortality (including vital status (day 1440), including vital status (day 1470), and on-treatment). Additional subgroups for mortality can be found in the clinical trial report (U08-3718-04, Sections 15.3.2.2.3 and 15.3.3).

(a) Baseline characteristics and concomitant respiratory medications

	Placebo n/N	Tiotropium n/N	Hazard Ratio (95% CI)
Overall	**491/3006**	**430/2986**	**0.87 (0.76, 0.99)**
Age			
<55	30/382	25/384	0.82 (0.48, 1.39)
>=55, <65	126/1055	105/1054	0.82 (0.64, 1.07)
>=65, <75	223/1198	215/1208	0.95 (0.79, 1.15)
>=75	112/371	85/340	0.79 (0.60, 1.05)
Gender			
Male	397/2222	345/2251	0.84 (0.73, 0.97)
Female	94/784	85/735	0.96 (0.72, 1.29)
Smoking*			
Former	358/2108	293/2112	0.80 (0.68, 0.93)
Current	133/898	137/874	1.07 (0.84, 1.36)
LABA			
No	213/1198	184/1190	0.86 (0.71, 1.05)
Yes	278/1808	246/1796	0.88 (0.74, 1.04)
ICS			
No	192/1146	180/1146	0.94 (0.76, 1.15)
Yes	299/1860	250/1840	0.83 (0.70, 0.98)
LABA/ICS			
No	272/1544	236/1522	0.87 (0.73, 1.04)
Yes	219/1462	194/1464	0.87 (0.72, 1.05)
Anticholinergics			
No	253/1656	220/1620	0.88 (0.73, 1.05)
Yes	238/1350	210/1366	0.86 (0.71, 1.03)



n: number of patients with events
N: total number of patients
*p<0.05 for test of subgroup by treatment interaction

(b) GOLD stage* and regions

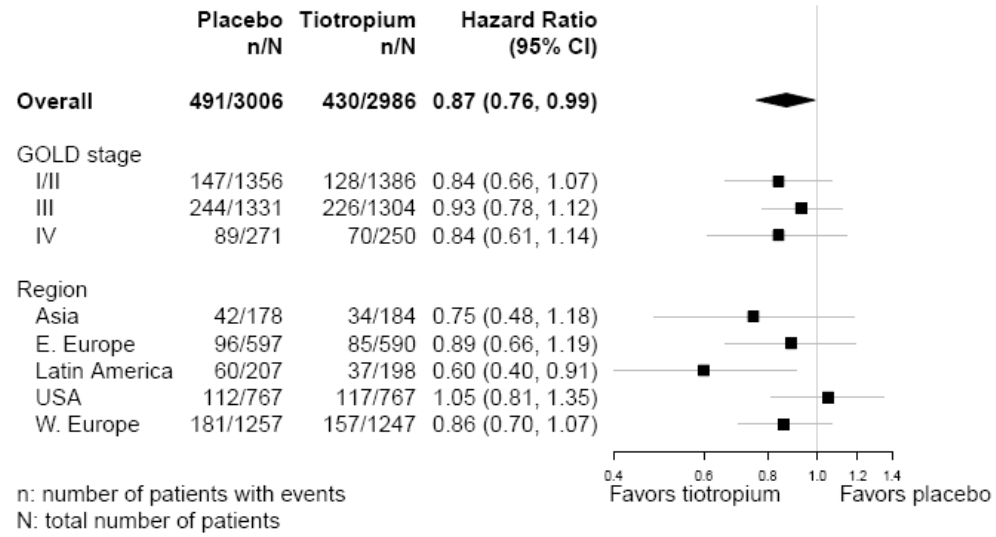
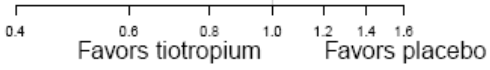


Figure 9.1.4: 1 Hazard ratio and 95% CI (tiotropium/placebo) for all-cause fatal events (on-treatment and vital status until day 1440) according to (a) baseline characteristics and concomitant respiratory medications and (b) GOLD stage and regions - UPLIFT

*Including 3 patients with GOLD stage I disease.
Source data: data on file, Tables 7a and 7b

(a) Baseline characteristics and concomitant respiratory medications

	Placebo n/N	Tiotropium n/N	Hazard Ratio (95% CI)
Overall	**495/3006**	**446/2986**	**0.89 (0.79, 1.02)**
Age			
<55	30/382	27/284	0.88 (0.53, 1.49)
>=55, <65	127/1055	108/1054	0.84 (0.65, 1.08)
>=65, <75	224/1198	225/1208	0.99 (0.82, 1.19)
>=75	114/371	86/340	0.79 (0.60, 1.04)
Gender			
Male	400/2222	357/2251	0.86 (0.75, 1.00)
Female	95/784	89/735	1.00 (0.75, 1.33)
Smoking*			
Former	360/2108	304/2112	0.82 (0.71, 0.96)
Current	135/898	142/874	1.09 (0.86, 1.38)
LABA			
No	216/1198	188/1190	0.86 (0.71, 1.05)
Yes	279/1808	258/1796	0.92 (0.77, 1.09)
ICS			
No	194/1146	184/1146	0.95 (0.77, 1.16)
Yes	301/1860	262/1840	0.86 (0.73, 1.02)
LABA/ICS			
No	275/1544	241/1522	0.88 (0.74, 1.04)
Yes	220/1462	205/1464	0.91 (0.76, 1.11)
Anticholinergics			
No	255/1656	227/1620	0.90 (0.75, 1.08)
Yes	240/1350	219/1366	0.88 (0.74, 1.06)



n: number of patients with events
N: total number of patients
*p<0.05 for test of subgroup by treatment interaction

(b) GOLD stage* and regions

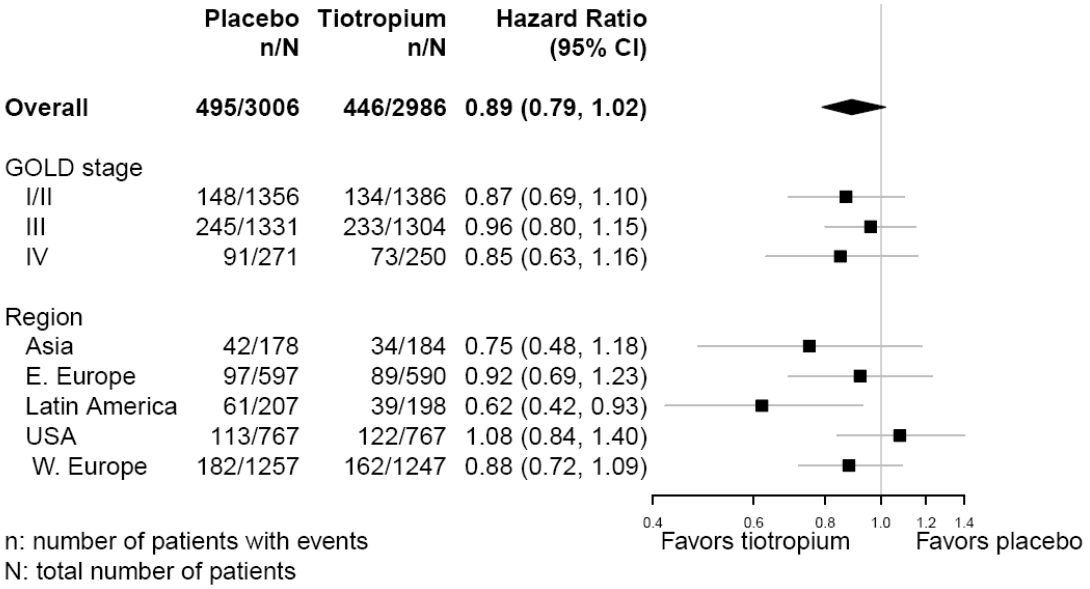
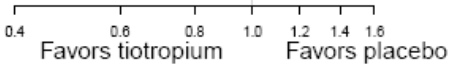


Figure 9.1.4: 2 Hazard ratio and 95% CI (tiotropium/placebo) for all-cause fatal events (on-treatment and vital status until day 1470) according to (a) baseline characteristics and concomitant respiratory medications and (b) GOLD stage and regions - UPLIFT

*Including 3 patients with GOLD stage I disease.
Source data: data on file, Tables 8a and 8b

(a) Baseline characteristics and concomitant respiratory medications

	Placebo n/N	Tiotropium n/N	Hazard Ratio (95% CI)
Overall	**411/3006**	**381/2986**	**0.84 (0.73, 0.97)**
Age			
<55	26/382	24/384	0.82 (0.47, 1.43)
>=55, <65	108/1055	96/1054	0.79 (0.60, 1.04)
>=65, <75	191/1198	194/1208	0.95 (0.78, 1.17)
>=75	86/371	67/340	0.69 (0.50, 0.95)
Gender			
Male	335/2222	310/2251	0.84 (0.72, 0.98)
Female	76/784	71/735	0.84 (0.61, 1.16)
Smoking			
Former	299/2108	256/2112	0.77 (0.65, 0.91)
Current	112/898	125/874	1.04 (0.80, 1.34)
LABA			
No	178/1198	168/1190	0.87 (0.70, 1.08)
Yes	233/1808	213/1796	0.82 (0.68, 0.99)
ICS			
No	169/1146	158/1146	0.87 (0.70, 1.08)
Yes	242/1860	223/1840	0.83 (0.69, 0.99)
LABA/ICS			
No	233/1544	211/1522	0.84 (0.70, 1.01)
Yes	178/1462	170/1464	0.85 (0.69, 1.05)
Anticholinergics			
No	221/1656	199/1620	0.87 (0.72, 1.05)
Yes	190/1350	182/1366	0.80 (0.65, 0.98)



n: number of patients with events
N: total number of patients

(b) GOLD stage* and region

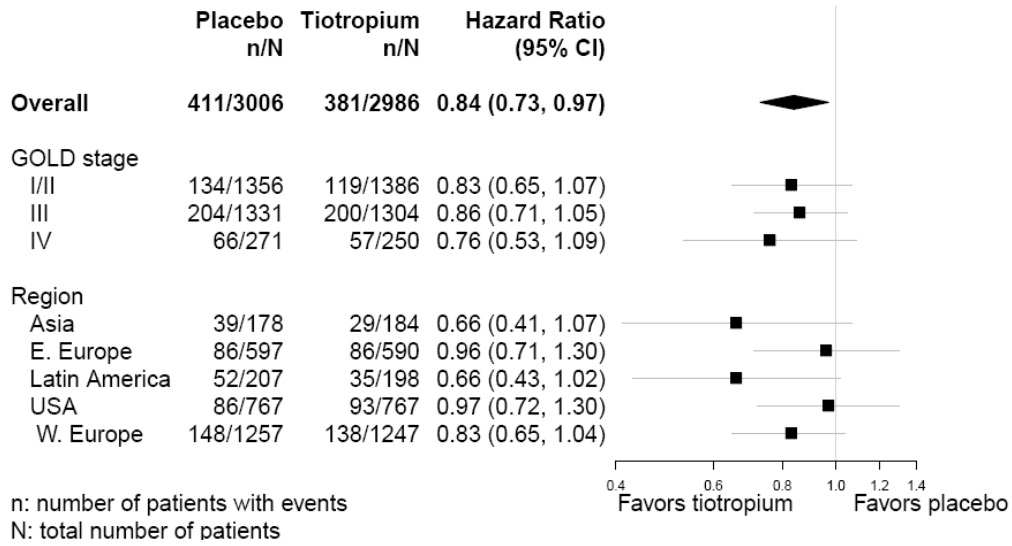


Figure 9.1.4: 3 Hazard ratio and 95% CI (tiotropium/placebo) for all-cause fatal events (on-treatment) according to baseline subgroups (without censoring) according to (a) baseline characteristics and concomitant respiratory medications and (b) GOLD stage and region - UPLIFT

*Including 3 patients with GOLD stage I disease.
Source data: data on file, Table 9a and 9b

A review of the analysis indicated that there was a general consistency across subgroups, which showed no increased risk for fatal events with tiotropium HandiHaler®.

9.2 UPLIFT: OVERVIEW OF ADVERSE EVENTS

Adverse events and serious adverse events were experienced by 92% and 51% of patients during the treatment period (including last day of study drug + 30 days), respectively. Non-serious adverse events and non-fatal serious adverse events were collected for the treatment period only.

Table 9.2: 1 Summary of adverse events in placebo and tiotropium groups during the treatment period (including last day of study drug + 30 days) - UPLIFT

	Placebo	**Tiotropium**	**Total**
	N (%)	**N (%)**	**N (%)**
Number of patients	3006 (100.0)	2986 (100.0)	5992 (100.0)
Any adverse events	2774 (92.3)	2764 (92.6)	5538 (92.4)
Adverse events related to study drug	233 (7.8)	306 (10.2)	539 (9.0)
Adverse events leading to discontinuation	735 (24.5)	618 (20.7)	1353 (22.6)
Serious adverse events	1509 (50.2)	1540 (51.6)	3049 (50.9)
Fatal adverse events	411 (13.7)	381 (12.8)	792 (13.2)

Source data: see U08-3718-04, Table 12.2.1: 1

Most patients (5,538 (92.4%)) experienced at least one adverse event during the trial, and the proportion of patients reporting adverse events was similar in both treatment groups. Seven of the 10 most common adverse events were due to respiratory causes (Table 9.2: 2). The most common adverse events were COPD exacerbations (65% of patients), pneumonia (14% of patients), and dyspnea (14% of patients). Given the duration of the trial and differences in discontinuation rates, comparisons between study drugs are most appropriately assessed by examination of incidence rates that are adjusted for time at risk. The RDs (95% CI) for the aforementioned events were -7.45 (-10.1, -4.82) [exacerbations], -0.20 (-0.88, 0.48) [pneumonia], and -1.39 (-2.06, -0.73) [dyspnea], respectively.

Table 9.2: 2 Frequency [N(%)] of patients, incidence rates, rate differences (tiotropium - placebo) per 100 patient years for adverse events (preferred term) occurring with an incidence >3% during the treatment period (including last day of study drug + 30 days) - UPLIFT

	Placebo N=3,006		Tiotropium N=2,986		Tiotropium - Placebo
	N (%)	IR[2]	N (%)	IR[2]	RD (95% CI)
Total with adverse events	2774 (92.3)	145.0	2764 (92.6)	128.8	-16.2 (-23.4, -8.95)*
COPD exacerbations	1986 (66.1)	45.5	1934 (64.8)	38.1	-7.45 (-10.1, -4.82)*
Pneumonia	418 (13.9)	5.14	433 (14.5)	4.94	-0.20 (-0.88, 0.48)
Dyspnea	443 (14.7)	5.49	364 (12.2)	4.09	-1.39 (-2.06, -0.73)*
Nasopharyngitis	324 (10.8)	4.06	373 (12.5)	4.33	0.27 (-0.35, 0.90)
Upper respiratory tract infection	290 (9.6)	3.57	298 (10.0)	3.38	-0.19 (-0.75, 0.38)
Hypertension	284 (9.4)	3.45	275 (9.2)	3.08	-0.38 (-0.92, 0.16)
Bronchitis	233 (7.8)	2.82	232 (7.8)	2.57	-0.24 (-0.73, 0.25)
Cough	213 (7.1)	2.57	238 (8.0)	2.64	0.08 (-0.41, 0.56)
Back pain	188 (6.3)	2.25	198 (6.6)	2.18	-0.07 (-0.51, 0.37)
Urinary tract infections	169 (5.6)	2.00	190 (6.4)	2.08	0.08 (-0.34, 0.50)
Sinusitis	160 (5.3)	1.90	194 (6.5)	2.14	0.24 (-0.19, 0.66)
Influenza	158 (5.3)	1.87	158 (5.3)	1.73	-0.14 (-0.54, 0.25)
Headache	136 (4.5)	1.61	171 (5.7)	1.88	0.28 (-0.11, 0.67)
Oedema	130 (4.3)	1.52	145 (4.9)	1.57	0.05 (-0.32, 0.42)
Constipation	111 (3.7)	1.29	151 (5.1)	1.63	0.34 (-0.01, 0.70)
Diarrhoea	122 (4.1)	1.43	138 (4.6)	1.50	0.06 (-0.29, 0.42)
Cataract	123 (4.1)	1.45	120 (4.0)	1.30	-0.15 (-0.49, 0.20)
Atrial Fibrillation	113 (3.8)	1.32	119 (4.0)	1.28	-0.04 (-0.37, 0.30)
Mouth dry	80 (2.7)	0.93	152 (5.1)	1.68	0.75 (0.41, 1.08)*
Depression	98 (3.3)	1.14	131 (4.4)	1.42	0.28 (-0.05, 0.61)
Insomnia	91 (3.0)	1.06	131 (4.4)	1.42	0.36 (0.03, 0.69)*
Arthralgia	94 (3.1)	1.10	125 (4.2)	1.36	0.26 (-0.07, 0.59)
Benign prostatic hyperplasia	96 (3.2)	1.12	122 (4.1)	1.32	0.20 (-0.12, 0.53)
Rhinitis	112 (3.7)	1.32	101 (3.4)	1.09	-0.23 (0.55, 0.10)
Abdominal pain	96 (3.2)	1.12	113 (3.8)	1.22	0.10 (-0.21, 0.42)
Respiratory failure	120 (4.0)	1.39	88 (2.9)	0.94	-0.45 (-0.77, -0.14)*
Hypercholesterolemia	97 (3.2)	1.13	104 (3.5)	1.12	-0.01 (-0.32, 0.30)
Nausea	94 (3.1)	1.09	93 (3.1)	1.00	-0.09 (-0.39, 0.21)
Dizziness	81 (2.7)	0.94	103 (3.4)	1.11	0.17 (-0.13, 0.47)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; *p<0.05
Source data: data on file, Table 3.17.1.4.1.1

Expected adverse events associated with tiotropium that could be explained by anticholinergic pharmacology were observed. The most frequent of these events included dry mouth, constipation, benign prostatic hyperplasia, sinusitis, nasopharyngitis and cough. While the incidence of urinary tract infection exceeded that of the placebo group, the risk difference was only 0.08 cases per 100 patient years (Table 9.2: 2). Less commonly reported were intestinal obstruction, gastroesophageal reflux disease, dysphonia, epistaxis, rash, pruritis, dysuria and urinary retention. Several other terms previously considered associated with anticholinergic effects showed no imbalances in the safety database (i.e. atrial

fibrillation, palpitations, tachycardia, bronchospasm, glaucoma, dysphagia, oral candidiasis, angioedema, urticaria or dental caries). There was an increase in atrial tachycardia although the event was reported at a low rate. Further details of these and other events can be found in Table 15.3.2.1.1.1: 7 of the clinical trial report (U08-3718-04).

9.3 UPLIFT: SERIOUS ADVERSE EVENTS

Other than lung cancer, serious adverse events reported by >1% of patients in either treatment group were either cardiac or respiratory in nature (Table 9.3: 1). The incidence of serious adverse events for the system organ classes (SOC) cardiac and respiratory system disorders (lower) was lower with tiotropium relative to the placebo group. On a preferred term basis, this included reduced incidence rates for the terms cardiac failure congestive, COPD exacerbation, dyspnea, myocardial infarction and respiratory failure.

Table 9.3: 1 Incidence rates and rate differences (tiotropium – placebo) per 100 patient years of patients experiencing serious adverse events[1] reported by >1% of patients in any treatment group according to preferred term and organ class during the treatment period (from first to last day of study drug + 30 days) - UPLIFT

	Placebo N=3,006		**Tiotropium N=2,986**		**Tiotropium - Placebo**
	N (%)	**IR**	**N (%)**	**IR**	**RD (95% CI)**
Cardiac SOC	350 (11.6)	4.21	322 (10.8)	3.56	-0.65 (-1.24, -0.07)*
Angina	31 (1.0)	0.36	48 (1.6)	0.51	0.16 (-0.04, 0.35)
Atrial fibrillation	67 (2.2)	0.77	69 (2.3)	0.74	-0.04 (-0.29, 0.22)
Cardiac failure	42 (1.4)	0.48	57 (1.9)	0.61	0.12 (-0.09, 0.34)
Cardiac failure congestive	42 (1.4)	0.48	27 (0.9)	0.29	-0.20 (-0.38, -0.02)*
Coronary artery disease	32 (1.1)	0.37	20 (0.7)	0.21	-0.16 (-0.31, 0.00)
Myocardial infarction	84 (2.8)	0.97	65 (2.2)	0.69	-0.28 (-0.55, -0.01)*
Respiratory (lower) SOC	985 (32.8)	13.5	911 (30.5)	11.3	-2.16 (-3.27, -1.04)*
Bronchitis	27 (0.9)	0.31	35 (1.2)	0.37	0.06 (-0.11, 0.23)
COPD exacerbation	742 (24.7)	9.70	688 (23.0)	8.19	-1.51 (-2.44, -0.58)*
Dyspnea	54 (1.8)	0.62	36 (1.2)	0.38	-0.24 (-0.45, -0.03)*
Pneumonia	290 (9.6)	3.46	296 (9.9)	3.28	-0.18 (-0.73, 0.36)
Respiratory failure	113 (3.8)	1.31	85 (2.8)	0.90	-0.40 (-0.71, -0.09)*

[1]excluding lung cancer, terms listed are MedDRA preferred terms as per tiotropium project standards; n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; *p<0.05
Source data: data on file, Table 3.17.1.4.1.2 and U08-3718-04, Table 15.3.2.1.1.2: 2

Incidence rates and rate differences for serious adverse events by treatment and system organ class are presented in Table 9.3: 2 below (see Section 6.4.4 for description of modifications to MedDRA SOC used in the analyses).

Table 9.3: 2 Incidence rates and rate differences (tiotropium – placebo) per 100 patient years of patients experiencing serious adverse events by system organ system during the treatment period (from first to last day of study drug + 30 days) - UPLIFT

	Placebo N=3,006		**Tiotropium N=2,986**		**Tiotropium - Placebo**
	N (%)	**IR**	**N (%)**	**IR**	**RD (95% CI)**
Total with serious adverse events	1509 (50.2)	23.7	1540 (51.6)	22.5	-1.24 (-2.88, 0.40)
Respiratory system (Lower)	985 (32.8)	13.5	911 (30.5)	11.3	-2.16 (-3.27, -1.04)*
Cardiac	350 (11.6)	4.21	322 (10.8)	3.56	-0.65 (-1.24, -0.07)*
Neoplasms	170 (5.7)	1.99	197 (6.6)	2.14	0.15 (-0.27, 0.57)
Gastrointestinal	167 (5.6)	1.97	171 (5.7)	1.86	-0.11 (-0.52, 0.30)
Respiratory system (Other)	156 (5.2)	1.80	170 (5.7)	1.82	0.02 (-0.38, 0.41)
Nervous system	138 (4.6)	1.61	136 (4.6)	1.47	-0.15 (-0.51, 0.22)
Infections and infestations	118 (3.9)	1.37	127 (4.3)	1.37	0.00 (-0.35, 0.34)
Injury, poisoning & procedural complications	100 (3.3)	1.16	140 (4.7)	1.52	0.36 (0.02, 0.69)*
General	117 (3.9)	1.36	120 (4.0)	1.28	-0.07 (-0.41, 0.26)
Vascular	96 (3.2)	1.11	117 (3.9)	1.26	0.14 (-0.17, 0.46)
Musculoskeletal & connective tissue	68 (2.3)	0.79	87 (2.9)	0.93	0.15 (-0.12, 0.42)
Renal and urinary	57 (1.9)	0.66	66 (2.2)	0.70	0.05 (-0.19, 0.29)
Metabolism and nutrition	50 (1.7)	0.58	44 (1.5)	0.47	-0.11 (-0.32, 0.10)
Hepatobiliary	42 (1.4)	0.48	38 (1.3)	0.40	-0.08 (-0.27, 0.12)
Respiratory system (Upper)	37 (1.2)	0.43	41 (1.4)	0.44	0.01 (-0.18, 0.20)
Psychiatric	36 (1.2)	0.41	26 (0.9)	0.28	-0.14 (-0.31, 0.03)
Reproductive system & breast	28 (0.9)	0.32	32 (1.1)	0.34	0.02 (-0.15, 0.19)
Blood and lymphatic system	27 (0.9)	0.31	32 (1.1)	0.34	0.03 (-0.14, 0.20)
Eye	28 (0.9)	0.32	30 (1.0)	0.32	0.00 (-0.17, 0.16)
Surgical & medical procedures	14 (0.5)	0.16	22 (0.7)	0.23	0.07 (-0.06, 0.20)
Investigations	9 (0.3)	0.10	23 (0.8)	0.24	0.14 (0.02, 0.26)*
Skin & subcutaneous tissue	15 (0.5)	0.17	10 (0.3)	0.11	-0.07 (-0.17, 0.04)
Ear and labyrinth	12 (0.4)	0.14	11 (0.4)	0.12	-0.02 (-0.13, 0.08)
Congenital, familial and genetic	6 (0.2)	0.07	9 (0.3)	0.10	0.03 (-0.06, 0.11)
Endocrine	5 (0.2)	0.06	4 (0.1)	0.04	-0.01 (-0.08, 0.05)
Social circumstances	3 (0.1)	0.03	4 (0.1)	0.04	0.01 (-0.05, 0.06)
Immune system	2 (0.1)	0.02	4 (0.1)	0.04	0.02 (-0.03, 0.07)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; *p<0.05
All primary system organ classes are defined by MedDRA with the exception of Respiratory, thoracic and mediastinal disorders which has been divided into separate classes of Respiratory system disorders, Lower, Upper, and Other.
Source data: data on file, Table 3.17.1.4.1.2 and U08-3718-04, Table 15.3.2.1.1.2: 1

The displays of serious adverse events are consistent with the known safety profile of tiotropium and do not indicate additional safety signals.

9.4 UPLIFT: CARDIOVASCULAR ADVERSE EVENTS

The following section summarizes adverse events due to cardiac disorders, vascular disorders, and stroke.

The tables displayed in this section include an abbreviated list of pooled terms representing the cardiovascular terms and categories of particular interest. The selection was based on clinical categories that are of public health interest or where there have been possible pathophysiologic associations from either previous published reports or hypothetical biologic mechanisms. Individual patients may be represented in multiple categories, but a patient is only represented once within a category or at the SOC level (i.e. Cardiac Disorder SOC total). For example, all patients reported to have a myocardial infarction would be counted with the pooled term "ischemic heart disease".

Overall, there were 1,147 patients with at least one cardiac adverse event and 959 patients with at least one vascular adverse event (Table 9.4: 1). The RD (95% CI) for any cardiac event (tiotropium - placebo) was -0.78 (-1.59, 0.03) and for any vascular event was -0.25 (-0.99, 0.49). Tiotropium was not associated with an increased risk for a cardiac adverse event or a vascular adverse event.

Table 9.4: 1 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for cardiac and vascular adverse events - UPLIFT

	Placebo N=3,006		**Tiotropium N=2,986**		**Tiotropium – Placebo RD (95% CI)**
	N	**IR**	**N**	**IR**	
Cardiac disorders (SOC)	582	7.37	565	6.59	-0.78 (-1.59, 0.03)
Atrial fibrillation/flutter	113	1.32	119	1.28	-0.04 (-0.37, 0.30)
Cardiac arrest	23	0.26	16	0.17	-0.09 (-0.23, 0.04)
Cardiac failure	215	2.53	186	2.01	-0.52 (-0.97, -0.08)*
Ischemic heart disease[+]	217	2.58	212	2.33	-0.25 (-0.72, 0.21)
Myocardial infarction	85	0.98	67	0.71	-0.27 (-0.54, 0.00)
Palpitations	40	0.46	43	0.46	-0.00 (-0.20, 0.20)
Supraventricular tachycardia	18	0.21	27	0.29	0.08 (-0.06, 0.22)
Tachycardia (non-ventricular)	43	0.49	41	0.44	-0.06 (-0.26, 0.14)
Ventricular tachycardia/fibrillation	19	0.22	12	0.13	-0.09 (-0.21, 0.03)
Vascular disorders (SOC)	471	5.95	488	5.70	-0.25 (-0.99, 0.49)
Aneurysm	32	0.37	33	0.35	-0.02 (-0.19, 0.16)
Hypertension	310	3.80	293	3.30	-0.50 (-1.07, 0.06)
Stroke	80	0.93	82	0.88	-0.05 (-0.33, 0.23)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval) per 100 patient years of time at risk; terms used are composed of multiple MedDRA preferred terms

[+]categorized in Appendix 17.1 under the category angina/ischemia/MI expanded; *p<0.05

Source data: data on file, Tables 3.17.1.4.1.1, 3.17.1.5.1.1 and 3.17.1.6.1.1

9.4.1 Cardiovascular serious adverse events

Serious adverse events in the cardiac SOC were experienced by 672 patients (11.2% of the population). Serious adverse events in the vascular SOC were experienced by 213 patients (3.6% of the population (Table 9.4.1: 1). An abbreviated list representing the categories and terms of particular interest is provided within the text (Table 9.4.1: 1).

Table 9.4.1: 1 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for cardiac and vascular serious adverse events - UPLIFT

	Placebo N= 3,006		**Tiotropium N= 2,986**		**Tiotropium – Placebo RD (95% CI)**
	N	**IR**	**N**	**IR**	
Cardiac disorders (SOC)	350	4.21	322	3.56	-0.65 (-1.24, -0.07)*
Atrial fibrillation/flutter	67	0.77	69	0.74	-0.04 (-0.29, 0.22)
Cardiac arrest	22	0.25	16	0.17	-0.08 (-0.22, 0.05)
Cardiac failure	134	1.56	121	1.29	-0.26 (-0.61, 0.08)
Ischemic heart disease[+]	149	1.75	130	1.40	-0.34 (-0.71, 0.03)
Myocardial infarction	84	0.97	65	0.69	-0.28 (-0.55, -0.01)*
Palpitations	3	0.03	4	0.04	0.01 (-0.05, 0.06)
Supraventricular tachycardia	8	0.09	12	0.13	0.04 (-0.06, 0.13)
Tachycardia (non-ventricular)	6	0.07	4	0.04	-0.03 (-0.10, 0.04)
Ventricular tachycardia/fibrillation	16	0.18	10	0.11	-0.08 (-0.19, 0.03)
Vascular disorders (SOC)	96	1.11	117	1.26	0.14 (-0.17, 0.46)
Aneurysm	21	0.24	20	0.21	-0.03 (-0.17, 0.11)
Hypertension	17	0.19	13	0.14	-0.06 (-0.18, 0.06)
Stroke	63	0.73	66	0.70	-0.02 (-0.27, 0.22)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval) per 100 patient years of time at risk; terms used are composed of multiple MedDRA preferred terms

[+]categorized in Appendix 17.1 under the category angina/ischemia/MI expanded; *=p<0.05

Source data: data on file, Tables 3.17.1.4.1.2, 3.17.1.6.1.2 and 3.17.1.5.1.2

9.4.2 Fatal cardiovascular events

There were 156 and 21 fatal cases in the cardiac and vascular SOCs respectively, representing 2.6% and 0.4% of the population. An abbreviated list of pooled terms of particular interest is provided within the text (Table 9.4.2: 1).

The incidence rate for a fatal cardiac event was lower with tiotropium (RD (95% CI) = -0.24 (-0.52, 0.03)) and showed a trend for a reduced rate for a fatal vascular event (RD (95% CI) = -0.11 (-0.21, -0.01)). For myocardial infarction and stroke, the RDs (95% CI) were -0.10 (-0.23, 0.03) and -0.01 (-0.12, 0.10) respectively.

The preferred terms cardiac death (tiotropium n= 0, placebo n= 1), sudden cardiac death (tiotropium n= 1, placebo n= 2) and sudden death (tiotropium n= 10, placebo n= 11) are listed in MedDRA under the SOC General and Administrative Site Disorders and are not listed in Table 9.4.2: 1. These preferred terms were reported infrequently and showed no evidence of

an increased risk with tiotropium. For sudden death, the RD (95% CI) was -0.02 (-0.12, 0.08).

Table 9.4.2: 1 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for cardiac and vascular fatal adverse events - UPLIFT

	Placebo N= 3,006		**Tiotropium N= 2,986**		**Tiotropium – Placebo RD (95% CI)**
	N	**IR**	**N**	**IR**	
Cardiac disorders (SOC)	86	0.99	70	0.74	-0.24 (-0.52, 0.03)
Atrial fibrillation/flutter	2	0.02	0	0.00	-0.02 (-0.05, 0.01)
Cardiac arrest	19	0.22	13	0.14	-0.08 (-0.20, 0.04)
Cardiac failure	37	0.42	41	0.43	0.01 (-0.18, 0.20)
Ischemic heart disease	28	0.32	15	0.16	-0.16 (-0.31, -0.02)*
Myocardial infarction	22	0.25	14	0.15	-0.10 (-0.23, 0.03)
Palpitations	0	0	0	0	0
Supraventricular tachycardia	1	0.01	0	0.00	-0.01 (-0.03, 0.01)
Tachycardia (non-ventricular)	0	0	0	0	0
Ventricular tachycardia/fibrillation	2	0.02	2	0.02	-0.00 (-0.04, 0.04)
Vascular disorders (SOC)	15	0.17	6	0.06	-0.11 (-0.21, -0.01)*
Aneurysm	5	0.06	3	0.03	-0.03 (-0.09, 0.04)
Hypertension	1	0.01	0	0.00	-0.01 (-0.03, 0.01)
Stroke	12	0.14	12	0.13	-0.01 (-0.12, 0.10)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval) per 100 patient years of time at risk; terms used are composed of multiple MedDRA preferred terms

[+]categorized in Appendix 17.1 under the category angina/ischemia/MI expanded; *=p<0.05

Source data: data on file, Tables 3.17.1.4.1.3, 3.17.1.6.1.3 and 3.17.1.5.1.3

9.4.3 Stroke

As previously noted, in March 2008 the U.S. Food and Drug Administration (FDA) issued an Early Communication on their website to provide patients and health care professionals with emerging drug safety information about a possible increased risk of stroke observed in a retrospective pooled analysis of completed clinical trials among patients taking tiotropium. Therefore, an analysis of stroke, including incidence rate, Kaplan Meier estimates and Cox regression were carried out to analyze mortality from stroke, on-treatment adverse events and serious adverse events reported as stroke. The term "stroke" in the analysis represents a pooled safety endpoint of preferred terms indicative of stroke (Appendix 17.1). The methodology and terms used in the analysis that was provided by BI to the FDA that led to the March March 2008 has been applied to the UPLIFT trial database.

The analysis of the UPLIFT data showed that there was no evidence for an increased risk for stroke overall as well as for stroke considered as a serious adverse event, which constituted the majority of events (Tables 9.4: 1 and 9.4.1: 1). No evidence of an increased risk of death from stroke was observed. When including vital status follow-up (4 years plus 30 days) from investigator reported cases, there were 14 fatal strokes in tiotropium patients and 14 in

placebo patients (Table 9.4. 3: 1). For on-treatment fatal events, there were 12 tiotropium patients and 12 placebo patients. There was no evidence of increased risk when adjudicated fatal stroke events were considered.

Table 9.4.3: 1 Incidence rates and rate differences (tiotropium – placebo) per 100 patient years for patients experiencing stroke events (all adverse events, serious adverse events and fatal events) - UPLIFT

	Placebo (N = 3,006)		**Tiotropium (N = 2,986)**		**Tiotropium/Placebo**
	N	**IR**	**N**	**IR**	**RD (95% CI)**
Adverse Event	80	0.93	82	0.88	-0.05 (-0.33, 0.23)
Serious Adverse Event	63	0.73	66	0.70	-0.02 (-0.27, 0.22)
Fatal Events – Investigator judgement					
Vital status, day 1470	14	0.13	14	0.13	−0.00 (−0.10, 0.09)
Vital status, day 1440	14	0.13	14	0.13	−0.00 (−0.09, 0.09)
On-treatment	12	0.14	12	0.13	-0.01 (-0.12, 0.10)
Fatal Events – Adjudication					
Vital status, day 1470	17	0.15	14	0.13	−0.03 (−0.13, 0.07)
Vital status, day 1440	17	0.16	14	0.13	−0.03 (−0.13, 0.07)
On-treatment	13	0.15	12	0.13	-0.02 (-0.13, 0.07)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk
Source data: see U08-3718-04, Tables 15.3.2.1.1.3:1, 15.3.2.1.1.3:3, 15.3.2.2.1.2: 3, 15.3.2.2.1.1: 5

Table 9.4.3: 2 lists all preferred terms included in the analysis of stroke as reported by investigators, as well as the associated incidence rates and rate differences.

Table 9.4.3: 2 Incidence rates, rate differences (tiotropium – placebo) per 100 patient years for stroke (any seriousness) - UPLIFT

	Placebo N= 3,006		Tiotropium N= 2,986		Tiotropium – Placebo
	N	IR	N	IR	**RD (95 % CI)**
Stroke (pooled term)	80	0.93	82	0.88	-0.05 (-0.33, 0.23)
Amaurosis fugax	2	0.02	0	0.00	-0.02 (-0.05, 0.01)
Brain stem infarction	0	0.00	1	0.01	0.01 (-0.1, 0.03)
Carotid artery occlusion	5	0.06	5	0.05	0.00 (-0.07, 0.06)
Cerebral haematoma	1	0.01	0	0.00	-0.01 (-0.03, 0.01)
Cerebral haemorrhage	6	0.07	3	0.03	-0.04 (-0.10, 0.03)
Cerebral infarction	9	0.10	8	0.08	-0.02 (-0.11, 0.07)
Cerebral ischaemia	2	0.02	5	0.05	0.03 (-0.03, 0.09)
Cerebrovascular accident	30	0.34	29	0.31	-0.04 (-0.20, 0.13)
Embolic stroke	0	0.00	1	0.01	0.01 (-0.01, 0.03)
Haemorrhage intracranial	0	0.00	1	0.01	0.01 (-0.01, 0.03)
Haemorrhagic stroke	0	0.00	1	0.01	0.01 (-0.01, 0.03)
Intracranial haematoma	1	0.01	1	0.01	0.00 (-0.03, 0.03)
Ischaemic cerebral infarction	2	0.02	0	0.00	-0.02 (-0.05, 0.01)
Ischaemic stroke	3	0.03	8	0.08	0.05 (-0.02, 0.12)
Lacunar infarction	2	0.02	0	0.00	-0.02 (-0.05, 0.01)
Ruptured cerebral aneurysm	1	0.01	0	0.00	-0.01 (-0.03, 0.01)
Subarachnoid haemorrhage	0	0.00	1	0.01	0.01 (-0.01, 0.03)
Thalamic infarction	0	0.00	1	0.01	0.01 (-0.01, 0.03)
Transient ischaemic attack	23	0.26	27	0.29	0.02 (-0.13, 0.18)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk
Source data: data on file, Table 3.17.1.5.1.1

9.4.4 Major adverse cardiovascular events

The incidence rates and rate differences for the composite cardiovascular (CV) endpoint for major adverse cardiovascular events are displayed in Table 9.4.4: 1. There was a lower incidence rate for a major adverse cardiovascular event and a fatal cardiovascular event in the tiotropium group relative to the placebo group. A further analysis was performed that includes the non-specific preferred term "death" assuming that the cause of death in all cases was cardiovascular. For this expanded endpoint, the RD (95%CI) was -0.33 (-0.70, 0.03).

Table 9.4.4: 1 Incidence rates, rate difference (tiotropium - placebo) per 100 patient years for major cardiovascular (CV) events - UPLIFT

	Placebo N= 3,006		Tiotropium N= 2,986		Tiotropium – Placebo
	N	**IR**	**N**	**IR**	**RD (95 % CI)**
Major adverse CV event	246	2.89	208	2.25	-0.64 (-1.12, -0.17)*
Fatal CV event	124	1.42	98	1.04	-0.39 (-0.71, -0.06)*

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; *p<0.05

Source data: data on file, Table 3.17.1.7.3

In summary, an analysis of cardiovascular adverse event reporting in the UPLIFT trial demonstrates a pattern indicating no increased risk for cardiovascular event, including those that were serious and fatal.

9.5 UPLIFT: ADVERSE EVENTS LEADING TO TREATMENT DISCONTINUATION

Of the 5,992 patients treated, 4,383 (73%) completed 2 years, 3,891 (65%) completed 3years, and 3569 (60%) completed ≥45 months. A higher proportion of patients failed to complete ≥45 months of treatment in the placebo group (44.6%) compared with the tiotropium group (36.2%, $p<0.001$). The majority of discontinuations were due to adverse events.

A total of 1353 (22.6%) patients experienced adverse events that led to treatment discontinuation. Table 15.3.2.1.1.1: 4 of the clinical trial report (U08-3718-04) displays the individual adverse events by system organ class and preferred term for the 735 (24.5%) patients in the placebo group and the 618 (20.7%) patients in the tiotropium group who discontinued treatment due to an adverse event. The reasons were varied; however, the most common reasons for premature discontinuation from treatment were due to respiratory events (lower or other system organ class) or cardiac events. Fewer patients treated with tiotropium 291 (9.7%) discontinued due to a lower respiratory adverse event compared to patients in the placebo group 412 (13.7%).

9.6 UPLIFT: SERIOUS AND RELATED ADVERSE EVENTS

Events reported as related to treatment were uncommon. A total of 34 patients (21 tiotropium and 13 placebo patients) experienced serious adverse events judged related to study medication by the investigator during the course of the trial. As displayed below in Table 9.6: 1, the events were listed events for tiotropium (i.e. expected as per the company core data sheet) in 13 cases. The most common listed events were atrial fibrillation and urinary retention. There were no unlisted events reported as related to tiotropium by more than a single patient.

Table 9.6: 1 Serious adverse events judged related to treatment by the investigator - UPLIFT

	Placebo N=3,006	Tiotropium N=2,986	Total
	N	N	N
Listed serious adverse events			
Atrial fibrillation	3	4	7
Urinary retention	2	4	6
Glaucoma	0	2	2
Dizziness	1	0	1
Epistaxis	0	1	1
Gastroesophageal reflux disease	0	1	1
Post-operative ileus	1	0	1
Supraventricular tachycardia	0	1	1
Total	**7**	**13**	**20**
Unlisted serious adverse events			
COPD exacerbation	3	1	4
Atrial flutter	0	1	1
Bladder neck obstruction	0	1	1
Hoarseness	1	0	1
Interstitial lung disease	0	1	1
Laryngitis	1	0	1
Myocardial infarction	0	1	1
Prostatic hyperplasia	0	1	1
Respiratory failure	1	0	1
Sudden death	0	1	1
Ventricular fibrillation	0	1	1
Total*	**6**	**8**	**14**

*Three patients (10680, 14044, 22815) experienced more than one event deemed related to study drug.
Listed adverse events=adverse drug reactions for tiotropium
Source data: see U08-3718-04, Table 12.3: 6

9.7 UPLIFT: SUMMARY OF SAFETY

A total of 921 deaths were reported for the full 4 year (1440 days) including vital status with a hazard ratio less than 1 for tiotropium relative to placebo (HR (95% CI) = 0.87 (0.76, 0.99). For the period of 4 years plus 30 days (1470 days) there were 941 deaths with a HR of 0.89 (0.79, 1.02). The most common causes of death (including on treatment and prematurely discontinued until day 1470) as adjudicated were: COPD exacerbation (150 on placebo, 120 on tiotropium), lung neoplasm malignant (70 on placebo, 78 on tiotropium), death (59 on placebo, 56 on tiotropium), and pneumonia (21 on placebo, 32 on tiotropium). The associated rate differences (tiotropium – placebo) (95%CI) per 100 patient years were -0.28 (-0.57, 0.01), 0.07 (-0.15, 0.29), -0.03 (-0.22, 0.16) and 0.10 (-0.03, 0.23) respectively (data on file, Tables 3.20.28-3.20.31).

The total number of deaths from any cause during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tiotropium group. The hazard ratio (HR) for death from any cause (tiotropium/placebo) was 0.84 (95% CI = 0.73, 0.97). The most common causes of death (reported in >1% of patients

in either treatment group) during study drug treatment as assessed by the adjudication committee were COPD exacerbation (121 on placebo, 103 on tiotropium), lung neoplasm malignant (66 on placebo, 73 on tiotropium) and death of unknown cause (36 on placebo, 29 on tiotropium). The associated rate differences (tiotropium – placebo) (95% CI) per 100 patient years were: -0.30 (-0.62, 0.03), 0.02 (-0.24, 0.27) and -0.11 (-0.28, 0.07), respectively.

Subgroup analyses of mortality indicated a general consistency of results and that there was no individual subgroup that could have unduly skewed the results or that appeared to be at an increased risk of death with tiotropium.

Most patients reported at least one adverse event during the course of the trial (92.4%) and serious adverse events were reported by approximately half the patients (50.9%). The most frequently reported adverse events were due to respiratory causes. COPD exacerbations were reported for 65% of patients, pneumonia for 14% and dyspnea for 14% of patients. Of the respiratory events reported in at least 1% of patients, tiotropium was associated with a lower incidence rate for COPD exacerbation, dyspnea and respiratory failure. Anticholinergic events such as dry mouth, constipation, intestinal obstruction, gastroesophageal reflux disease, dysuria, dysphonia and urinary retention were more common with tiotropium.

Other than lung cancer, serious adverse events reported by >1% of patients were either respiratory or cardiac in nature. Fewer serious adverse events in the tiotropium group were observed for several events under these two SOC, with a lower incidence rate for the preferred terms myocardial infarction, cardiac failure congestive, COPD exacerbation, and dyspnea. The most frequently reported serious adverse event was COPD exacerbation, occurring in 24% of patients overall.

Additional analyses were performed to evaluate the safety of tiotropium. An evaluation of stroke events did not identify an increased risk of stroke events or death from stroke in patients taking tiotropium. Similarly, an evaluation of cardiac events showed no adverse effect on ischemic heart disease and there was evidence for reduced cardiac morbidity.

Adverse events that led to discontinuation were reported for 22.6% of patients and their occurrence were more frequent in the placebo treatment group (25% placebo, 21% tiotropium). The most common reason for discontinuation was due to an exacerbation of a patient's underlying respiratory disease and, as stated, fewer patients in the tiotropium treatment group discontinued treatment due to respiratory events.

Previously recognized inhaled anticholinergic events were confirmed, although atrial fibrillation, an event associated with tiotropium, was balanced compared to placebo. There was no imbalance overall with ischemic heart disease nor was there evidence of an increased risk of stroke. The adverse event reporting in the 4-year UPLIFT indicated that tiotropium does not increase the risk for death or cardiovascular morbidity (including myocardial infarction and stroke) and reduced the risk for exacerbations of COPD and reports of respiratory failure.

10. SAFETY OVERVIEW FROM POOLED TIOTROPIUM HANDIHALER® TRIALS: FATAL EVENTS, CARDIOVASCULAR ADVERSE EVENTS, AND RESPIRATORY FAILURE

The methodology for the safety analysis was described in Section 8.1. In brief, a total of 26 tiotropium HandiHaler® trials including UPLIFT have been identified meeting the criteria noted in Section 8.1. Incidence rates of selected events were computed as the number of patients experiencing an event divided by the person-years at risk. Time at risk is time of exposure + 30 days for subjects who did not experience a specific event, and time from start of treatment to onset of a specific event for subjects who experienced this event. To measure the strength of the effect, incidence rate differences (tiotropium minus placebo) were estimated based on the method described in Greenland and Robins (R09-1299) with trial as stratum. Rates are presented per 100 person-years of time at risk to tiotropium or placebo. For fatal events, a separate section on data from an alternate formulation of tiotropium (Respimat®) has been included.

10.1 FATAL EVENTS

In the pooled analysis of 26 tiotropium HandiHaler® clinical trials, there were 917 deaths during the period at risk, with 472 and 445 deaths in the placebo and tiotropium groups respectively. The RD (95%CI) (tiotropium minus placebo) was -0.63 (-1.14, -0.12). The following figure displays RDs (95%CI) for all 26 trials as well as the pooled total.

Source	Treatment # events	Treatment Yrs at risk	Control # events	Control Yrs at risk	Weight	Rate difference (95% CI)
205.114	3	244	5	155	1.6	-1.99 (-5.14,1.15)
205.115	4	232	2	141	1.5	0.31 (-2.29,2.90)
205.123	0	16	0	8	0.1	
205.124	0	10	1	4	0.1	-23.37 (-69.17,22.43)
205.130	0	107	4	91	0.8	-4.40 (-8.72,-0.09)
205.131	0	19	1	19	0.2	-5.17 (-15.31,4.96)
205.137	1	95	1	95	0.8	-0.00 (-2.91,2.91)
205.214	7	451	8	441	3.8	-0.26 (-1.97,1.44)
205.215	0	14	0	16	0.1	
205.218	1	6	0	6	0.1	16.07 (-15.43,47.56)
205.223	0	26	0	25	0.2	
205.230	1	25	0	24	0.2	3.96 (-3.80,11.71)
205.235	381	9281	411	8575	76.6	-0.69 (-1.31,-0.07)
205.247	0	57	0	58	0.5	
205.256	3	202	6	199	1.7	-1.53 (-4.47,1.41)
205.257	5	356	2	113	1.5	-0.37 (-3.12,2.38)
205.259	13	527	2	249	2.9	1.66 (-0.08,3.41)
205.266	22	489	19	453	4.0	0.31 (-2.36,2.97)
205.269	0	39	0	40	0.3	
205.270	1	60	2	67	0.5	-1.33 (-6.59,3.93)
205.276	1	59	4	56	0.5	-5.48 (-13.26,2.30)
205.281	0	33	1	37	0.3	-2.71 (-8.02,2.60)
205.282	2	45	0	51	0.4	4.42 (-1.71,10.55)
205.284	0	30	0	28	0.2	
205.294	0	19	1	20	0.2	-4.96 (-14.68,4.76)
205.301	0	73	2	77	0.6	-2.61 (-6.23,1.01)
Total	**445**	**12519**	**472**	**11048**	**100.0**	**-0.63 (-1.14,-0.12)**

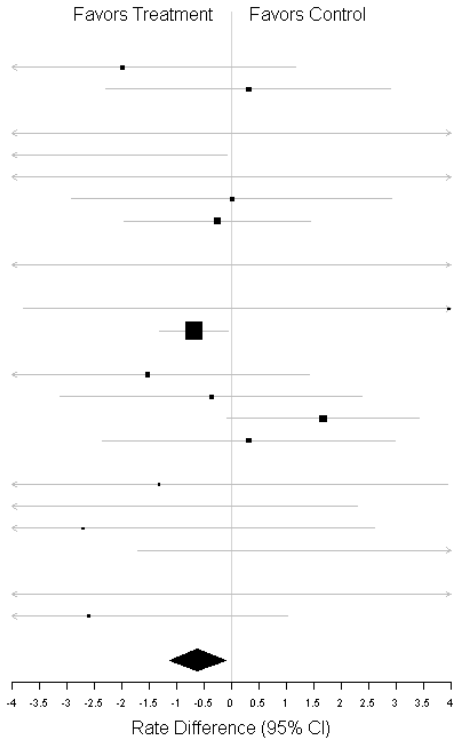


Figure 10.1: 1 Meta-analysis of incidence rates, rate differences (tiotropium - placebo) and 95% confidence intervals for all-cause mortality in 26 tiotropium HandiHaler® trials

Source data: data on file, Tables 3.17.1.3.3 and 3.17.1.4.4.3

10.1.1 Most common causes of death

Causes of death are presented according to system organ class where the frequency was at least 3% of the total number of deaths in either treatment period. The most common causes of death occurred in the system organ classes of lower respiratory and cardiac disorders. In the SOCs listed, there was no imbalance indicating an excess risk with tiotropium.

Table 10.1.1: 1 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for fatal cases according to system organ class with a frequency of at least 3% of the total number of fatal cases reported in the pooled analysis of 26 tiotropium HandiHaler® trials.

System Organ Class	Placebo N= 7,865		Tiotropium N= 9,149		Tiotropium – Placebo RD (95% CI)
	N	IR	N	IR	
Respiratory disorders (lower)**	165	1.48	147	1.16	-0.30 (-0.59, -0.00)*
Cardiac disorders	105	0.94	88	0.69	-0.24 (-0.47, -0.01)*
Respiratory disorders (other)**	77	0.69	86	0.68	0.01 (-0.20, 0.23)
General disorders and administration site conditions	55	0.49	59	0.46	-0.01 (-0.19, 0.17)
Neoplasms benign, malignant and unspecified	52	0.46	47	0.37	-0.08 (-0.24, 0.09)
Infections and infestations	32	0.29	21	0.17	-0.11 (-0.23, 0.01)
Nervous system disorders	16	0.14	18	0.14	0.00 (-0.09, 0.10)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval) per 100 patient years of time at risk, *=p<0.05
Source data: data on file, Table: 3.17.1.4.4.3
**All primary system organ classes are defined by MedDRA with the exception of 'Respiratory, thoracic and mediastinal disorders which has been divided into separate classes of Respiratory system disorders, Lower, Upper, and Other. Respiratory (other) includes lung cancer.

Causes of death are presented according to preferred term where the frequency is at least 1% of the total number of deaths. The most common causes of death were reported as COPD exacerbation, respiratory failure and pneumonia. Overall, there was no imbalance indicating an excess risk with tiotropium.

Table 10.1.1: 2 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for fatal cases according to preferred term with a frequency of at least 1% of the total number of fatal cases reported in the pooled analysis of 26 HandiHaler trials

Preferred term	Placebo N= 7,865		Tiotropium N= 9,149		Tiotropium – Placebo RD (95% CI)
	N	IR	N	IR	
COPD exacerbation	68	0.61	65	0.51	-0.09 (-0.28, 0.10)
Respiratory failure	51	0.46	33	0.26	-0.19 (-0.34, -0.03)*
Pneumonia	36	0.32	33	0.26	-0.05 (-0.19, 0.09)
Death	28	0.25	36	0.28	0.04 (-0.09, 0.17)
Myocardial infarction	24	0.21	20	0.16	-0.05 (-0.16, 0.06)
Lung neoplasm malignant	19	0.17	21	0.17	0.00 (-0.11, 0.11)
Cardiac arrest	17	0.15	9	0.07	-0.08 (-0.16, 0.01)
Sepsis	17	0.15	8	0.06	-0.08 (-0.17, -0.00)*
Cardiac failure	10	0.09	14	0.11	0.02 (-0.06, 0.10)
Sudden death	11	0.10	12	0.09	-0.00 (-0.08, 0.08)
Cardiopulmonary failure	8	0.07	9	0.07	0.00 (-0.07, 0.07)
Cerebrovascular accident	7	0.06	9	0.07	0.01 (-0.05, 0.08)
Acute respiratory failure	8	0.07	8	0.06	-0.01 (-0.07, 0.06)
Cardiac failure congestive	10	0.09	6	0.05	-0.04 (-0.11, 0.02)
Bronchial carcinoma	7	0.06	7	0.06	-0.00 (-0.07, 0.06)
Pulmonary embolism	8	0.07	6	0.05	-0.02 (-0.08, 0.04)
Non-small cell lung cancer	5	0.04	8	0.06	0.02 (-0.04, 0.08)
Septic shock	8	0.07	6	0.05	-0.02 (-0.08, 0.04)
Multi-organ failure	9	0.08	4	0.03	-0.05 (-0.11, 0.01)
Cardio-respiratory arrest	6	0.05	7	0.06	0.00 (-0.06, 0.07)
Small cell lung cancer stage unspecified	5	0.04	7	0.06	0.01 (-0.04, 0.07)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval) per 100 patient years of time at risk, *=p<0.05
Source data: data on file, Table 3.17.1.4.4.3

A more detailed description of fatal cardiovascular events is found in Section 10.2.3 (Cardiovascular Fatal Adverse Events).

In summary, the evaluation of fatal events in the pooled HandiHaler® clinical trial safety database do not indicate an increased risk in patients receiving tiotropium HandiHaler®.

10.2 CARDIOVASCULAR ADVERSE EVENTS

The tables displayed in this section include an abbreviated list of pooled terms representing the cardiovascular terms and categories of particular interest. The selection was based on clinical categories that are of public health interest or where there have been possible pathophysiologic associations from either previous published reports or potential biologic mechanisms. As mentioned previously, individual patients may be represented in multiple categories, but a patient is only represented once within a category or at the SOC level (i.e. Cardiac Disorder SOC total). For example, all patients reported to have a myocardial infarction would be counted with the pooled term “ischemic heart disease”.

10.2.1 All cardiovascular adverse events

Overall, there were 1,511 patients with at least one cardiac adverse event and 1,233 patients with at least one vascular adverse event (Table 10.2.1: 1). The RD (95% CI) for any cardiac event (tiotropium minus placebo) was -0.79 (-1.48, -0.09) and for any vascular event was -0.14 (-0.77, 0.49). Tiotropium was associated with a lower rate for a cardiac adverse event and a comparable rate for a vascular adverse event relative to the control group.

Table 10.2.1: 1 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for cardiac and vascular adverse events in the pooled analysis of 26 tiotropium HandiHaler® trials

	Placebo N=7,865		Tiotropium N=9,149		Tiotropium – Placebo RD (95% CI)
	N	IR	N	IR	
Cardiac disorders (SOC)	750	7.26	761	6.47	-0.79 (-1.48, -0.09) *
Atrial fibrillation/flutter	141	1.27	143	1.14	-0.12 (-0.40, 0.17)
Cardiac arrest	31	0.28	22	0.17	-0.09 (-0.22, 0.03)
Cardiac failure	254	2.32	229	1.83	-0.47 (-0.84, -0.10) *
Ischemic heart disease[+]	279	2.56	282	2.29	-0.28 (-0.69, 0.12)
Myocardial infarction	105	0.94	95	0.75	-0.18 (-0.42, 0.05)
Palpitations	54	0.48	67	0.53	0.04 (-0.14, 0.22)
Supraventricular tachycardia	25	0.22	32	0.25	0.03 (-0.09, 0.16)
Tachycardia (non-ventricular)	49	0.44	60	0.48	0.02 (-0.15, 0.19)
Ventricular tachycardia/fibrillation	27	0.24	19	0.15	-0.09 (-0.20, 0.03)
Vascular disorders (SOC)	588	5.68	645	5.50	-0.14 (-0.77, 0.49)
Aneurysm	40	0.36	51	0.40	0.05 (-0.10, 0.21)
Hypertension	368	3.47	379	3.13	-0.34 (-0.82, 0.13)
Stroke	94	0.85	109	0.87	0.04 (-0.20, 0.27)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD(95% CI) = rate difference (95% confidence interval) per 100 patient years of time at risk; terms used are composed of multiple MedDRA preferred terms

[+]categorized in Appendix 17.1 under the category angina/ischemia/MI expanded; *p<0.05

Source data: data on file, Tables 3.17.1.6.4.1 and 3.17.1.4.4.1

10.2.2 Cardiovascular serious adverse events

Serious adverse events were experienced by 25.4% of patients with a lower incidence rate of experiencing a serious adverse event in the tiotropium group (0.8 patients per 100 patient-years at risk) (Table 10.2.2: 1). An abbreviated list representing the categories and terms of particular interest is provided within the text (Table 10.2.2: 1).

There were 899 patients with at least one serious cardiac event and 274 with at least one serious vascular event (Table 10.2.2: 1). The RD (95% CI) for any serious cardiac event (tiotropium – placebo) was -0.79 (-1.30, -0.27) and 0.14 (-0.13, 0.42) for any serious vascular event. Tiotropium was not associated with a significantly increased risk for either a cardiac or vascular serious adverse event, including the most common events in the categories of ischemic heart disease and cardiac failure.

Table 10.2.2: 1 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for cardiac and vascular serious adverse events in the pooled analysis of 26 tiotropium HandiHaler® trials

	Placebo N= 7865		Tiotropium N= 9149		Tiotropium – Placebo RD (95% CI)
	N	IR	N	IR	
Cardiac disorders (SOC)	466	4.33	433	3.53	-0.79 (-1.30, -0.27) *
Atrial fibrillation/flutter	84	0.75	81	0.64	-0.10 (-0.32, 0.11)
Cardiac arrest	30	0.27	22	0.17	-0.09 (-0.21, 0.03)
Cardiac failure	165	1.49	154	1.22	-0.26 (-0.56, 0.04)
Ischemic heart disease+	196	1.78	180	1.45	-0.33 (-0.66, -0.01)*
Myocardial infarction	101	0.91	92	0.73	-0.17 (-0.40, 0.06)
Palpitations	5	0.04	6	0.05	0.00 (-0.05, 0.05)
Supraventricular tachycardia	13	0.12	15	0.12	0.01 (-0.08, 0.09)
Tachycardia (non-ventricular)	6	0.05	7	0.06	-0.01 (-0.06, 0.05)
Ventricular tachycardia/fibrillation	21	0.19	17	0.13	-0.05 (-0.15, 0.05)
Vascular disorders (SOC)	122	1.10	152	1.21	0.14 (-0.13, 0.42)
Aneurysm	27	0.24	31	0.24	0.01 (-0.12, 0.14)
Hypertension	21	0.19	16	0.13	-0.06 (-0.16, 0.04)
Stroke	74	0.66	91	0.72	0.07 (-0.14, 0.29)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval) per 100 patient years of time at risk; terms used are composed of multiple MedDRA preferred terms

+categorized in Appendix 17.1 under the category angina/ischemia/MI expanded; *=p<0.05

Source data: data on file, Table 3.17.1.4.4.2 and 3.17.1.6.4.2

10.2.3 Cardiovascular fatal adverse events

There were 917 fatal cases, representing 5.4% of the population. An abbreviated list of pooled terms of particular interest is provided within the text (Table 10.2.3: 1).

The risk of experiencing a fatal adverse event was significantly lower in the tiotropium group (Table 10.2.3: 1). There were 193 patients with a fatal cardiac event and 25 with a fatal vascular event. The RD (95% CI) for a fatal cardiac event (tiotropium- placebo) was lower with tiotropium -0.24 (-0.47, -0.01) and was less than 0 for a fatal vascular event was -0.08 (-0.17, 0.00).

The preferred terms cardiac death (tiotropium n= 0, placebo n= 1), sudden cardiac death (tiotropium n= 1, placebo n= 2) and sudden death (tiotropium n= 12, placebo n= 11) are listed in MedDRA under the SOC General and Administrative Site Disorders and are not listed in Table 10.2.3: 1. These preferred terms were reported infrequently and showed no evidence of an increased risk with tiotropium. For sudden death, the RD (95% CI) was 0.00 (-0.08, 0.08).

Table 10.2.3: 1 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for cardiac and vascular fatal adverse events in the pooled analysis of 26 tiotropium HandiHaler® trials

	Placebo N= 7,865		**Tiotropium N= 9,149**		**Tiotropium – Placebo RD (95% CI)**
	N	**IR**	**N**	**IR**	
Cardiac disorders (SOC)	105	0.94	88	0.69	-0.24 (-0.47, -0.01) *
Atrial fibrillation/flutter	2	0.02	0	0	-0.02 (-0.04, 0.01)
Cardiac arrest	26	0.23	18	0.14	-0.08 (-0.19, 0.03)
Cardiac failure	41	0.37	44	0.35	-0.01 (-0.17, 0.14)
Ischemic heart disease[+]	33	0.29	23	0.18	-0.11 (-0.24, 0.01)
Myocardial infarction	24	0.21	20	0.16	-0.05 (-0.16, 0.06)
Palpitations	0	0	0	0	0
Supraventricular tachycardia	1	0.01	0	0	-0.01 (-0.03, 0.01)
Tachycardia (non-ventricular)	0	0	0	0	0
Ventricular tachycardia/fibrillation	2	0.02	3	0.02	0.00 (-0.03, 0.04)
Vascular disorders (SOC)	17	0.15	8	0.06	-0.08 (-0.17, 0.00)
Aneurysm	6	0.05	5	0.04	-0.01 (-0.07, 0.04)
Hypertension	1	0.01	0	0	-0.01 (-0.03, 0.01)
Stroke	12	0.11	14	0.11	0.01 (-0.08, 0.09)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval) per 100 patient years of time at risk; terms used are composed of multiple MedDRA preferred terms

[+]categorized in Appendix 17.1 under the category angina/ischemia/MI expanded; *=p<0.05

Source data: data on file, Tables 3.17.1.4.4.3, 3.17.1.6.4.3

10.2.4 Stroke

As with the previous analyses, all reported events were coded using MedDRA version 11.1 preferred terms. Terms consistent with stroke syndrome overlap several system organ classes. A grouping of preferred terms was combined to represent stroke based on a narrowed version of the Standardized MedDRA Query (SMQ) for stroke (Appendix 17.1). Several terms in the SMQ were eliminated as the terms could be used (i.e. coded) for an event other than stroke.

The rate difference (RD) comparing the rate of stroke in patients receiving tiotropium with the rate of stroke in placebo treated patients was 0.04 (-0.20, 0.27) (Table 10.2.4: 1). The rate difference (RD) for serious stroke in patients receiving tiotropium compared with placebo treated patients was 0.04 (95% CI= -0.20, 0.27) (Table 10.2.4: 2). For fatal strokes, there were 14 tiotropium patients and 12 placebo patients (RD (95%CI) = 0.01 (-0.08, 0.09) (Table 10.2.4: 3). The pooled clinical trial data do not indicate an excess risk of stroke in patients treated with tiotropium.

Table 10.2.4: 1 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for pooled adverse event endpoint of stroke in 26 tiotropium HandiHaler® trials

	Placebo N= 7,865		**Tiotropium N= 9,149**		**Tiotropium – Placebo**
	N	**IR**	**N**	**IR**	**RD (95% CI)**
Stroke (pooled term)	94	0.85	109	0.87	0.04 (-0.20, 0.27)
Amaurosis fugax	2	0.02	0	0	-0.02 (-0.04, 0.01)
Brain stem infarction	0	0	1	0.01	0.01 (-0.01, 0.02)
Carotid artery occlusion	5	0.04	5	0.04	-0.00 (-0.06, 0.05)
Cerebral hematoma	1	0.01	0	0	-0.01 (-0.03, 0.01)
Cerebral hemorrhage	6	0.05	3	0.02	-0.03 (-0.08, 0.02)
Cerebral infarction	9	0.08	9	0.07	-0.01 (-0.08, 0.06)
Cerebral ischemia	2	0.02	7	0.06	0.04 (-0.01, 0.08)
Cerebrovascular accident	34	0.30	41	0.32	0.03 (-0.11, 0.17)
Embolic stroke	0	0	1	0.01	0.01 (-0.01, 0.02)
Hemorrhage intracranial	0	0	1	0.01	0.01 (-0.01, 0.02)
Hemorrhage stroke	0	0	1	0.01	0.01 (-0.01, 0.02)
Intracranial hematoma	1	0.01	1	0.01	-0.00 (-0.02, 0.02)
Ischemic cerebral infarction	2	0.02	0	0	-0.02 (-0.04, 0.01)
Ischemic stroke	3	0.03	8	0.06	0.04 (-0.02, 0.09)
Lacunar infarction	2	0.02	0	0	-0.02 (-0.04, 0.01)
Ruptured cerebral aneurysm	1	0.01	0	0	-0.01 (-0.03, 0.01)
Subarachnoid hemorrhage	0	0	1	0.01	0.01 (-0.01, 0.02)
Thalamic stroke	0	0	1	0.01	0.01 (-0.01, 0.02)
Transient ischemic attack	31	0.28	40	0.32	0.04 (-0.10, 0.18)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk);
RD (95% CI) = rate difference (95% confidence interval) per 100 patient years of time at risk, *=p<0.05
Source data: data on file, Table 3.17.1.5.4.1

Table 10.2.4: 2 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for pooled serious adverse event endpoint of stroke in 26 tiotropium HandiHaler® trials

	Placebo N= 7,865		Tiotropium N= 9,149		Tiotropium – Placebo
	N	IR	N	IR	RD (95% CI)
Stroke (pooled term)	74	0.66	91	0.72	0.07 (-0.14, 0.29)
Amaurosis fugax	1	0.01	0	0	-0.01 (-0.03, 0.01)
Brain stem infarction	0	0	1	0.01	0.01 (-0.01, 0.02)
Carotid artery occlusion	3	0.03	2	0.02	-0.01 (-0.05, 0.03)
Cerebral hematoma	1	0.01	0	0	-0.01 (-0.03, 0.01)
Cerebral hemorrhage	5	0.04	3	0.02	-0.02 (-0.07, 0.03)
Cerebral infarction	7	0.06	8	0.06	0.00 (-0.06, 0.07)
Cerebral ischemia	2	0.02	5	0.04	0.02 (-0.02, 0.06)
Cerebrovascular accident	31	0.28	40	0.32	0.05 (-0.09, 0.19)
Embolic stroke	0	0	1	0.01	0.01 (-0.01, 0.02)
Hemorrhage intracranial	0	0	1	0.01	0.01 (-0.01, 0.02)
Hemorrhage stroke	0	0	1	0.01	0.01 (-0.01, 0.02)
Intracranial hematoma	1	0.01	1	0.01	-0.00 (-0.02, 0.02)
Ischemic cerebral infarction	2	0.02	0	0	-0.02 (-0.04, 0.01)
Ischemic stroke	3	0.03	8	0.06	0.04 (-0.02, 0.09)
Lacunar infarction	0	0	0	0	0
Ruptured cerebral aneurysm	1	0.01	0	0	-0.01 (-0.03, 0.01)
Subarachnoid hemorrhage	0	0	1	0.01	0.01 (-0.01, 0.02)
Thalamic stroke	0	0	0	0	-0
Transient ischemic attack	19	0.17	24	0.19	0.02 (-0.08, 0.13)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval) per 100 patient years of time at risk, *=p<0.05
Source data: data on file, Table 3.17.1.5.4.2

Table 10.2.4: 3 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for pooled fatal adverse event endpoint of stroke in 26 tiotropium HandiHaler® trials

	Placebo N= 7,865		Tiotropium N= 9,149		Tiotropium – Placebo
	N	**IR**	**N**	**IR**	**RD (95% CI)**
Stroke (pooled term)	12	0.11	14	0.11	0.01 (-0.08, 0.09)
Amaurosis fugax	0	0	0	0	0
Brain stem infarction	0	0	0	0	0
Carotid artery occlusion	0	0	0	0	0
Cerebral hematoma	1	0.01	0	0	-0.01 (-0.03, 0.01)
Cerebral hemorrhage	3	0.03	2	0.02	-0.01 (-0.05, 0.03)
Cerebral infarction	1	0.01	2	0.02	0.01 (-0.02, 0.04)
Cerebral ischemia	0	0	0	0	0
Cerebrovascular accident	7	0.06	9	0.07	0.01 (-0.05, 0.08)
Embolic stroke	0	0	0	0	0
Hemorrhage intracranial	0	0	1	0.01	0.01 (-0.01, 0.02)
Hemorrhage stroke	0	0	0	0	0
Intracranial hematoma	0	0	0	0	0
Ischemic cerebral infarction	0	0	0	0	0
Ischemic stroke	0	0	0	0	0
Lacunar infarction	0	0	0	0	0
Ruptured cerebral aneurysm	0	0	0	0	0
Subarachnoid hemorrhage	0	0	0	0	0
Thalamic stroke	0	0	0	0	0
Transient ischemic attack	0	0	0	0	0

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval) per 100 patient years of time at risk, *=p<0.05
Source data: data on file, Table 3.17.1.5.4.3

10.2.5 Major adverse cardiovascular events

The incidence rates and rate differences for the composite cardiovascular (CV) endpoint for major adverse cardiovascular events are displayed in Table 10.2.5: 1. There was a reduction in the risk of a major adverse cardiovascular event in the tiotropium group relative to the placebo group (-0.45 patients per 100 patient-years at risk) and a reduction for fatal cardiovascular events (-0.32 patients per 100 patient-years at risk). A further analysis was performed that includes the non-specific preferred term “death” assuming that the cause of death in all cases was cardiovascular. For this expanded endpoint, the rate difference remained less than zero (RR (95%CI) = -0.28 (-0.58, 0.02)) (data on file, Table 3.17.1.7.6).

Table 10.2.5: 1 Incidence rates, rate differences (tiotropium - placebo) per 100 patient years for major adverse cardiovascular (CV) events in 26 tiotropium HandiHaler® trials

	Placebo N= 7,865		Tiotropium N= 9,149		Tiotropium – Placebo
	N	IR	N	IR	RD (95% CI)
Major adverse CV event	297	2.71	277	2.22	-0.45 (-0.85, -0.05)*
Fatal CV event	145	1.30	121	0.96	-0.32 (-0.59, -0.05)*

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval) per 100 patient years of time at risk; *=p<0.05
Source data: data on file, Table 3.17.1.7.6

In summary, a thorough analysis of cardiovascular adverse event reporting in the tiotropium HandiHaler® clinical trial pooled database involving over 17,000 patients demonstrated that there was no increased risk for cardiovascular event, including those that were serious and fatal associated with tiotropium HandiHaler® 18 mcg daily.

10.3 RESPIRATORY FAILURE

The adverse event reports from UPLIFT indicated a lower incidence rate for respiratory failure with tiotropium HandiHaler® compared to placebo that was present for all events, serious adverse events and fatal events. The previous analysis reviewed the totality of the tiotropium HandiHaler pooled clinical trial database. However, for the evaluation of respiratory failure, we sought to evaluate whether the other trials (i.e. excluding UPLIFT) could serve as supportive data suggesting that the finding was true rather than a random observation. The absolute number of events in the 25 HandiHaler® trials was much lower compared to UPLIFT. For the pooled term of "respiratory failure", there were 64 patients. There was a lower incidence rate of respiratory failure in the tiotropium group (RD (95%CI) = -0.25 (-0.82, 0.32)), albeit with a wide confidence interval. Eighty-eight percent of the events were considered serious (n=56). The associated RD (95%CI) for serious respiratory failure was -0.37 (-0.90, -0.16). There were only 10 fatal events reported under the pooled term (3 in the tiotropium group and 7 in the placebo group). The RD (95%CI) was -0.19 (95% CI = -0.42, 0.04)). Tables 10.3: 1, 10.3: 2, and 10.3: 3 display the incidence rates and rate differences for adverse events, serious adverse events and fatal events, respectively according to the individual and pooled terms "respiratory failure".

Table 10.3: 1 Incidence rates and rate differences (tiotropium - placebo) per 100 patient years for adverse event reporting of pooled term "respiratory failure" from 25 tiotropium HandiHaler® COPD trials

	Placebo (N = 4,859)		Tiotropium (N = 6,163)		Tiotropium - Placebo
	N	IR	N	IR	RD (95% CI)
Respiratory failure (total)	33	1.34	31	0.96	-0.25 (-0.82, 0.32)
Acute respiratory failure	12	0.48	9	0.28	-0.15 (-0.48, 0.18)
Cardiopulmonary failure	0	0.00	3	0.09	0.10 (-0.01, 0.21)
Chronic respiratory failure	1	0.04	0	0.00	-0.04 (-0.11, 0.04)
Hypoxia	3	0.12	6	0.19	0.07 (-0.12, 0.27)
Respiratory acidosis	1	0.04	0	0.00	-0.04 (-0.11, 0.04)
Respiratory distress	2	0.08	4	0.12	0.06 (-0.11, 0.22)
Respiratory failure	16	0.65	9	0.28	-0.33 (-0.69, 0.03)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk
Source data: data on file, Table 3.17.1.5.2.1

Table 10.3: 2 Incidence rates and rate differences (tiotropium - placebo) per 100 patient years for serious adverse event reporting of pooled term "respiratory failure" from 25 tiotropium HandiHaler® COPD trials

	Placebo (N = 4,859)		Tiotropium (N = 6,163)		Tiotropium - Placebo
	N	IR	N	IR	RD (95%CI)
Respiratory failure (total)	31	1.25	25	0.77	-0.37 (-0.90, -0.16)*
Acute respiratory failure	12	0.48	9	0.28	-0.15 (-0.48, 0.18)
Cardiopulmonary failure	0	0.00	2	0.06	0.06 (-0.02, 0.14)
Chronic respiratory failure	1	0.04	0	0.00	-0.04 (-0.11, 0.04)
Hypoxia	3	0.12	2	0.06	-0.05 (-0.20, 0.11)
Respiratory acidosis	1	0.04	0	0.00	-0.04 (-0.11, 0.04)
Respiratory distress	1	0.04	3	0.09	0.06 (-0.07, 0.19)
Respiratory failure	15	0.61	9	0.28	-0.29 (-0.65, 0.06)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; *p<0.05
Source data: data on file, Table: 3.17.1.5.2.2

Table 10.3: 3 Incidence rates and rate differences (tiotropium - placebo) per 100 patient years for fatal adverse event reporting of pooled term "respiratory failure" from 25 tiotropium HandiHaler® COPD trials

	Placebo (N = 4,859)		Tiotropium (N = 6,163)		Tiotropium - Placebo
	N	IR	N	IR	RD (95% CI)
Respiratory failure (total)	7	0.28	3	0.09	-0.19 (-0.42, 0.04)
Cardiopulmonary failure	0	0.00	1	0.03	0.02 (-0.02, 0.07)
Hypoxia	1	0.04	0	0.00	-0.04 (-0.11, 0.04)
Respiratory distress	1	0.04	0	0.00	-0.04 (-0.11, 0.04)
Respiratory failure	5	0.20	2	0.06	-0.14 (-0.34, 0.06)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk
Source data: data on file, Table: 3.17.1.5.2.3

The data for the pooled term of "respiratory failure" from both data sources (UPLIFT and the 25 HandiHaler® trials) are summarized in Table 10.3: 4.

Table 10.3: 4 Incidence rates and rate differences (tiotropium - placebo) per 100 patient years for fatal adverse event reporting of pooled term "respiratory failure" from the UPLIFT trial and from 25 tiotropium HandiHaler® COPD trials

	Placebo (N = 7,865)		Tiotropium (N = 9,149)		Tiotropium – Placebo
	N	IR	N	IR	RD (95% CI)
UPLIFT: Adverse event	179	2.09	157	1.68	-0.40 (-0.81, -0.00)*
25 Trials: Adverse event	33	1.34	31	0.96	-0.25 (-0.82, 0.32)
UPLIFT: Serious adverse event	160	1.86	136	1.45	-0.41 (-0.79, -0.03)*
25 Trials: Serious adverse event	31	1.25	25	0.77	-0.37 (-0.90, 0.16)
UPLIFT: Fatal adverse event	64	0.73	48	0.51	-0.23 (-0.46, 0.00)
25 Trials: Fatal adverse event	7	0.28	3	0.09	-0.19 (-0.42, 0.04)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = incidence rate difference (95% confidence interval) per 100 patient years of time at risk; *p<0.05
Source data: data on file, Tables: 3.17.1.5.1.1, 3.17.1.5.1.2, 3.17.1.5.1.3, 3.17.1.5.2.1, 3.17.1.5.2.2, 3.17.1.5.2.3

In summary, the data from the previously conducted tiotropium HandiHaler® trials are consistent with the findings in UPLIFT with regard to a reduced risk for reporting of respiratory failure. The analysis of the 25 trials substantiates the association observed in UPLIFT and further supports the positive impact of tiotropium HandiHaler® on exacerbations of COPD.

11. DATA FROM TIOTROPIUM RESPIMAT® DEVELOPMENT PROGRAM

The previous analyses in this Briefing Document described clinical trial data from the tiotropium formulation marketed in the United States (Spiriva® HandiHaler® dry powder capsule for inhalation). An alternative formulation of tiotropium (Spiriva® Respimat® inhalation spray 5 mcg) was approved in Europe in 2007. The overall clinical trial program is considerably smaller than the tiotropium HandiHaler® program; however, the Respimat® trials contribute safety data in the context of the Early Communication and in the context of demonstrating consistency of findings regarding reductions in exacerbations of COPD. This section contains relevant background information, a focused summary of fatal event data, data regarding major adverse cardiovascular events and data regarding stroke.

Pooled data from the tiotropium Respimat® clinical trial program are presented. The one-year tiotropium Respimat® trial 205.372 is discussed separately for the following reasons: (a) it is the largest tiotropium Respimat® trial, (b) collection of vital status information was prospectively collected from the onset of the trial, and (c) the imbalance in fatal events is inconsistent the largest single HandiHaler® trial (UPLIFT 205.235) and the more extensive HandiHaler® clinical trial safety database.

11.1 BACKGROUND: TIOTROPIUM RESPIMAT® CLINICAL TRIALS

This alternative formulation is comprised of an aqueous solution of tiotropium formulated with the excipients benzalkonium chloride and ethylenediaminetetraacetic acid disodium salt (EDTA). The tiotropium inhalation solution is intended for oral inhalation only via the Respimat® inhaler, a novel, propellant-free delivery system.

A total of five trials involving tiotropium Respimat® 5 mcg met the same selection criteria for pooling of trials as described with the previously described 26 HandiHaler® trials (i.e. randomized, placebo-controlled, double-blind, parallel group studies with a treatment duration of at least 4 weeks). Two of the trials were 12-weeks in duration (205.251/U04-3400/U05-2162, 205.252/U04-3343/U05-2162) and three were 1-year in duration (205.254/U05-2112-01/U05-2249, 205.255/U05-2113/U05-2249, 205.372/U09-1128). The 1-year trials (205.254, 205.255) and the 12-week trials (205.251, 205.252) were part of the initial phase III registration program and included two active treatment groups (tiotropium Respimat® 5 mcg and 10 mcg daily) in order to determine the optimal dose. The 5 and 10 mcg formulations had similar efficacy profiles but a higher rate of expected anticholinergic effects was observed for the 10 mcg dose; hence the selection of 5 mcg as the marketed dose. The initial 1-year phase III trials demonstrated improvements in lung function over 24 hours with once daily dosing along with improvements in symptoms and a reduced risk for exacerbations of COPD and were the pivotal trials that were the basis of approval in Europe. The third 1-year trial (205.372) was subsequently initiated with the marketed dose of tiotropium Respimat® (5 mcg) and was designed with morning pre-dose FEV_1 (trough) and exacerbations of COPD as co-primary endpoints, both of which were statistically significant in favor of tiotropium Respimat®.

11.2 FORMULATION COMPARISON: FATAL ADVERSE EVENTS

As there are differences in adverse events incidence rates between the two formulations, Table 11.2: 1 contains side by side comparisons of the two pooled safety databases (26 tiotropium HandiHaler® 18 mcg trials, 5 tiotropium Respimat® 5 mcg trials).

The formulation comparisons (tiotropium HandiHaler® 18 mcg and tiotropium Respimat® 5 mcg) based on the respective pooled analyses for all-cause mortality and mortality within the system organ classes cardiac disorders, vascular disorders, general disorders (including death of unknown cause and sudden death) and lower respiratory disorders are displayed in Table 11.2: 1.

Table 11.2: 2 provides a comparison of tiotropium Respimat® 5 mcg and 10 mcg, which are limited to the phase III trials containing both doses.

Table 11.2: 1 Incidence rates, rate differences (tiotropium - placebo) and 95% confidence intervals for fatal cases according to selected SOCs and stroke in the pooled analysis of 26 HandiHaler® trials and 5 tiotropium Respimat® 5 mcg trials.

	Tiotropium HandiHaler® 18 mcg Trials					**Tiotropium Respimat® 5 mcg**				
	Placebo (N=7,865)		**Tiotropium (N=9,149)**		**RD (95% CI)**	**Placebo (N=2,799)**		**Tiotropium (N=2,802)**		**Tiotropium – Placebo RD (95% CI)**
	N	**IR**	**n**	**IR**		**N**	**IR**	**N**	**IR**	
All-cause	472	4.27	445	3.55	-0.63 (-1.14, -0.12)*	39	1.66	62	2.51	0.87 (0.06, 1.68)*
Cardiac disorders	105	0.94	88	0.69	-0.24 (-0.47, -0.01)*	10	0.42	22	0.897	0.48 (0.02, 0.93)*
General disorders	55	0.49	59	0.46	-0.01 (-0.19, 0.17)	4	0.17	10	0.40	0.24 (-0.07, 0.54)
Lower respiratory disorders	165	1.48	147	1.16	-0.30 (-0.59, -0.00)	17	0.72	18	0.73	0.01 (-0.47, 0.48)
Vascular	17	0.15	8	0.06	-0.08 (-0.17, 0.00)	1	0.04	0	0	-0.04 (-0.12, 0.04)
Stroke**	12	0.11	14	0.11	0.01 (-0.08, 0.09)	1	0.04	1	0.04	-0.00 (-0.12, 0.12)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval); terms used are composed of multiple MedDRA preferred terms; *p<0.05

**composed of preferred terms from different SOCs

Source Data: data on file, Tables 3.17.1.4.4.3, 3.17.1.6.4.3 and U09-0059-02, Tables 3.18.1.4.3.3, 3.18.1.5.3.3

Table 11.2: 2 Incidence rates, rate differences (tiotropium 10 mcg - tiotropium 5 mcg) and 95% confidence intervals for fatal cases according to selected SOCs and stroke in the pooled analysis of Respimat® 5 mcg and 10 mcg (restricted to four trials where both doses were included as treatment groups)

	Tiotropium 5 mcg (N=850)		**Tiotropium 10 mcg (N=847)**		**Tiotropium 10 mcg – 5 mcg RD (95%CI)**
	N	**IR**	**N**	**IR**	
All-cause	12	1.80	19	2.92	1.12 (-0.54, 2.78)
Cardiac disorders	3	0.45	2	0.31	-0.14 (-0.81, 0.52)
General disorders	0	0.00	6	0.92	0.91 (0.18, 1.65)*
Lower respiratory disorders	6	0.90	6	0.92	0.02 (-1.01, 1.06)
Vascular disorders	0	0	0	0	0
Stroke**	0	0.00	1	0.15	0.15 (-0.15, 0.45)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval); terms used are composed of multiple MedDRA preferred terms; *p<0.05
**composed of preferred terms from different SOCs
Source Data: data on file, Tables 3.17.1.4.6.3, 3.17.1.6.6.3

The incidence rate difference was less than 0 for fatal events with tiotropium HandiHaler® relative to the placebo group, including those under the cardiac and lower respiratory SOCs. The incidence rate differences were above 0 for fatal events in the cardiac and general SOCs with the Respimat® formulation. In addition, a modest imbalance may be present with a higher incidence rate for Respimat® 10 mcg data relative to the 5 mcg dose; however, the data set from the 4 trials (excluding trial 205.372 as a 10 mcg was not included) was smaller relative to 205.372 alone and to the HandiHaler® database. The number of events was low and the confidence intervals were wide in the analysis of the four trials of 5 mcg and 10 mcg Respimat formulations.

11.3 MAJOR ADVERSE CARDIOVASCULAR EVENTS AND STROKE

Major adverse cardiovascular (CV) events and stroke based on the pooled analysis of five Respimat® 5 mcg trials are displayed in the following two tables. As with the other tables for the major adverse CV event endpoint, the analysis is based on the on-treatment period.

The number of events was relatively small with a negative rate difference for major adverse cardiovascular events but positive when this was restricted to fatal events (Table 11.3: 1). In each analysis, the 95% confidence intervals included zero.

Table 11.3: 1 Incidence rates, rate differences (tiotropium - placebo) and 95% confidence intervals for a major adverse CV events in 5 tiotropium Respimat® 5 mcg trials.

	Placebo (N=2,799)		Tiotropium 5 mcg (N=2,802)		Tiotropium - Placebo
	N	IR	n	IR	RD (95% CI)
Major adverse CV event	42	1.79	39	1.58	-0.21 (-0.94, 0.53)
Fatal CV event	13	0.55	25	1.01	0.47 (-0.03, 0.97)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval); terms used are composed of multiple MedDRA preferred terms
Source Data: data on file, Table 3.18.1.7.3

There were relatively few stroke events. Incidence rate differences showed no increased risk with tiotropium Respimat for all stroke events, serious stroke events or fatal stroke events (Table 11.3: 2).

Table 11.3: 2 Incidence rates, rate differences (tiotropium - placebo) and 95% confidence intervals for stroke in 5 tiotropium Respimat® 5 mcg trials.

	Placebo (N=2,799)		Tiotropium 5mcg (N=2,802)		Tiotropium - Placebo
	N	IR	n	IR	RD (95% CI)
All stroke adverse events	16	0.68	12	0.48	-0.20 (-0.63, 0.24)
Serious stroke adverse events	12	0.51	9	0.36	-0.14 (-0.52, 0.24)
Fatal stroke events	1	0.04	1	0.04	-0.00 (-0.12, 0.12)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval); terms used are composed of multiple MedDRA preferred terms
Source Data: data on file, Tables 3.18.1.5.3.1, 3.18.1.5.3.2 and 3.18.1.5.3.3

11.4 RESPIMAT® TRIAL 205.372 (U09-1128-01)

Trial 205.372 is a 1-year international, placebo-controlled, double-blind, randomised efficacy and safety clinical trial with tiotropium Respimat® 5 mcg daily. The co-primary endpoints were morning pre-dose (trough) FEV_1 and time to first COPD exacerbation. Vital status of all patients (including those who discontinued prematurely) was sought and all fatal events were adjudicated as to the primary cause of death by an independent expert committee. A total of 3,991 patients with COPD were randomized, of which 1,952 patients were exposed to tiotropium and 1,965 patients to placebo Respimat®. The average age of the study population was 65 years; the lung function at baseline is characterised by a pre-bronchodilator FEV_1 of 1.11 L (40% predicted). The groups were generally balanced for demographic variables. Patients were allowed concomitant therapy with all respiratory medications according to treatment guidelines other than inhaled anticholinergics.

The estimated patient exposure to study drug during the trial was 1,649 patient years on tiotropium Respimat® and 1,611 patient years on placebo. As with other tiotropium trials, fewer patients prematurely discontinued trial medication in the tiotropium group compared to the placebo group (318 (16%) vs. 373 (19%)). Vital status of all patients including the

discontinued patients was followed up for the planned treatment period (Day 337) and including the 30 days following discontinuation of trial medication (Day 367). Complete vital status data was obtained from approximately 99% of patients until Day 337, 83% of patients until Day 365 and 60% of patients until Day 367. In addition, an independent expert committee adjudicated the cause of death in fatal cases.

The study demonstrated statistically significant differences for all pre-specified primary and nearly all secondary endpoints (not presented). Clinically relevant increases of 102 mL ($p<0.0001$) and 168 mL ($p<0.0001$) in trough FEV_1 and FVC (i.e. at the end of the 24-hour dosing interval) were achieved with tiotropium Respimat compared to placebo. There was a significant delay in the time to first COPD exacerbation and for the time to first hospitalisation due to an exacerbation with tiotropium compared to placebo. The HRs (95% confidence intervals [CI]) for an exacerbation or exacerbation leading to hospitalization were 0.69 (0.63, 0.77) and 0.73 (0.59, 0.90) respectively. At the end of the trials, there was a mean reduction (improvement) of 2.9 units ($p<0.0001$) in the SGRQ total score with tiotropium Respimat® compared to placebo.

Adverse events were reported in 1,361 (69.3%) and 1,369 (70.1%) of placebo and tiotropium Respimat® treated patients respectively. Corresponding serious adverse events were reported in 336 (17.1%) and 342 (17.5%) of patients. The primary analysis for the evaluation of mortality in trial 205.372 was based on the collection of complete data from all patients (including those who prematurely discontinued trial medication) until the end of the protocol-defined treatment period (data censored beyond Day 337). There was a nominal imbalance for the incidence rate of any fatal adverse event with 2.94 per 100 patient-years (52 cases) in the tiotropium Respimat group, compared to 2.13 (38 cases) in the placebo group (RD (95%CI) = 0.81 (-0.23, 1.86)). During treatment (until 30 days following the last dose of study medication), the data for any fatal event are: tiotropium: 50 cases, incidence rate 2.77; placebo: 34 cases, incidence rate 1.92 (RD (95%) = 0.85 (-0.15, 1.86)) (data on file, Table 3.20.1).

More fatal adverse events occurred in the tiotropium Respimat group in the SOC Cardiac Disorders and General Disorders (includes “death” (unexplained, not further specified) and sudden death), Neoplasms and Respiratory Disorder (other) (Table 11.4: 1). Respiratory Disorder (other) included lung neoplasms (5 tiotropium vs. 1 placebo). The event rate in the SOC Respiratory System (Lower), which included mainly COPD exacerbations, respiratory failure and pneumonia, was lower for tiotropium than placebo.

Table 11.4: 1 Incidence rate, rate differences (tiotropium – placebo) and 95%CI for fatal adverse events in trial 205.372 by treatment and SOC, expert panel adjudicated causes of death, for the planned observation until day 337*

	Placebo (N=1,965)		Tiotropium Respimat 5 mcg (N=1,952)		Tiotropium-Placebo RD (95%CI)
	n	IR	n	IR	
Any Fatal Adverse Event	38	2.13	52	2.94	0.81 (-0.23, 1.86)
Cardiac Disorders	4	0.22	9	0.51	0.28 (-0.11, 0.68)
Gastrointestinal disorders	1	0.06	1	0.06	0.00 (-0.16, 0.16)
General Disorders (death /sudden death)	12	0.67	19	1.07	0.40 (-0.21, 1.01)
Infections/Infestations	5	0.28	3	0.17	-0.11 (-0.42, 0.20)
Neoplasms	2	0.11	4	0.23	0.11 (-0.16, 0.38)
Nervous system disorders	0	0.00	1	0.06	0.06 (-0.05, 0.17)
Psychiatric disorders	1	0.06	0	0.00	-0.06 (-0.17, 0.05)
Renal and urinary disorders	0	0.00	1	0.06	0.06 (-0.05, 0.17)
Reproductive system	0	0.00	1	0.06	0.06 (-0.05, 0.17)
Respiratory (Lower)	16	0.89	9	0.51	-0.39 (-0.94, 0.16)
Respiratory (Other) (mostly neoplasms)	2	0.11	5	0.28	0.17 (-0.12, 0.46)
Respiratory (Upper)	0	0.00	1	0.06	0.06 (-0.05, 0.17)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate difference (95% confidence interval)
Source data: see U09-1128-01, Table 15.3.2.2: 2 and data on file, Tables 3.20.1 and 3.20.11-22
*an individual patient may be represented in more than 1 category if there was more than 1 assigned cause of death

With regard to fatal cases of neoplasm documented in the SOCs Neoplasm and Respiratory (other), five of the tiotropium treated patients who died were treated for less then 100 days or diagnosed within this period. The remaining four patients received treatment for about 200 to 300 days. In addition, imbalances in adverse events (RD (95%CI) = 0.98 (0.02, 1.94)) and serious adverse events (RD (95%CI) = 0.59 (-0.16, 1.35)) reporting in the SOC Neoplasms were observed (data on file, Table 3.18.1.4.1.1 and 3.18.1.4.1.2). A higher rate of lung cancers was also reported. There is no biologically plausible relationship between treatment with tiotropium and the observed neoplasms. The observation suggests an imbalance in the randomised treatment groups in pre-existing undiagnosed neoplasms or an undetected bias within the trial.

The assignment of causes of death and to SOCs exposed the difficulty in differentiating the cause of death (i.e. COPD exacerbation) from the mode of death (i.e. cardiac arrest), especially among the SOCs Respiratory System (Lower), Infections and Infestations, Cardiac Disorders and the General SOC (including the terms death and sudden death). Several deaths had a preceding lower respiratory event; however, the ultimate cause of death was assigned to the Cardiac or General SOC. These issues are described in a summary document of the results of trial 205.372 submitted to regulatory agencies in March 2009 (U09-0060-01). Such limitations in determining the primary cause of death may, at least, partially explain

inconsistencies between the studies 205.372 to the tiotropium HandiHaler® database. In order to compensate for the inherent variability in the assignment of cause of death, minimize ambiguities of diagnoses, and improve the precision of the estimate for associations to cardiorespiratory mortality, the aforementioned SOCs were combined in a post-hoc analysis. The rate difference (95% CI) for the combination of fatal cases in the SOCs General-Infections-Cardiac-Lower Respiratory at Day 337 was 0.41 (-0.53, 1.35) (data on file, Table 3.20.4).

For the composite endpoint of major adverse cardiovascular events, the incidence rates between treatment groups were similar (RD (95%CI) = -0.08 (-0.80, 0.95)). In addition, there was no evidence for an increased risk of stroke with tiotropium Respimat® compared to placebo (RD (95%CI) = -0.07 (-0.57, 0.43)). The analysis of the composite cardiovascular endpoint was divergent to the imbalance in fatal events described. However, when the composite endpoint was restricted to fatal cardiovascular events, the RD was above 0 (RD (95% CI) = 0.54 (-0.10, 1.18)) (data on file, Tables 3.18.1.5.1.1, 3.18.1.7.1).

Subgroup analyses were performed to determine whether patterns of events suggest specific populations at risk. As expected, the risk of a fatal event increased with the severity of COPD (based on GOLD stage) in both treatment and placebo groups. The imbalance between treatment groups in all-cause mortality occurred in the less severe stages, with no imbalance in patients with very severe disease (GOLD stage IV). Subgroup analyses based on age and smoking status did not reveal any interactions which would require special consideration (U09-0060-01). However, the higher risk for all-cause mortality and fatal events in the cardiac SOC appeared to be concentrated in patients with known rhythm disorders at randomization (as recorded on the baseline history case report form), which included a wide range of disorders. There was a certain inconsistency in that concomitant use of cardiovascular medication or restriction to known coronary artery disease at baseline did not distinguish such patients as having a significant increased risk for a fatal event (all-cause or cardiac) (U09-3488-01). The contribution of the baseline known cardiac disorder to the fatal outcome is uncertain and a causal relationship with tiotropium Respimat® 5 mcg has not been established. Similar subgroup analyses examining patients with and without baseline cardiac disorders, rhythm disorders, cardiovascular medications and coronary arter disease were performed in the tiotropium HandiHaler® pooled clinical trial safety database and did not show an elevated risk in tiotropium treated patients.

11.5 CROSS-FORMULATION COMPARISONS FOR ALL-CAUSE MORTALITY INCLUDING VITAL STATUS INFORMATION FROM PREMATURELY DISCONTINUED PATIENTS

Incidence rates and rate differences were determined for all-cause mortality between formulations (tiotropium Respimat® 5, Respimat® 10 mcg and HandiHaler® 18 mcg) studied in trials where vital status information from prematurely discontinued patients was collected. The purpose of the analysis was to examine for differences using the most complete information on all-cause mortality considering an intention-to-treat approach (Respimat trials 205.254 (placebo N=319, tiotropium 5 mcg N=332, tiotropium 10 mcg N=332), 205.255 (placebo N=334, tiotropium 5 mcg N=338, tiotropium 10 mcg N=335)), and 205.372 (placebo N=1,965, tiotropium 5 mcg N=1,952), HandiHaler® trial 205.235 (UPLIFT)

(placebo N=3,006, tiotropium 18 mcg N=2,986)). In order to adjust for differences in trial duration, the analysis was restricted to fatal adverse events with the date of death occurring prior to day 337. It should be noted that vital status information from prematurely discontinued patients was initiated only after unblinding of trials 205.254 and 205.255 (pivotal Respimat® 1-year trials), during the conduct of the UPLIFT trial (collection completed while study was blinded) and prospectively collected from trial initiation in Respimat® trial 205.372. The incidence rate for fatal cases in the placebo group was lower in the Respimat® 5 mcg trials (0.66 to 2.44 events per 100 patient-years) compared to 2.57 in the UPLIFT HandiHaler® trial. Active treatment incidence rates ranged from 1.98 to 2.94 with tiotropium Respimat® 5 mcg and from 2.33 to 3.34 with tiotropium Respimat® 10 mcg, compared to 2.36 with tiotropium HandiHaler® in the UPLIFT trial. The incidence rates for the active treatments fell into a similar range but seemed to differ among the placebo arms suggesting a study bias that has not been identified. As was previously noted, the rate difference (tiotropium – placebo) was below 0 for tiotropium HandiHaler® in UPLIFT (reduced risk) and higher than 0 for tiotropium Respimat® (increased risk). The incidence rates for all-cause mortality based on pooling of the three 1-year tiotropium Respimat 5 mcg trials was 1.98 (placebo) vs. 2.78 (tiotropium) per 100 patient years (RD (95%CI) = 0.82 (-0.07, 1.68)). The corresponding numbers from UPLIFT for the protocol-defined treatment period (day 1440) were 4.66 and 4.04 per 100 patient years (RD (95%CI) = -0.62 (-1.18, -0.06)).

Table 11.5: 1 Incidence rates, rate differences (tiotropium - placebo) and 95% confidence intervals for all-cause mortality including vital status information from prematurely discontinued patients across trials 205.372, 205.254, 205.255 and UPLIFT (data censored beyond day 337)

	Placebo		Tiotropium		
	N	IR	N	IR	RD (95% CI)
Respimat® 5 mcg					
205.372	38	2.13	52	2.94	0.81 (-0.23, 1.86)
205.254	7	2.44	8	2.67	0.23 (-2.36, 2.81)
205.255	2	0.66	6	1.98	1.31 (-0.52, 3.14)
Respimat® 10 mcg					
205.254	7	2.44	7	2.33	-0.11 (-2.61, 2.38)
205.255	2	0.66	10	3.34	2.67 (0.41, 4.94)
HandiHaler® 18 mcg					
205.235 UPLIFT	70	2.57	64	2.36	-0.21 (-1.04, 0.63)

n=number of patients with an event; IR = incidence rate (per 100 patient years of time at risk); RD(95% CI) = rate difference (95% confidence interval)
Source data: data on file, Tables 3.20.1, 3.20.7, 3.20.8, 3.20.9, 3.20.38, 3.20.39

Subgroup analysis for all-cause mortality were performed based on several baseline characteristics using equivalent datasets as in Table 11.5: 1 (i.e. including vital status information from prematurely discontinued patients with data censored beyond day 337) in the tiotropium HandiHaler® UPLIFT trial and tiotropium Respimat® trial 205.372. Patients with a known rhythm disorder at baseline, appeared at higher risk for a fatal event in trial

205.372 but not in the UPLIFT trial (Table 11.6: 1). Differences in incidence rates for baseline rhythm disorders between the trials may represent an artefact as a baseline ECG was performed as part of the protocol in trial 205.372 whereas it was not required for the UPLIFT trial. Of note, the incidence rates remained lower with tiotropium HandiHaler® compared to placebo in UPLIFT when the full duration of the trial is considered.

Table 11.5: 2 Incidence rates, rate differences (tiotropium - placebo) and 95% confidence intervals for all-cause mortality including vital status information from prematurely discontinued patients in trials 205.372 and UPLIFT (data censored beyond day 337)

	Placebo		Tiotropium		Tiotropium - Placebo
	N	IR	N	IR	RD (95%CI)
Baseline cardiac disorder absent					
205.372	28	2.07	28	2.11	0.05 (−1.05, 1.14)
UPLIFT	44	2.16	43	2.15	−0.01 (−0.91, 0.90)
Baseline cardiac disorder present					
205.372	10	2.31	24	5.37	3.06 (0.48, 5.64)
UPLIFT	26	3.76	21	2.93	−0.83 (−2.75, 1.08)
Baseline rhythm disorder absent					
205.372	34	2.13	37	2.38	0.25 (-0.80, 1,30)
UPLIFT	61	2.39	60	2.38	-0.01 (-0.86, 0.84)
Baseline rhythm disorder present					
205.372	4	2.05	15	6.85	4.80 (0.80, 8.80)
UPLIFT	9	5.10	4	2.08	-3.02 (-6.93, 0.89)

n=number of patients with an event; IR= incidence rate (per 100 patient years of time at risk); RD (95% CI) = rate differences (95% confidence interval) per 100 patient years of time at risk
Trial 205.372: cardiac disorder absent/present: placebo (n= 1489/476), tiotropium (n= 1453/499); rhythm disorder absent/present: placebo (n= 1750/215), tiotropium (n= 1705/247)
UPLIFT trial: cardiac disorder absent/present: placebo (n=2241/765), tiotropium (n=2196/790); rhythm disorder absent/present: placebo (n=2810/196), tiotropium (n=2775/211)
Source data: data on file, UPLIFT Tables 3.23.1.1.4.13.2.1, 3.23.1.1.4.13.3.1, 3.23.1.1.4.18.2.1 and 3.23.1.1.4.18.3.1; Trial 205.372 Tables 3.22.1.1.4.13.2.1, 3.22.1.1.4.13.3.1, 3.22.1.1.4.18.2.1 and 3.22.1.1.4.18.3.1

11.6 DIFFERENCES IN DELIVERY SYSTEMS

The Respimat® delivers proportionally more drug to the lung than the HandiHaler®, thus the delivered or nominal dose has been reduced. Comparative pharmacokinetic (PK) evaluations were undertaken in three (205.249, 205.250, 205.291) crossover trials, in COPD patients. Table 11.6: 1 summarises the PK parameters of tiotropium at steady state (Day 29 after commencement of trial treatment dosing) with once daily inhalations via the Respimat® inhaler and the HandiHaler®. In two (205.250, 205.291) of the three trials the tiotropium PK parameters were comparable for the two formulations and in the third trial (205.249) there

was an increase (depending on the PK parameter, range = 1.29-1.72) in systemic exposure for tiotropium Respimat® compared to tiotropium HandiHaler®.

Table 11.6: 1 Geometric means (gMean) and geometric coefficients of variation (gCV) [%] of pharmacokinetic parameters of tiotropium Respimat® 5 mcg and tiotropium HandiHaler® 18 mcg for 4 weeks

	Unit	N	Tiotropium Respimat 5 mcg gMean	gCV [%]	Tiotropium HandiHaler 18 mcg gMean	gCV [%]
Study 205.249						
$AUC_{0-6,ss}$	[pg·h/mL]	52/54	26.1	77.4	20.2	73.8
$C_{0.167,ss}$	[pg/mL]	53/53	11.7	99.1	7.77	106
$Ae_{0-2,ss}$	[ng]	54/50	189	85.3	110	109
$Ae_{0-12,ss}$	[ng]	53/49	561	73.4	428	73.4
Study 205.250						
$AUC_{0-6,ss}$	[pg·h/mL]	34/35	26.8	78.4	24.2	71.0
$C_{0.167,ss}$	[pg/mL]	34/35	10.5	114	9.66	90.0
$Ae_{0-2,ss}$	[ng]	30/32	144	84.6	126	84.4
$Ae_{0-12,ss}$	[ng]	29/32	479	59.0	410	65.7
Study 205.249 and 205.250						
$AUC_{0-6,ss}$	[pg·h/mL]	87/89	26.4	76.7	21.7	73.0
$C_{0.167,ss}$	[pg/mL]	87/88	11.2	104	8.48	99.8
$Ae_{0-2,ss}$	[ng]	84/82	171	86.1	116	98.9
$Ae_{0-12,ss}$	[ng]	82/81	530	68.6	421	69.9
Study 205.291						
$AUC_{0-4,ss}$	[pg·h/mL]	141/140	30.4	60.4	29.6	66.5
$C_{0.167,ss}$	[pg/mL]	141/140	17.1	68.3	16.2	82.5
$Ae_{0-2,ss}$	[ng]	137/136	200	64.8	185	80.5

Abbreviations: AUC0-6,ss = area under the curve value for 6 hours post-dosing at steady-state; C0.167,ss = plasma concentration 10 minutes post-dosing at steady-state; Ae0-2,ss = amount of drug excretion unchanged in urine during 2 hours post-dosing at steady-state; Ae0-12,ss = amount of drug excretion unchanged in urine during 12 hours post-dosing at steady-state

Source Data: see U09-0060-01

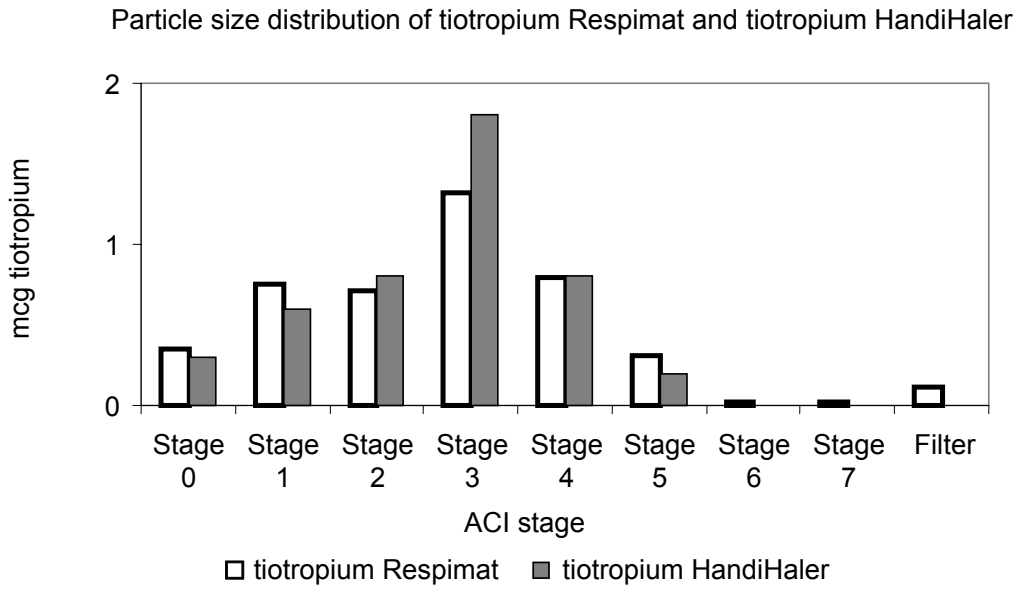
The earliest time point for measurement of plasma concentrations in the preceding table was 10 minutes. Data from earlier measurements has been compiled from open-label pharmacokinetic studies in different programs, where sampling as early as 2 minutes has been performed. Definitive conclusions are limited due to the data being from different studies. In steady state in COPD patients, the maximum plasma concentration was seen somewhat earlier following Respimat® and the maximum concentration (Cmax) trends higher, but not more than 1.5 fold. A direct comparison study focusing on early time points is currently being planned.

Table 11.6: 2 Time to maximum plasma concentration (tmax) and maximum plasma concentration (Cmax) of tiotropium Respimat® 5 mcg and HandiHaler® 18 mcg in COPD patients at steady state

Trial	Sampling	N	Tmax, median (min)	Cmax gMean (pg/mL)	Cmax gCV (%)
1237.3	Day 21 Time: 2, 5, 10 …minutes	45	5	15.9	63.8
205.117	Day 50 (92) Time: 5, 10…….minutes	84 (92)	5	17.3 (19.1)	65 (62)
1184.24	Day 28 Time: 2, 5, 10 …minutes	47	7	11.0	51.8

Source data: U09-1422-01, U99-3169, U09-2123-01

Figure 11.6: 1 shows the comparable dose distribution for tiotropium across the various stages of the Andersen Cascade Impactor for the two formulations. Of note, the conditions to determine the *in vitro* particle size distributions (e.g. flow time, humidity) have been optimised for each product and, therefore, differ between the two products. The flow rate of the Andersen Cascade Impactor measurement was set at 28.3 l/min for both formulations.



Source Data: see U09-0060-01

Figure 11.6: 1 Particle size distribution of tiotropium Respimat® 5 mcg and tiotropium HandiHaler® 18 mcg

A scintigraphy trial (P07-11816) conducted in healthy subjects and in patients with mild, moderate and severe COPD showed that 19% of the tiotropium HandiHaler® 18 mcg dose is

deposited in the lungs (approximately 3.4 mcg). In a separate scintigraphy trial not involving tiotropium (P08-10899) conducted in patients with COPD using an aqueous formulation (similar to that for tiotropium from the Respimat® inhaler) resulted in a lung deposition of 53% of the declared dose. This would amount to approximately 2.7 mcg tiotropium administered from the Respimat® 5 mcg formulation.

The difference in excipients (lactose in HandiHaler® vs. small amounts of BAC, EDTA and hydrochloric acid in the Respimat®) is unlikely to lead to differences in either reduced efficacy or worsened safety when comparing different formulations. Within formulation comparisons of the active and placebo Respimat® drug products indicate that excipient differences could not be driving the imbalances in the Respimat® studies as all placebo treated patients used identical formulations with the exception of the presence/absence of active drug.

The similarity in efficacy between the two formulations has been reported in 207 European and North American COPD patients in two randomised, placebo-controlled, double-blind, double-dummy, crossover trial (205.249, 205.250) (P09-02122) of 4-weeks treatment for each arm of the trial. The mean trough FEV_1 response, compared to placebo, at the end of the 4-week treatment period was 126 mL and 97 mL for the tiotropium Respimat® and tiotropium HandiHaler®, respectively. Both responses were significantly greater than placebo ($p<0.0001$). In another trial (205.291), conducted in Japanese COPD patients, the efficacy of the two formulations was investigated in a randomised, placebo-controlled, double-blind, double-dummy, crossover trial (U07-3262) of 4-weeks treatment for each arm of the trial. The data on 134 evaluable patients showed that the trough FEV_1 response at 4 weeks for tiotropium Respimat® was non-inferior to tiotropium HandiHaler® (mean treatment difference, 8 mL; 95% CI, -9 to +24 mL, $p<0.001$).

Both tiotropium formulations have similar *in vitro* dose characteristics, they deliver comparable doses of the drug to the lungs with similar pharmacokinetic profiles resulting in comparable efficacy response, as evaluated by trough FEV_1 at Day 29 (steady state) following commencement of drug administration. However, modest differences in systemic exposure to tiotropium Respimat® relative to the HandiHaler® were observed in 205.249/205.250 but not in trial 205.291.

11.7 SUMMARY OF FORMULATION DIFFERENCES

Both formulations have demonstrated consistent efficacy in patients with COPD. Tiotropium Respimat® 5 mcg daily offers significant improvements in lung function, symptom reduction, improvement in health-related quality of life as measured by the SGRQ and reduction in exacerbations and associated hospitalisations in patients with COPD compared to placebo. For fatal adverse events, an imbalance in favor of placebo was observed in study 205.372 and when combined with the other one-year Respimat® trials (205.254, 205.255). In study 205.372, an imbalance in fatal events in the SOC neoplastic disorders and in lung neoplasms was observed, which was also observed for the corresponding categories for all adverse events and serious adverse events. The observations relating to neoplasms are inconsistent with previous studies using either tiotropium Respimat® or HandiHaler®. There are no biologically plausible mechanisms to suggest the induction or promotion of neoplasms by

tiotropium treatment, independent of administration device. There is no preclinical evidence for such a relationship. When analysing fatal events excluding neoplasms / lung neoplasms, the imbalance in trial 205.372 (until day 337 including vital status of prematurely discontinued patients) was reduced (RD (95%CI) = 0.41 (-0.57, 1.39)); however, the rate difference remained above zero. The fatal event results are contrary to those observed for the UPLIFT trial from the HandiHaler® formulation where the data indicated an incidence rate in the tiotropium group less than that observed for the placebo group.

Clinical pharmacokinetic comparisons of tiotropium Respimat® and HandiHaler® in patients with COPD have shown a relatively small numerical difference in systemic exposure (approximately 20% higher with tiotropium Respimat® 5 mcg in trials 205.249 and 205.250 in Caucasians), or no appreciable difference (trial 205.291, in Japanese).

In summary, the pooled clinical trial data of the product presently marketed in the United States (tiotropium HandiHaler®) indicates a rate difference (tiotropium - placebo) less than zero for all-cause mortality and for cardiac mortality. Tiotropium HandiHaler studies demonstrated that cardiovascular morbidity was not increased as assessed through adverse event reporting (overall rate differences are less than 0). The Respimat® formulation indicated an effect in the opposite direction for fatal events. Tiotropium Respimat® was associated with a higher incidence rate of fatal events relative to placebo, including those considered cardiac in origin; however, there were inconsistencies when extending the observations to overall major adverse cardiovascular events. Additionally, findings related to neoplasms in the Respimat® program suggest a failure of randomization and/or the presence of unmeasured confounders.

In the pooled analysis of the five tiotropium Respimat® 5 mcg clinical trials, there were 101 deaths during the period at risk, with 62 and 39 deaths in the tiotropium Respimat® and placebo groups respectively. A 6-month clinical trial in a different development program (1205.14) for COPD has recently been completed. The protocol inclusion/exclusion criteria were similar to those used in the tiotropium HandiHaler and Respimat COPD protocols presented in this briefing document. Tiotropium Respimat 5 mcg (N=427) and placebo Respimat (N=429) were two of the treatment arms in trial 1205.14, in which there were 2 and 5 deaths reported respectively. A Forest plot of the rate differences including this 6-month trial is displayed in 11.7: 1. The RD (95%CI) (tiotropium minus placebo) for all 6 trials was 0.68 (-0.09, 1.45).

Source	Treatment # events	Treatment Yrs at risk	Control # events	Control Yrs at risk	Weight	Rate difference (95% CI)
0205.0251	0	27	0	28	1.0	
0205.0252	0	28	0	27	1.0	
0205.0254	7	306	5	263	10.8	0.39 (-1.99,2.76)
0205.0255	5	307	0	264	10.8	1.63 (0.20,3.06)
0205.0372	50	1803	34	1770	68.0	0.85 (-0.15,1.86)
1205.0014	2	224	5	215	8.3	-1.43 (-3.81,0.96)
Total	**64**	**2695**	**44**	**2568**	**100.0**	**0.68 (-0.09,1.45)**

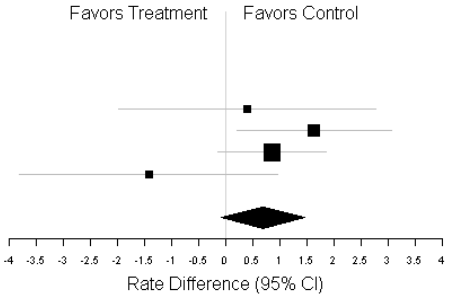


Figure 11.7: 1 Incidence rates and rate differences (tiotropium - placebo) per 100 patient-years for all-cause mortality in 6 tiotropium Respimat® 5 mcg trials.

Source data: data on file, Tables 3.17.1.3.3 and 3.17.1.1.4

The mortality observations from the Respimat® database (5 trials, 6,448 patients, 5,487 patient-years at risk) are inconsistent with the larger tiotropium HandiHaler database (26 trials, 17,014 patients, 23,934 patient years at risk). In addition, the tiotropium HandiHaler® database includes a large study of 4 years duration, whereas the Respimat® database is limited to studies of up to 1 year in duration. An examination of the formulation properties indicates that there is no known scientific rationale to expect an apparent difference in fatal event reporting based on the pharmacology of the substance, the pharmacokinetics of the formulations or excipients of each device. Given the observations with the tiotropium Respimat® formulation, a large, long-term clinical trial will be initiated in 2010 examining the relative benefits and risks of tiotropium Respimat® (employing two doses, 2.5 mcg and 5 mcg once daily) to tiotropium HandiHaler® 18 mcg once daily in patients with COPD. A treatment arm with tiotropium Respimat® 2.5 mcg is included to establish the long-term safety profile of the 2.5 mcg formulation relative to the two marketed tiotropium products as the 2.5 mcg is part of an on-going development program for the combination of tiotropium and a once-daily inhaled beta-agonist in the Respimat® formulation.

12. ADVERSE EVENTS FROM SPONTANEOUS AND HEALTH AUTHORITY SOURCES

Spontaneous reporting was evaluated for fatal events, cardiovascular events, stroke and lower respiratory events. A detailed description of the data can be found in an expanded Section 12 contained in Appendix 17.4. The summaries are presented from the global database and limited to the United States. The frequency and distribution of fatal events, cardiovascular adverse events, stroke and respiratory events seen in the spontaneous safety data with tiotropium are consistent with what would be expected in the population of patients where tiotropium would be prescribed. The events are expected in patients with COPD given the increased age of patients, medical complications associated with COPD, illnesses often associated with prolonged tobacco use (cardiovascular and neoplastic) and the common use of concomitant medications. However, the lack of a reliable denominator, expected reporting frequency and reference data limit definitive conclusions based on spontaneous data.

Disproportionality analysis is a statistical approach that attempts to quantify whether the rate of spontaneous reporting may constitute a safety signal. Disproportionality analysis determines whether the observed number of reports for a drug-event combination is higher than the expected number as calculated from the distribution of drugs and events in the database and are discussed in the following section. The results of the analysis indicate that the number of reports of all-cause mortality, cardiac mortality, stroke and COPD outcomes associated with tiotropium is within or below the numerical expectation.

12.1 DISPROPORTIONALITY ANALYSIS OF SPONTANEOUS REPORTS FROM THE UNITED STATES

In March 2005, the FDA published a Guidance for Industry (*Good Pharmacovigilance Practices and Pharmacologic Assessment*). This guidance describes the use of statistical and mathematical methods to provide additional information about the existence of an excess of adverse events reported for a product. One method described in the guidance is the disproportionality analysis. Disproportionality analysis determines whether the observed number of reports for a drug-event combination is higher than the expected number calculated from the distribution of drugs and events in the database.

Disproportionality is computed using the Multi-Item Gamma Poisson Shrinker (MGPS) statistical algorithm. The MGPS computes the Empirical Bayes Geometrical Mean (EBGM) and associated two-sided 90% confidence interval (EB05, EB95) for each drug-event pair in a database. EBGM represents the reporting for a drug-event pair relative to all other reports in the database. An EBGM of 2 can be interpreted to mean that a drug-event pair has been reported 2 times as frequently as would be expected if reports involving the drug and reports involving the event were independent. An EB05 of 2 indicates 95% confidence that the relative reporting ration (EBGM) is at least 2. An EB05 $\geq$ 2 is recognized as a possible threshold for identifying a drug-event association to be medically reviewed for its clinical relevance.

Although disproportionality analysis is useful in detecting safety signals that may warrant further investigation, there are limitations to the method.

- The analysis only provides information about relative reporting of adverse events. It does not provide an estimate of the incidence of adverse events.
- Disproportionality is not a tool for establishing a causal relationship between a drug and an event.
- Reporting of spontaneous events can be affected by many factors, including, population of interest, publicity about an event or drug, awareness of adverse event reporting systems, length of time a drug has been available in the marketplace and association of an adverse event with another similar drug.

Disproportionality analysis was used to evaluate the reporting for tiotropium and reports of all cause mortality, cardiac mortality, stroke and COPD outcomes. The analysis was performed using public FDA Adverse Event Reporting System (AERS) data through the end of December 2008. This release of the AERS data is known as "2008Q4". Only those cases where tiotropium was reported as a suspect drug were selected. For the COPD outcomes analysis, the background was limited to reports where drugs used to treat obstructive airway disease were considered suspect. Drugs categorized in the ATC/DDD Index 2009 as R03; Drugs for Obstructive Airway disease were used to select the background.

Disproportionality analysis computed from all data through the end of December 2008 is shown in the following table.

Table 12.1: 1 Disproportionality analysis for tiotropium from 2004 until December 2008.

	N	EB05	EBGM	EB95
All-cause mortality	511	0.5	0.5	0.5
Cardiac mortality	121	0.5	0.5	0.6
Stroke	70	0.2	0.2	0.2
COPD Outcomes	728	1.1	1.2	1.3

Source data: data on file, see Spontaneous Adverse Event Disproportionality Analysis

All cause mortality was defined as an event outcome of death or any MedDRA v 11.1 Preferred Term (PT) within the MedDRA Higher Level Group Term (HLT) of “Death and sudden death”. Cardiac mortality was defined as any PT with an outcome of death within the MedDRA System Organ Class (SOC) of Cardiac disorders or the PT “Sudden cardiac death” or the PT “Sudden death”. The list of PTs used to select Stroke and COPD outcomes are displayed in Appendix 17.1.

The results of the disproportionality analysis indicate that for tiotropium, the number of reports referring to all-cause mortality, cardiac mortality, stroke and COPD outcomes is within or below the numerical expectation.

A cumulative disproportionality analysis is shown in the table below. The cumulative analysis covers the period from the initial marketing of tiotropium in the United States through the end of 2008. The data display the expected trend of lower EBGM and narrower confidence intervals the longer the product is in the marketplace.

Table 12.1: 2 Cumulative disproportionality analyses for tiotropium from 2004 until December 2008.

	Year	N	EB05	EBGM	EB95
All-cause mortality	2008	511	0.5	0.5	0.5
	2007	398	0.6	0.6	0.7
	2006	309	0.6	0.7	0.8
	2005	247	0.7	0.8	0.9
	2004	96	0.7	0.8	0.9
Cardiac mortality	2008	121	0.5	0.5	0.6
	2007	100	0.6	0.7	0.8
	2006	81	0.6	0.7	0.9
	2005	65	0.7	0.8	1.0
	2004	32	0.9	1.2	1.5
Stroke	2008	70	0.2	0.2	0.2
	2007	34	0.1	0.1	0.2
	2006	18	0.1	0.1	0.1
	2005	7	0.0	0.1	0.1
	2004	1	0.0	0.0	0.1

Source data: data on file, see Spontaneous Adverse Event Disproportionality Analysis

The results of the analysis indicated that the number of reports of all-cause mortality, cardiac mortality, stroke and COPD outcomes associated with tiotropium was within or below the numerical expectation. Results of an annual cumulative analysis of tiotropium reports throughout the period of time that tiotropium has been available in the United States showed the expected trend of lower EBGM and narrower confidence intervals the longer the product has been in the marketplace.

12.2 CONCLUSIONS

Within the acknowledged limitations of evaluation of spontaneous reporting, it can be generally concluded that there are no new safety signals that have emerged from the post-marketing spontaneous reports, including cardiovascular events, stroke or mortality.

13. EPIDEMIOLOGIC DATA

Several epidemiological projects regarding the characteristics of COPD populations and the safety of tiotropium have been conducted. The studies highlighted the increased risk of fatal events and cardiovascular morbidity that is expected in patients with COPD. Studies specifically addressing tiotropium did not indicate an increased risk for fatal events.

13.1 CARDIOVASCULAR MORBIDITY AND MORTALITY AMONG PATIENTS WITH COPD AND BY SEVERITY OF COPD. TWO STUDIES IN THE SASKATCHEWAN HEALTH DATABASE

Two observational studies have been conducted in the Saskatchewan Health Database, one on the cardiovascular morbidity and all-cause mortality among patients with COPD and one on the association between predictors of COPD severity and the risk of cardiovascular outcomes (R09-0579, P07-09136).

13.1.1 Cardiovascular morbidity and all-cause mortality among patients with COPD

The first cohort study was conducted in the Saskatchewan Health Database on a prevalent COPD cohort to estimate the prevalence and incidence of cardiovascular comorbidities in a COPD population of at least 40 years of age (R09-0579). For each COPD patient (study diagnosis included chronic airway obstruction, emphysema or chronic bronchitis) in the database during 1997-2000 two randomly selected age and gender-matched comparison patients without a COPD diagnosis, asthma, other respiratory conditions or respiratory medications were selected among all individuals in the database. For the COPD cohort, the follow-up period started on the earliest date after 1 January 1998 and prior to 31 December 2000 by which the patient fully qualified for entry into the cohort (index day). Each control patient was assigned the same index date as the corresponding COPD patient. Baseline characteristics were assessed for the 12-month period prior to the index day. The COPD and the matched comparison cohort were followed up for hospitalizations due to cardiovascular outcomes until 31 December 2001. Chart review was conducted on a sample of incident cardiovascular outcomes. Incidence rate ratios (IRR) and 95% confidence intervals (CI) for first hospitalization of each cardiovascular outcome were adjusted for history of cardiac outcomes and diabetes, hypertension and hypercholesterolemia using multivariate Poisson regression. Furthermore, a survey was conducted to quantify the smoking pattern in the study populations.

The study population consisted of 11,493 COPD patients and 22,986 controls. The prevalence of cardiovascular morbidities was significantly higher in the COPD population compared to patients without COPD. The COPD group had a very high percentage of "ever" smokers, 80%, compared to 53% in the non-COPD group. Sixteen percent of the COPD cohort and 11% of the cohort without COPD were current smokers.

The incidence rate ratios for cardiovascular events are summarized in Table 13.1.1: 1. COPD was associated with an increased risk of arrhythmia, angina, congestive heart failure (CHF) and of any first cardiovascular disease (CVD) hospitalization when compared to patients without COPD. The rate ratios for acute myocardial infarction (AMI), stroke, and pulmonary

embolism were not statistically significantly increased although the respective point estimates were elevated. After adjustment for baseline cardiovascular risk factors, including prior hospitalization for the outcome, the rate ratios were still all higher than one; however, the 95%CI for AMI, stroke and pulmonary embolism included one (Table 13.1.1: 1).

Table 13.1.1: 1 Incidence rates and adjusted incidence rate ratios (95% CI) of first hospitalization due to cardiovascular endpoints (Saskatchewan study)

	COPD Patients (N=11,493)	**Control Patients (N=22,986)**	
	Event/1,000 PY (95% CI)	**Event/1,000 PY (95% CI)**	**Adjusted Rate Ratio* (95% CI)**
Arrhythmia	16.4 (14.9, 18.1)	8.18 (7.47, 8.94)	1.67 (1.27, 2.22)
Angina	6.02 (5.14, 7.02)	2.34 (1.97, 2.76)	2.08 (1.52, 2.86)
Acute myocardial infarction	10.9 (9.65, 12.2)	6.56 (5.93 , 7.24)	1.49 (0.71, 3.13)
Congestive heart failure	32.0 (29.8, 34.2)	6.10 (5.50, 6.76)	3.45 (2.78, 4.17)
Stroke	12.4 (11.1, 13.9)	9.77 (9.00, 10.6)	1.23 (0.68, 2.22)
Pulmonary embolism	1.72 (1.27, 2.29)	0.31 (0.19, 0.49)	4.76 (0.79, 25.0)
Other Cardiovascular Disease**	54.1 (51.3, 57.0)	21.4 (20.3, 22.7)	2.17 (1.96, 2.38)
Any first cardiovascular disease hospitalization	109.5 (105.4, 113.8)	44.7 (43.0, 46.4)	2.17 (2.00, 2.33)

PY person-years, CI Confidence interval

* Rate ratio and 95% confidence interval adjusted for history of cardiovascular events, diabetes, hypertension, and hypercholesterolemia using Poisson regression.

**defined by ICD-9 codes for acute rheumatic fever, chronic rheumatic heart disease, hypertensive disease, ischemic heart disease (excluding acute myocardial infarction), diseases of pulmonary circulation, other forms of heart disease (excluding conduction disorders, cardiac dysrhythmias and heart failure), ill-defined descriptions and complications of heart disease, subarachnoid hemorrhage, other and ill-defined cerebrovascular disease, late effects of cerebrovascular disease and diseases of arteries, arterioles, and capillaries, and diseases of veins and lymphatics, and other diseases of circulatory system, and other ill-defined and unknown causes of morbidity and mortality

Source Data: R09-0579, Table 6

Incidence rates and adjusted rate ratios for cardiovascular and all-cause mortality are summarized in Table 13.1.1: 2. COPD was associated with a 2.1-fold increased risk of any cardiovascular mortality and a 2.8-fold increased risk of all-cause mortality.

Table 13.1.1: 2 Incidence rates and adjusted rate ratios (95% CI) of cardiovascular and all-cause mortality for COPD (Saskatchewan study)

	COPD Patients (N=11,493)	**Control Patients (N=22,986)**	
	Event/1,000 PY	**Event/1,000 PY**	**Adjusted Rate Ratio* (95% CI)**
Underlying cause of death			
Arrhythmia	1.94	0.69	2.81 (1.59, 4.98)
Acute myocardial infarction	5.89	3.90	1.51 (1.14, 2.01)
Congestive heart failure	4.10	1.00	4.09 (2.64, 6.33)
Stroke	4.17	3.37	1.24 (0.90, 1.71)
Any cardiovascular mortality	31.9	15.4	2.07 (1.82, 2.36)
All-cause mortality	106.6	37.8	2.82 (2.61, 3.05)

PY person-years, CI Confidence interval. * Rate ratios and 95% confidence interval adjusted for history of cardiovascular events, diabetes, hypertension, and hypercholesterolemia using Poisson regression.
Source Data: R09-0579, Table 6

This study showed that the incidence estimates of hospitalization due to arrhythmia, angina, AMI, congestive heart failure (CHF), stroke, pulmonary embolism and other cardiovascular disease were also significantly higher in the COPD population. Additionally, the above study demonstrated that COPD was strongly associated with all-cause mortality and all cardiovascular mortality endpoints including stroke.

13.1.2 Cardiovascular morbidity and all-cause mortality by COPD severity

An ancillary study was performed based on the COPD cohort of 11,493 patients identified in the first Saskatchewan study with the purpose to determine how to measure severity of COPD using administrative data sources and to define the association between the degree of severity of COPD and cardiovascular outcomes (P07-09136). The likelihood of being hospitalized for COPD was estimated in a nested case-control study within the COPD cohort. Each patient was characterized according to quintiles of COPD severity. Then, the severity levels were used as independent predictors of cardiovascular outcomes in multivariate Poisson regression models.

Predictors of COPD severity included emphysema, recent nebulizer use, home oxygen services, corticosteroid use, frequency bronchodilator use, pneumonia and prior COPD exacerbation. Age groups, gender, and diabetes, hypertension, hypercholesterolemia and obesity assessed during the baseline period were included in the model.

Two different specifications of quintiles were used. The first defining the two quintiles of patients (40%) with the highest severity as high, those in the middle quintile (20%) as medium, and those in the lowest two quintiles (40%) as low. The second specification defined the top 20% for high, the middle 60% for medium, and the bottom 20% for low. The study results for the relationship between COPD severity defined by severity category 20, 60, 20% and the incidence of cardiovascular disease are presented in Table 13.1.2: 1. This category was chosen as the 20, 60, 20% quintiles more accurately identify extreme COPD severity strata.

Table 13.1.2: 1 Relationship of severity of chronic obstructive pulmonary disease (COPD) to incidence of hospitalization and mortality due to cardiovascular diseases (Saskatchewan study)

	Severity categories[a] 20, 60, 20%		
	High vs. low	**High vs. middle**	**Middle vs. low**
Cardiovascular diseases[b]	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Arrhythmia (n= 338)	0.80(0.54, 1.18)	0.98(0.70, 1.38)	0.81(0.59, 1.11)
Acute myocardial infarction (n = 208)	1.18(0.77, 1.81)	1.24(0.87, 1.75)	0.95 (0.66, 1.37)
Ischemic heart disease (n = 371)	1.17(0.85, 1.62)	1.30(1.00, 1.70)	0.90 (0.68, 1.19)
Angina (n = 116)	1.71(0.95, 3.08)	2.16(1.35, 3.45)	0.79 (0.45, 1.38)
Congestive heart failure (n = 651)	1.42(1.06, 1.90)	1.22(0.97, 1.52)	1.17 (0.91, 1.50)
Other cardiovascular diseases (n = 717)	0.96(0.75, 1.24)	1.08(0.87, 1.33)	0.90 (0.73, 1.11)
Any cardiovascular hospitalization (n = 1780)	1.00(0.83, 1.21)	1.11(0.96, 1.30)	0.90 (0.77, 1.05)
Cardiovascular mortality (n = 590)	1.63(1.22, 2.16)	1.17(0.95, 1.43)	1.39 (1.09, 1.79)
Overall mortality (n = 1975)	3.07(2.45, 3.86)	1.79(1.56, 2.07)	1.71 (1.38, 2.13)

*All rate ratios (RR) were adjusted for gender and age group using multivariate Poisson regression. Additionally, the AMI and angina risk ratios were adjusted for hypertension, the arrhythmia, other CVD and CVD hospitalization risk ratios were adjusted for diabetes, the CHF risk ratio was adjusted for diabetes and hypertension, and the ischemic heart disease risk ratio was adjusted for diabetes, hypertension and hypercholesterolemia.

[a] ‘Severity categories’’ refers to the proportions of patients in each severity category. The category labeled 20, 60, 20% means that ‘‘high’’ includes the most severe 20% of patients, ‘‘middle’’ includes the next 60% of patients and ‘‘low’’ includes the least severe 20% of patients.

[b] The number of patients with a first hospitalization for each cardiovascular disease and the number of mortalities are listed in this column. For example, of 7575 patients with COPD, 338 were hospitalized at least once with arrhythmia, 1975 died during the follow-up period and 590 of these died of cardiovascular disease.

Source Data: P07-09136, Table 5

Severity of COPD was positively related to the prevalence of arrhythmia, acute myocardial infarction, ischemic heart disease, angina, congestive heart failure, cardiovascular mortality and overall mortality. With the exception of arrhythmia, COPD severity was positively associated with the incidence of hospitalization due to these cardiovascular diseases. Severity of COPD was also positively associated with cardiovascular mortality and all-cause mortality.

13.2 COPD AND INCIDENT CARDIOVASCULAR DISEASE HOSPITALIZATION AND MORTALITY: KAISER PERMANENTE MEDICAL CARE PROGRAM

A cohort study was conducted in the Northern California Kaiser Permanente Medical Carfe Program (KPNC) health –care system (R07-2623). Among all KPNC members approximately 3.2 million members, a total of 45,966 members with COPD were identified during a 4-year period from January 1996 through December 1999. An equal number of subjects without COPD (non-COPD) were selected from KPNC membership and matched for gender, year of birth, and length of KPNC membership. Follow-up was conducted for hospitalization and mortality from cardiovascular disease (CVD) endpoints through December 31, 2000. CVD study end points included cardiac arrhythmias, angina pectoris,

acute myocardial infarction (MI), congestive heart failure (CHF), stroke, pulmonary embolism, all of the aforementioned study end points combined, other CVD, and all CVD end points. Because of too few deaths from ventricular tachycardia (VT)/ventricular fibrillation (VF)/cardiac arrest, atrial fibrillation, other arrhythmia and pulmonary embolism, the authors did not report respective rates and rate ratios. Multivariable hazard ratios were estimated using Cox proportional hazard models and age, gender, and cardiovascular risk morbidities (ie, diabetes, hypertension, and hyperlipidemia) and the presence of baseline CVD detected during the 6-month period prior to the index date (e.g., MI or stroke). The mean follow-up time was 2.75 years for the COPD cohort and 2.99 years for non-COPD cohort. Adjusted hazard ratios for hospitalization for all cardiovascular endpoints are presented in Table 13.2: 1.

COPD was associated with a significantly increased risk of all study endpoints when compared to non-COPD patients. Hazard ratios ranged from 1.33 (95% CI = 1.21, 1.47) for stroke to 3.75 (95% CI = 3.39, 4.15) for CHF and to 2.09 (95% CI = 1.99, 2.20) for the measure of all study end points (Table 13.2: 1).

Table 13.2: 1 Incidence and adjusted hazard ratios of hospitalization during follow-up for study end points in COPD and non-COPD cohort (Kaiser Permanente study)

	COPD cohort		**Non-COPD cohort**		
Outcome	**Cases**	**Rate***	**Cases**	**Rate***	**Adjusted hazard ratios (95% CI)****
VT/VF/cardiac arrest	123	97.5	32	23.3	2.80 (1.87, 4.20)
Atrial fibrillation	741	592.1	342	249.7	1.98 (1.73, 2.25)
Other arrhythmia	372	295.9	206	151.1	1.71 (1.43, 2.03)
Angina	664	530.6	319	232.9	1.98 (1.73, 2.27)
MI	1,184	949.6	619	453.1	1.89 (1.71, 2.09)
CHF	2,233	1,807.3	482	352.0	3.75 (3.39, 4.15)
Stroke	1,010	808.1	753	551.7	1.33 (1.21, 1.47)
Pulmonary embolism	163	129.4	59	42.9	2.72 (2.00, 3.68)
Other CVD***	2,846	2,333.9	1,477	1,092.9	1.85 (1.73, 1.97)
Any study end point****	5,410	4,557.3	2,460	1,837.3	2.09 (1.99, 2.20)
Any CVD	7,378	6,401.8	3,678	2,792.5	1.95 (1.88, 2.03)

*Age-adjusted rate per 100,000 person-years. **Adjusted for age, gender, hypertension, hyperlipidemia, and diabetes.
***Includes all CVD diagnostic codes (ICD-9 codes 390x to 459x) not included in the main study end points (i.e. the first eight end points on the list in this table).
**** Includes VT/VF/cardiac arrest, atrial fibrillation, other arrhythmia, angina, myocardial infarction (MI), CHF, stroke and pulmonary embolism.
Source Data: R07-2623, Table 3

The adjusted HR for mortality for the measure of all study end points was 1.68 (95% CI, 1.50 -1.88) (Table 13.2: 2).

Table 13.2: 2 Cardiovascular mortality rates by cardiovascular endpoint during follow-up for COPD and non-COPD cohort (Kaiser Permanente study)

	COPD cohort		Non-COPD cohort		
	Deaths	**Rate***	**Deaths**	**Rate***	**Adjusted hazard ratios (95% CI)****
Myocardial infarction	487	385.8	241	213.8	1.81 (1.54, 2.12)
Congestive heart failure	138	109.3	32	30.5	3.53 (2.38, 5.25)
Stroke	260	206.0	204	171.6	1.25 (1.03, 1.51)
Pulmonary embolism	29	19.8	12	10.2	1.89 (0.93, 3.85)
Other CVD***	1,407	1,114.7	614	542.0	1.96 (1.77, 2.16)
Any study end points****	918	727.2	498	434.9	1.68 (1.50, 1.88)
All cardiovascular diseases	2,325	1,842.2	1,112	977.2	1.84 (1.70, 1.98)

CI, Confidence Interval; *Age-adjusted rates per 100,000 person-years. **Adjusted for age, gender, hypertension, hyperlipidemia, and diabetes. ***Includes all CVD diagnostic codes (ICD-9 codes 390x to 459x) not included in the main study end points (*ie*, VT/VF/cardiac arrest, atrial fibrillation, other arrhythmia, angina, myocardial infarction (MI), CHF, stroke and pulmonary embolism). There were too few cases of VT/VF/cardiac arrest, atrial fibrillation, other arrhttymia and pulonary embolism to report meaningful rates and rate ratios.
**** Includes VT/VF/cardiac arrest, atrial fibrillation, other arrhythmia, angina, myocardial infarction (MI), CHF, stroke and pulmonary embolism.
Source Data: R07-2623, Table 4

COPD was associated with a significantly increased mortality risk from specific cardiovascular endpoints when compared to non-COPD patients: hazard ratios ranged from 1.25 (95% CI = 1.03, 1.51) for stroke to 3.53 (95% CI = 2.38, 5.25) for CHF and to 1.68 (95% CI = 1.50, 1.88) for the measure of all study end points.

The study concluded that COPD was a predictor of CVD hospitalization and mortality over an average follow-up time of nearly 3 years.

13.3 COMPARATIVE SAFETY OF LONG-ACTING INHALED BRONCHODILATORS: TWO STUDIES IN THE HEALTH INFORMATION NETWORK DATABASE (THIN)

Two cohort studies on the comparative safety of long-acting inhaled bronchodilators were conducted by the same investigators in The Health Information Network (THIN) primary care database in the United Kingdom (UK). The main difference between the two studies was the study period which lasted from 2002 to 2004 in Jara et al. 2007 (P07-13582) in contrast to 2002 to 2007 in Jara et al. 2008 (U08-3413-01).

13.3.1 Comparative safety of long-acting inhaled bronchodilators: a cohort study using the UK THIN primary care database I (study period 2002-2004)

This study compared the risk of cardiac adverse events and of total mortality among users of tiotropium and of single-ingredient long-term ß-agonists (LABA) (P07-13582). Cohort members were required to be at least 40 years old, to have at least one year of baseline data prior to their first or 'index' prescription for tiotropium or LABA between November 2002 and June 2004, and not have asthma listed as their only respiratory diagnosis. Study endpoints included angina, atrial fibrillation and flutter, heart failure, myocardial infarction,

tachycardia and all-cause mortality. All events were identified with medical codes only. Patients were followed up from the date of their first eligible prescription until the earliest of the following: date of study endpoint; date of long-acting bronchodilator switch or add-on; date of transfer to a new practice; date of death; or last collection date of the participating practice.

Cox proportional hazards models were used to compute hazard ratio (HR) estimates and 95% confidence intervals (CI) and to control for potential confounders including age, sex, BMI, number of hospitalizations in the year prior to cohort entry, cardiac co-morbidities, COPD symptoms and asthma. Propensity scores comprising various baseline demographic variables, medical therapies and comorbidities were used for adjustment. The study population consisted of 2,862 patients (1,061 tiotropium and 1,801 LABA). Hazard ratios for cardiovascular events are summarized in Table 13.3.1: 1.

Table 13.3.1: 1 Hazard ratios and 95% confidence intervals for cardiovascular endpoints (THIN study)

	Tiotropium N=1061 470 PY		**LABA N=1801 746 PY**		**Adjusted HR* (95% CI)***
Adverse Events	**N**	**Rate/ 100 PY**	**N**	**Rate/ 100 PY**	
Angina	11	2.34	26	3.49	0.77 (0.37, 1.59)
Atrial fibrillation/flutter	8	1.70	18	2.41	0.60 (0.25, 1.42)
Heart failure	20	4.26	44	5.90	0.65 (0.37, 1.12)
Myocardial infarction	7	1.49	9	1.21	1.29 (0.45, 3.66)
Tachycardia	9	1.91	18	2.41	0.66 (0.29, 1.51)

PY, person-years at risk; HR Hazard Ratios, CI Confidence interval, *Adjusted using a propensity score including respiratory diagnosis, age, sex, calendar year, smoking , BMI, number of hospitalizations at baseline, cardiac comorbidities, respiratory and cardiac medications
Source Data: P07-13582, Table II

Incidence rates and the adjusted hazard ratio for all-cause mortality are summarized in Table 13.3.1: 2.

Table 13.3.1: 2 Hazard ratios and 95% confidence intervals for all-cause mortality in new users of long-acting bronchodilators (THIN study)

	Tiotropium N=1061 470 PY		**LABA N=1801 746 PY**		**Adjusted HR* (95% CI)***
	N	**Rate/ 100 PY**	**N**	**Rate/ 100 PY**	
All-cause mortality	35	7.45	53	7.10	0.93 (0.59, 1.44)

PY, person-years at risk; CI, Confidence Interval*Adjusted using a propensity score HR Hazard Ratios, CI Confidence Interval, *Adjusted using a propensity score including respiratory diagnosis, age, sex, calendar year, smoking , BMI, number of hospitalizations at baseline, cardiac comorbidities, respiratory and cardiac medications
Source Data: P07-13582, Table II

Users of tiotropium and of single-ingredient LABA had similar risk of cardiovascular endpoints. Except for myocardial infarction, tiotropium was associated with 23% to 40%

decreased point estimates of risks for cardiac events. Users of tiotropium and of single-ingredient LABA had similar risk of all-cause mortality

13.3.2 Comparative safety of long-acting inhaled bronchodilators in the UK THIN primary care database II (study period 2002-2007)

This study was an extension of the previous, used the same methodology but required patients to have at least two years of baseline data prior to the index prescription which could have been between November 2002 and June 2007 (U08-3413-01). Cox proportional hazards models were used to compute hazard ratio (HR) estimates and 95% confidence intervals (CI) for tiotropium use vs. LABA use for cardiovascular endpoints and all-cause mortality. Propensity scores were used to adjust for potential confounding. Covariates included indication for tiotropium use (COPD, COPD and asthma, COPD symptoms), age, sex, smoking, body mass index (BMI), alcohol use, number of hospitalizations in the year prior to cohort entry, number of GP visits in the year prior to cohort entry, ischaemic heart disease, arrhythmias, hypertension, number of prescriptions for short-acting anticholinergics, short-acting ß-agonists, inhaled corticosteroids, oral corticosteroids, theophyllines, number of prescriptions for antiarrrhythmics, anticoagulants, antihypertensives, ACE inhibitors, diuretics, inotropics, lipid regulators, beta-adrenoceptor antagonists [ß-blockers], nitrates, use of other medications, malignancies and anti-infectives and oxygen use.

The extended study period yielded a 4-fold size of the study population comprising 10,840 patients (4,767 tiotropium and 6,073 LABA). Results for cardiovascular endpoints are displayed in Table 13.3.2: 1.

Table 13.3.2: 1 Hazard ratios and 95% confidence intervals for cardiovascular endpoints (THIN study II)

	Tiotropium N=4,767			LABA N=6,073			
Adverse Events	**N**	**PY**	**Rate/ 100 PY**	**N**	**PY**	**Rate/ 100 PY**	**HR* (95% CI)***
Angina	53	2,746	1.93	38	2,275	1.67	1.38 (0.88, 2.16)
Atrial fibrillation/flutter	87	2,725	3.19	76	2,272	3.34	0.99 (0.71, 1.38)
Heart failure	93	2,738	3.40	105	2,265	4.64	0.85 (0.63, 1.14)
Myocardial infarction	35	2,765	1.27	23	2,297	1.00	1.26 (0.72, 2.21)
Tachycardia	15	2,769	0.54	11	2,296	0.48	1.08 (0.48, 2.41)
Cardiac arrest	3	2,774	0.11	4	2,303	0.17	-
Coronary artery disease	125	2,712	4.61	102	2,255	4.52	1.11 (0.84, 1.47)
Hypertension	169	2,654	6.37	163	2,232	7.30	1.03 (0.81, 1.29)
Stroke	45	2,750	1.64	28	2,296	1.22	1.49 (0.91, 2.45)
Syncope	35	2,762	1.27	35	2,289	1.53	0.94 (0.57, 1.55)
Cardiovascular Aneurysm	17	2,765	0.61	13	2,298	0.57	0.96 (0.44, 2.05)
Ventricular tachycardia	2	2,774	0.07	1	2,302	0.04	-

PY, person-years at risk; HR Hazard Ratio, CI Confidence Interval *Adjusted using a propensity score including respiratory diagnosis, age, sex, calendar year, smoking , BMI, number of hospitalizations at baseline, cardiac comorbidities, respiratory and cardiac medications '—' adjusted results are not presented for less than < 5 events
Source Data: U08-3413-01, Table 3

Incidence rates and the adjusted hazard ratio for all-cause mortality are presented in Table 13.3.2: 2.

Table 13.3.2: 2 Hazard ratios and 95% confidence intervals for all-cause mortality in new users of long-acting bronchodilators (THIN study II)

	Tiotropium N=4,767			**LABA N=6,073**			
Adverse Events	**N**	**PY**	**Rate/ 100 PY**	**N**	**PY**	**Rate/ 100 PY**	**HR* (95% CI)***
All-cause mortality	152	2,775	5.48	170	2,303	7.38	0.70 (0.56, 0.89)

PY person-years at risk; HR Hazard Ratio; CI Confidence Interval. *Adjusted using a propensity score including respiratory diagnosis, age, sex, calendar year, smoking , BMI, number of hospitalizations at baseline, cardiac comorbidities, respiratory and cardiac medications
Source Data: U08-3413-01, Table 3

This study concluded that users of tiotropium had lower rates of heart failure than patients using LABA. With regard to other cardiovascular endpoints, there were imprecise higher rates of some medically-related ischemic events including angina, myocardial infarction and stroke. With regard to mortality, tiotropium users had a statistically significant 30% decrease in risk of death compared with patients using LABA (HR (95%CI) =0.70 (0.56, 0.89)).

13.4 CARDIOVASCULAR HOSPITALIZATIONS AND MORTALITY AMONG USERS OF TIOTROPIUM FOR COPD IN DENMARK

A population-based cohort study was conducted in Denmark to examine the risk of cardiovascular hospitalizations in COPD patients using tiotropium and other respiratory medications (P07-07347). Using Danish healthcare registries, all patients hospitalized for COPD from 1/1/1977 to 12/31/2003 were identified. Respiratory and cardiovascular medications were assessed from dispensing records. Exposed person-time was calculated to present the sum of all periods of tiotropium exposure while non-exposed person-time summarized all periods of no tiotropium exposure. Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for hospitalization and death between 1/1/2002 and 12/31/2003, associated with periods of tiotropium use compared to non-use, controlling for age, gender, time since COPD, concomitant respiratory and cardiovascular medications, prior hospitalizations and Charlson comorbidity index. Among persons with COPD (10,603), 75% were ≥60 years old. Follow-up was ≥18 months for 64%. There was no significant difference in the risk of cardiovascular events among periods of tiotropium use when compared to periods of non-use. Cardiovascular findings are summarized in Table 13.4: 1.

Table 13.4: 1 Adjusted cardiovascular hazard ratios and 95% CI for hospitalization endpoints (Denmark study)

	Cases tiotropium	Cases during non-use of tiotropium	Adjusted Hazard Ratio* (95% CI)
Atrial fibrillation/Flutter	41	425	1.21 (0.87, 1.69)
Congestive heart failure	36	405	1.03 (0.73, 1.47)
Angina	29	307	1.01 (0.68, 1.60)
Myocardial infarction	25	287	1.05 (0.69, 1.60)
Supraventricular tachycardia	5	82	0.65 (0.26, 1.65)
Ventricular arrhythmia	3	23	1.97 (0.56, 6.88)
Hospitalization for any reason	209	2,507	1.05 (0.91, 1.22)

CI Confidence Interval, *adjusted for age, gender, time since COPD respiratory and cardiovascular medications, prior hospitalizations, Charlson co-morbidity index, asthma diagnosis, and history of event.
Source Data: P07-07347, Table 2

Results for all-cause mortality are displayed in Table 13.4: 2.

Table 13.4: 2 Adjusted hazard ratios and 95% CI for all-cause mortality in Danish COPD patient (2002-2003) (Denmark study)

	Cases tiotropium	Cases during non-use of tiotropium	Adjusted Hazard Ratio* (95% CI)
All-cause mortality	142	2,378	0.77 (0.65, 0.91)

CI, Confidence Interval, *adjusted for age, gender, time since COPD respiratory and cardiovascular medications, prior hospitalizations, Charlson co-morbidity index, asthma diagnosis, and history of event.
Source Data: P07-07347, Table 3

There were no statistically significant differences between the hazard ratios of any endpoint for tiotropium use when compared to non-use of tiotropium. There was an imprecise lower hazard ratio for supraventricular arrhythmia and imprecise higher hazard ratios for ventricular arrhythmias and atrial fibrillation/flutter among tiotropium users. There was no evidence of an increased risk of all-cause mortality for tiotropium use when compared to non-use of tiotropium.

13.5 CARDIOVASCULAR, CEREBROVASCULAR, AND RESPIRATORY EVENTS IN ASSOCIATION WITH LONG-ACTING BRONCHODILATORS: A COMPARATIVE STUDY IN PATIENTS WITH COPD

A nested case control study in a cohort of COPD patients was conducted by investigators at Erasmus University Medical Center using the IPCI-PHARMO GP database in the Netherlands (U09-0099-03). This study compared the risk of cardiovascular events and mortality among current users of tiotropium with current user of single-ingredient LABAs. Cardiovascular events included stroke and transient ischemic attack (TIA), myocardial infarction, heart failure, ventricular arrhythmia and a combined cardiovascular endpoints consisting of stroke, MI, heart failure and ventricular arrhythmia.

The source population consisted of all individuals with a first diagnosis of COPD recorded from January 2000 to July 2007. Cohort members were required to be at least 40 years and to have a minimum of 365 days recorded history prior to the first diagnosis of COPD. The study

population included prevalent COPD and those with an incident diagnosis of COPD during the study period.

COPD was assessed by manual review of the medical files by searching on medical codes for COPD, spirometry and free text searching including “COPD”, “chronic bronchitis”, “emphysema” or “exacerbation”. From this set of patients, two COPD categories definite and probable COPD were defined. Definite COPD consisted of patients with a diagnosis recorded by a specialist (internal medicine, respiratory physician) or with a spirometry test of FEV1/FVC<70%. Probable COPD comprised COPD diagnosed by the GP only with at least 2 subsequent records of COPD (either by free text, medical code or specific bronchodilating drugs) within 1 year of the first record of COPD.

COPD severity was assessed at the time of study entry on the basis of available spirometry data and the following information during the 365-day baseline period: number of prescribed COPD pulmonary medications, hospitalizations for COPD, use of antibiotics for the treatment of respiratory infections, number of courses of systemic corticosteroids for the treatment of COPD exacerbations, a diagnosis of pneumonia, requiring hospitalization, long term use of systemic corticosteroids for the treatment of COPD and need for chronic oxygen therapy

A nested case-control study was then performed within the COPD cohort. Cases were defined as patients with a study outcome and the index day as the date of the study outcome. For each case the maximum number of person-moments from all individuals in the pool of COPD patients of the same gender and year of birth was matched (controls). Controls were required to be eligible on the index day of the respective case and to have a minimum recorded period of 365 days prior to the index day. For all COPD patients (both incident and prevalent), conditional logistic regression analysis was conducted to estimate the matched and adjusted odds ratio for the association between current use of tiotropium and LABA. Adjusted models included severity of COPD in the year prior to the index date, duration of COPD, and smoking and all covariates associated with the outcome ($p<0.10$) in the univariate analysis. The main result table of this study is presented in Table 13.5: 1.

Table 13.5: 1 Adjusted odds ratio (95% CI) for current tiotropium use compared to current LABA use (IPCI-PHARMO GP study)

	Cases N (%)		Control person-moments N (%)‡		
	Tiotropium	**LABA**	**Tiotropium**	**LABA**	**Adjusted OR (95% CI)***
Myocardial infarction	3 (1.9)	20 (12.9)	168 (2.5)	752 (11.1)	-
Ventricular arrhythmia	1 (5.9)	6 (35.3)	23 (2.6)	107 (12.1)	-
Heart failure	9 (2)	52 (11.7)	332 (2.1)	1849 (11.5)	0.93 (0.45,1.94)
Renal failure	3 (3.6)	3 (3.6)	82 (2.1)	426 (10.7)	-
Stroke	11 (3.1)	44 (12.3)	311 (2.2)	1575 (11.3)	1.05 (0.52, 2.09)
Combined cardiovascular endpoint	18 (1.7)	91 (8.8)	1089 (2.7)	4622 (11.4)	0.84 (0.50, 1.41)
All-cause mortality	18 (1.7)	91 (8.8)	1089 (2.7)	4622 (11.4)	0.76 (0.44, 1.32)

OR Odds ratio, CI Confidence interval, LABA long-acting beta-agonist
‡ control person-moments vary by outcome
*Adjusted for severity of COPD one year prior to the index date, duration of COPD and smoking
'—' adjusted results are not presented for less than < 5 exposed to current tiotropium
Source Data: U09-0099-03., Tables 5.3.5, 5.4.5, 5.5.5, 5.6.5, 5.7.5, 5.8.5 and 5.10.5

This study did not indicate any evidence for an increased risk of heart failure, stroke, the endpoint of all cardiovascular events, or all-cause mortality in current tiotropium use when compared to current use of LABA.

13.6 SUMMARY OF RISK ESTIMATES FOR CARDIOVASCULAR EVENTS FROM OBSERVATIONAL STUDIES

Epidemiologic data indicate that COPD is associated with an increased risk of death and of cardiovascular morbidity. The Saskatchewan studies provided evidence for COPD to be strongly associated increased mortality. The incidence of mortality due to cardiovascular causes was twice as high in the COPD population as in an age and gender matched population without COPD. The Kaiser Permanente study with 4-times greater study population than the Saskatchewan study found statistically increased associations between COPD and cardiovascular mortality. Death from acute myocardial infarction, congestive heart failure, stroke and pulmonary embolism was significantly increased in COPD patients. Severity of COPD was also positively associated with the incidence of cardiovascular mortality and of all-cause mortality

Several observational studies on mortality among COPD and among tiotropium users compared to LABA or non-tiotropium use have been conducted (P07-13582, U08-3413-01). The overall data did not indicate an excess risk of cardiovascular or fatal events with tiotropium relative to inhaled long-active beta-agonists (i.e. the other option for initial maintenance therapy). Some of the data suggested a reduced risk, which is consistent with the clinical trial data for tiotropium HandiHaler®.

14. LITERATURE REVIEW OF CLINICAL TRIALS

A literature review has been conducted for tiotropium covering the period from the time of the tiotropium HandiHaler® NDA submission (December 2001) to June 2009. This review includes all original clinical articles in the BiLit Database. This database archives and indexes papers referencing BI products via stored searches on Medline, Embase, and Current Contents, plus some supplementary manual journal scanning. Clinical articles discussed in this literature review are restricted to clinical trial publications that report adverse events, discontinuations, or exacerbations as study endpoints. Clinical trials conducted by Boehringer Ingelheim are excluded.

There are 163 citations indicating tiotropium as a treatment in a clinical trial. Of these, 38 publications mention adverse events, discontinuations for adverse events or other reasons, and exacerbations as study endpoints.

In the literature review, only one study (P09-00584) was a randomized, double-blind, placebo-controlled trial which compared tiotropium with placebo and reported COPD exacerbations as adverse events. This was a randomized, partially blinded, placebo controlled trial. Active treatment arms included formoterol, tiotropium and the combination of tiotropium and formoterol. There were 209 placebo treated patients and 221 tiotropium (monosubstance) treated patients. Thirty-three and 28 patients were reported to have COPD exacerbations in the placebo and tiotropium group respectively. No other lower respiratory events were reported. There were no fatal events.

None of the studies in the literature data-base that were randomized, double-blind, placebo-controlled trials comparing tiotropium with placebo reported cardiovascular adverse events, serious adverse events, or fatal events. The publications are described in more detail in Appendix 17.5.

15. DISCUSSION & SUMMARY

15.1 DISCUSSION

Tiotropium HandiHaler® 18 mcg once daily for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema, was initially introduced in June 2002 in Europe. It was approved by the Food and Drug Administration (FDA) on January 30, 2004 with United States market introduction beginning in the 2nd quarter of 2004. As of July 2009, the estimated patient exposure to tiotropium exceeded 16 million patient-years (all formulations), of which a minor contribution is from tiotropium Respimat® 5 mcg inhalation spray in Europe.

To support a reduction in COPD exacerbations claim, Boehringer Ingelheim is relying primarily on data generated from two large trials: the VA trial (205.266/U03-3575-01) and the UPLIFT trial (205.235/U08-3718-04) involving 7,821 patients. These two trials are supported by exacerbation data from other tiotropium HandiHaler® trials and a pooled analysis of 26 HandiHaler® trials.

The VA trial (205.266/U03-3575-01) was a 6-month randomized, double-blind, placebo-controlled, parallel group trial with tiotropium HandiHaler® once daily in 1,829 patients with COPD, who have been receiving their medical care in VA Medical System. The primary objective of this trial was to determine whether tiotropium HandiHaler® reduces the proportion of patients experiencing exacerbation and the proportion of patients hospitalized due to exacerbation in patients with COPD. The co-primary endpoints were the proportion of patients with at least one exacerbation (1st co-primary) and at least one hospitalized exacerbation (2nd co-primary). The FDA draft COPD guidance (R07-4789) indicates that COPD exacerbation studies may need to be at least 1 year in duration; however, statistical significance was achieved with the first co-primary endpoint in the VA study and supported by robust associated exacerbation endpoints, improvement in lung function and a general consistency across subgroups. It should be noted that as the randomization occurred over approximately a full year; the treatment period was not concentrated over a single season.

Compared to placebo, tiotropium HandiHaler® significantly reduced the percentage of patients who experienced at least one COPD exacerbation during the 6-month treatment period (28% vs. 32%, respectively, p= 0.037). Tiotropium HandiHaler® also reduced the percentage of patients who experienced one or more hospitalizations due to COPD exacerbation during the same period, although the results did not achieve statistical significance (7.0% vs. 9.5%, respectively, p = 0.056). Tiotropium HandiHaler® compared to placebo, extended the time to first exacerbation (p=0.03) and the time to first hospitalization due to an exacerbation of COPD (p=0.05) with relative risks of 0.83 and 0.72, respectively, and reduced the number of exacerbations, unscheduled medical visits due to COPD exacerbations, and hospitalizations due to COPD exacerbations. Decreases in total exacerbation days and the number of days receiving antibiotics and systemic corticosteroids were documented with a relative decrease between 15% and 30% for each of these events.

The UPLIFT trial (205.235/U08-3718-04) was a four-year, multicenter, multinational, double-blind, randomized, placebo-controlled, parallel-group clinical trial involving 5,992 patients with COPD, which examined the efficacy and safety of tiotropium HandiHaler®. The co-primary endpoints were the rate of decline in pre and post-bronchodilator FEV_1 from steady state tiotropium (day 30) to the last day of treatment. Two key secondary endpoints were specified in the statistical analysis plan prior to database lock and unblinding: (a) time to first exacerbation, (b) time to exacerbation leading to hospitalization. The UPLIFT study (205.235) demonstrated that in the presence of freely prescribed respiratory medications (i.e., inhaled long-acting beta-agonists, inhaled steroids, and theophyllines) other than inhaled anticholinergics, tiotropium HandiHaler® 18 mcg once daily maintained improvements in lung function over 4 years compared to placebo; however, tiotropium did not alter the rate of decline in FEV_1 (primary endpoint). Tiotropium HandiHaler® delayed the time to the first exacerbation and the time to first hospitalization for an exacerbation. The HRs (95% CI) for an exacerbation or exacerbation leading to hospitalization were 0.86 (0.81, 0.91) and 0.86 (0.78, 0.95), respectively. The mean number of exacerbations as well as exacerbation days was less for the tiotropium HandiHaler® group. The mean number of exacerbations leading to hospitalizations was low and comparable for the two treatment arms.

While all statistical testing for exacerbations in the UPLIFT trial is considered descriptive given that the primary endpoint did not achieve statistical significance, the UPLIFT exacerbation data is based on one of the largest and longest prospective interventional clinical trials in COPD and should be considered as providing substantial support to the exacerbation primary endpoint in the VA trial. The findings appear robust across multiple subgroups and present regardless of concomitant respiratory medication. Additionally, the exacerbation reduction can be explained physiologically by the effective bronchodilation throughout 24 hours with tiotropium HandiHaler®; an outcome that was maintained relative to the placebo control over 4 years of treatment.

The clinical meaningfulness of the lung function improvements in UPLIFT is demonstrated by the associated sustained improvements in symptoms (as measured by the St. George's Respiratory Questionnaire) and reduced exacerbations of COPD. Of note, all of these positive outcomes appeared in the presence of considerable utilization of concomitant respiratory therapy. These outcomes substantiate the clinical relevance of the lung function improvements with once-daily tiotropium HandiHaler®. Indeed, the improvements in lung function throughout 24 hours relative to the control group, including reductions in hyperinflation, likely are the primary mechanism for reductions in exacerbations of COPD.

From the adverse event data, the UPLIFT trial demonstrated that treatment with tiotropium HandiHaler® was associated with decreased reports of respiratory failure, which substantiates the exacerbation efficacy outcomes. There was no evidence of an increased risk of death or cardiovascular morbidity, including myocardial infarction and stroke.

Integrating information across multiple studies in a pooled analysis increased the size of the study population and thereby enhanced the precision of effect estimates permiting increased power for assessment of patient subgroups. Pooling of all clinical trials with tiotropium HandiHaler® can provided a comprehensive assessment of the effects of tiotropium on the

risk for COPD exacerbations through examination of adverse event reports of exacerbations. The pooled safety database consists of 26 completed clinical trials as of March 2009 in the tiotropium project database. For inclusion, all trials used a randomized, placebo-controlled, double-blind and parallel-group study design. Trials were restricted to COPD and with at least 4 weeks duration. The COPD protocols generally incorporated similar inclusion and exclusion criteria.

For the 26 HandiHaler® trials the number of patients (patient years of exposure) was 7,865 (10,578) for placebo and 9,149 (11,958) for tiotropium. In the pooled analysis, there were 6,187 patients with at least one COPD exacerbation. Tiotropium HandiHaler® was associated with a significant decrease in the rate (per 100 patient years) for a COPD exacerbation whether considered within a narrower range of preferred terms denoting an exacerbation (RD (95% CI) = -8.90 (-11.0, -6.83) or a broader range of terms (RD (95% CI) = -9.76 (-12.0, -7.50). There was no increase in the rate for pneumonia as seen by the RD (95% CI) = -0.25 (-0.83, 0.33). Furthermore, there were reductions in rates for exacerbations reported as serious adverse events (RD (95% CI) = -1.58 (-2.37, -0.78). While relatively infrequent, a total of 136 fatal COPD exacerbations were reported among the trials (RD (95%CI) = -0.09 (-0.28, 0.10)). In addition, the data were consistent in that there were reduced incidence rates for dyspnea and respiratory failure with tiotropium HandiHaler® in the pooled database relative to placebo.

The pooled analysis provided appropriate power to examine several important subgroups. Significant reductions in risk for an exacerbation with tiotropium were observed regardless of gender, smoking behavior (i.e. continued and ex-smokers), categories of age, concomitant respiratory medications and different lung function severities of COPD.

The pooled tiotropium HandiHaler® analysis provided evidence to support no overall increase in adverse events, including fatal adverse events, under the system organ classes of cardiac or vascular disorders. There was no evidence for an increased risk for stroke. Incidence rates and rate differences were calculated for a composite endpoint of major cardiovascular events (fatal events in the SOC cardiac disorders and SOC vascular disorders combined with non-fatal myocardial infarction, non-fatal stroke and the preferred terms sudden death, sudden cardiac death and cardiac death). There was a lower incidence rate for a major cardiovascular event and fatal cardiovascular events in the tiotropium group relative to the placebo, with the upper limits of the confidence interval being below zero.

An alternative formulation of tiotropium (Spiriva® Respimat® inhalation spray 5 mcg) was approved in Europe in 2007. A total of five trials involving tiotropium Respimat® 5 mcg met the same selection criteria for pooling of trials as described with the above 26 HandiHaler® trials (i.e. randomized, placebo-controlled, double-blind, parallel group studies with a treatment duration of at least 4 weeks). The trials demonstrated improvements in lung function over 24 hours with once daily dosing along with improvements in symptoms and a reduced risk for exacerbations of COPD.

In a pooled analysis of the five clinical trials (three of which were 1-year in duration), there were numerically more deaths in the tiotropium Respimat® 5 mcg compared to the placebo group. The first two (205.254, 205.255) of the three 1-year trials included a higher dose

treatment arm (tiotropium Respimat® 10 mcg), which also showed a higher number of deaths relative to the placebo group. An examination of the formulation properties indicates no known scientific rationale to expect a difference based on the pharmacology of the substance, the pharmacokinetics of the formulations or the excipients of each formulation. The tiotropium HandiHaler® database is larger than the Respimat® database in terms of patient numbers and exposure to tiotropium. In addition, the tiotropium HandiHaler® database includes a large study of 4-years duration, whereas the Respimat® database is limited to studies of up to 1-year in duration. Nevertheless, given the observations with the tiotropium Respimat® formulation, a large, long-term clinical trial will be initiated in 2010 examining the relative benefits of tiotropium Respimat® (in two doses, 2.5 mcg and 5 mcg once daily) to tiotropium HandiHaler® 18 mcg once daily in patients with COPD.

Only a few relevant clinical trials of inhaled anticholinergics have been conducted by sponsors other Boehringer Ingelheim. An association between ipratropium (a short-acting inhaled anticholinergic) and cardiovascular mortality was noted in an earlier report from the Lung Health Study (P02-05083). However, a re-analysis of the same data by Lanes et al showed that, other than supraventricular tachycardia, the increased risk of cardiovascular morbidity and mortality in that study was concentrated among patients who were randomized to the ipratropium group but who did not take ipratropium (i.e. were not compliant with study medication) (P03-02985). In a 2-year study in severe and very severe COPD patients with a history of exacerbations, tiotropium was associated with equivalent effects on exacerbations and a significantly lower rate of pneumonia but a higher number of fatal events compared to the combination of salmeterol and fluticasone (P07-11820). These results are confounded by the run-in with 2 weeks of prednisolone and salmeterol which was abruptly withdrawn at randomization (destabilization of patients) and the biases introduced by withdrawal of inhaled steroids, which were used by 51% of patients at baseline (P08-11365). There are no other published prospective trials, other than those sponsored by Boehringer Ingelheim, that provide additional relevant information.

In a meta-analysis of published clinical trials, Singh et al. selected randomized controlled trials of any inhaled anticholinergic for treatment of COPD that had at least 30 days of treatment and reported on cardiovascular events (P08-12019). The primary outcome was a composite of cardiovascular death, myocardial infarction, or stroke similar to the cardiovascular endpoint that is presented in this report using a much larger database. The secondary outcome was all-cause mortality. The authors concluded that inhaled anticholinergics significantly increased the risk of the composite cardiovascular endpoint, myocardial infarction and cardiovascular death without a statistically significant increase in the risk of stroke. There are numerous limitations to the analysis. The authors incorrectly assumed that the integration of placebo-controlled trials with active-controlled trials is valid. A comparison of the analysis results with source data identified multiple discrepancies in the numbers of cases and the number of patients. Certain studies were counted twice in the analysis. The analysis did not take into account differential discontinuation (i.e. in most of the trials, more patients in the placebo group prematurely discontinued the study than did patients taking active medication and were therefore followed for briefer periods of time during which adverse events were reported) and differences in exposure. Most of the evidence in the analysis was provided by a single study, the Lung Health Study and did not

consider the report by Lanes et al. Finally, reporting of adverse event from data available in peer reviewed publications is almost always incomplete and does not contain all patient level data. A more recent meta-analysis was published based on tiotropium clinical trials including UPLIFT (P09-08576). The primary endpoints analyzed were a composite of major adverse cardiovascular events, cardiovascular mortality, and nonfatal myocardial infarction (MI) or stroke during the treatment period. The authors concluded that compared with control (placebo or salmeterol), tiotropium did not significantly increase the risk of adverse major cardiovascular events among COPD patients. Two other publications, one meta-analysis and one review of publicly available data, have reached a similar conclusion (P08-15598, P09-12763).

Observational studies assessing mortality and inhaled anticholinergics have been reported. The most recent publication examined the association between various respiratory medications and risk for death in newly diagnosed COPD patients based on a retrospective nested case-control study using various databases (P08-11453). The authors concluded that ipratropium was associated with increased cardiovascular deaths, whereas inhaled corticosteroids were associated with reduced risk. By its design, this study contrasted groups that likely entailed important differences in their baseline risk. The authors were limited by the data available to them, which did not include information on smoking or lung function. The analyses reported indicated that the inability to control for these factors produced effect estimates that exaggerated actual risks and could fully explain the association between ipratropium and mortality noting that all-cause mortality risk ratio was 1.02 for ipratropium when accounting for severity as an unmeasured confounder. A recent analysis by the same lead author using the same database found that tiotropium in combination with inhaled corticosteroids and long-acting beta-agonists reduced the risk of death, exacerbations and COPD hospitalizations, but the results were not consistent in other treatment combinations including tiotropium (P09-10444). This analysis is subject to the same limitations as previously noted.

One retrospective meta-analysis of randomized trials found that inhaled anticholinergic but not beta-2 agonist medications offered reduced respiratory mortality; however, several of the aforementioned limitations also apply to this analysis (P07-07347). An epidemiologic study noted reduced respiratory and overall mortality with tiotropium and no excess in cardiac mortality (P07-10615). A recent longitudinal population-based cohort study indicated a reduced risk of mortality with tiotropium relative to salmeterol (hazard ratio (95% CI) = 0.80 (0.70 to 0.93) in COPD patients during the 6 months following discharge from hospital due to COPD (P08-10308).

Boehringer Ingelheim has sponsored several observational studies which indicated no increase in risk for cardiovascular events or all-cause mortality with tiotropium (P07-13582, P07-07347, U08-3413-01).

Observational reports have shown conflicting results with regards to cardiovascular events and fatal events. However, in general, such reports, suffer from confounding by severity or by diagnoses (P08-11453), which preclude definitive conclusions. These issues limit such analyses to hypothesis generation and are inferior to prospective studies where all patient

level data is available, such as in the presently reported analyses of the tiotropium HandiHaler® database.

Pooling of clinical trial data has recognized limitations, some of which may apply to this report and include differences in populations, study design, duration of trials, collection of data and the ability to adjust for differences in exposure. However, the 26 tiotropium HandiHaler® trial pooled analysis was based on complete patient level data in clinical trials that have a similar study design, similar inclusion and exclusion criteria, study population in one disease area (COPD), and a virtually identical manner of collecting adverse event information. Discrepancies in adverse event data were reconciled prior to locking the database and unblinding. We have consistently observed that a higher proportion of patients prematurely discontinued treatment in the control group compared to the tiotropium group. Discontinued patients in general have more severe disease and disproportionably discontinue trial participation in the placebo group, which may lead to a bias against tiotropium regarding safety evaluations. The bias can be reduced somewhat by adjusting for overall treatment exposure. This effect has been documented in a previous retrospective analysis of a 6 month trial (P07-10615). Perhaps more relevant is the UPLIFT trial, which as a single large long-term (4-years) trial provided substantial evidence supporting the efficacy and safety of tiotropium HandiHaler®.

Presently, there are expected adverse events listed in the tiotropium company core datasheet in the category of cardiac disorders. These included tachycardia, palpitations, supraventricular tachycardia, and atrial fibrillation, which appear in tiotropium labeling throughout the world. An increased heart rate may presumably be a side effect of anticholinergic medications based on muscarinic receptor pharmacology; yet the clinical trial data with inhaled tiotropium indicate that such events were infrequent or rare. As well, although they are expected events, the present accumulated data indicated there are no imbalances for atrial fibrillation. Additionally, imbalances in life-threatening ventricular tachyarrhythmias were not observed. Of note, there are no expected events under the system organ class of vascular disorders.

In summary, the original NDA submission for tiotropium HandiHaler® established the therapeutic benefit of tiotropium on the basis of clinically important improvements in spirometry (FEV_1, FVC) and symptoms (reduced requirement for short-acting beta-agonists, transition dyspnea index, St. George's Respiratory Questionnaire). The purpose of additional tiotropium HandiHaler® trials such as the VA study (205.266/U03-3575-01) was to characterize the therapeutic benefit of tiotropium in reducing the risk for an exacerbation of COPD and associated hospitalization. The VA study has demonstrated that tiotropium HandiHaler® reduced the risk for an exacerbation of COPD. While it is acknowledged that the UPLIFT trial (205.235) did not show differences in the primary endpoint, the trial has documented improvements in exacerbations that extend out to 4 years and corroborated findings in previous trials. Pooling of a large clinical trial safety database provides robust additional data indicating that the benefit was observed with tiotropium HandiHaler® across various subgroups of patients with COPD.

Although the rate of decline in FEV_1 was not altered by tiotropium HandiHaler®, the UPLIFT trial provided data indicating sustained improvements in lung function over 4 years. Furthermore, the improvements over 4 years in the SGRQ total score as well as the individual domains (symptoms, activity, impacts) indicated that there was symptomatic improvement compared to the control group, which are consistent with the exacerbation observations. It should be recognized that the exacerbation and symptom benefits occurred in the setting of freely prescribed respiratory medications other than inhaled anticholinergics.

Regarding safety, increased risk for cardiovascular morbidity and mortality is a consequence of COPD. The present report presents a robust and extensive analysis of a single large, long-term study involving approximately 6,000 patients and a pooled analysis of over 17,000 patients participating in placebo-controlled tiotropium HandiHaler® clinical trials and incorporation of all patient level data during treatment in a defined set of 26 randomized double-blind, placebo-controlled trials. The results indicated that tiotropium HandiHaler® does not increase the overall risk for cardiovascular events, myocardial infarction, stroke, cardiovascular mortality or all-cause mortality. With regard to lower respiratory events including reduced risks for reports of respiratory failure, the data are consistent and support the efficacy findings for exacerbations of COPD.

Based on the overall assessment of efficacy and safety as outlined, tiotropium is considered to continue to exhibit a highly favourable benefit to risk profile in the treatment of COPD. Boehringer Ingelheim is committed to a continuing evaluation of the safety of tiotropium through our established pharmacovigilance processes. We will continue to evaluate data from multiple sources including clinical trials, spontaneous reporting and the published literature. Our commitment is to provide the public, health care community and regulatory agencies with information that result in the most appropriate use of tiotropium in the treatment of COPD.

15.2 SUMMARY

COPD is a progressive disabling lung disease that is associated with significant morbidity and mortality. People with COPD have important limitations in daily function and quality of life. These patients often experience complications of respiratory disease and comorbid disease including premature mortality. Exacerbations contribute significantly to the morbidity and mortality associated with COPD which can be impacted with maintenance treatment with tiotropium HandiHaler®. The reductions in COPD exacerbations with tiotropium have been observed in individual trials with tiotropium HandiHaler®, including those of significant size and duration, and in an overall analysis of the clinical trial database. The pooled analysis indicates that tiotropium reduces exacerbation in the entire population of patients with COPD entered into clinical trials with tiotropium as well as in specific subgroups, thereby demonstrating that tiotropium can be provided to a broad group of patients requiring maintenance treatment with the realistic expectation of a reduced risk for a future COPD exacerbation. As patients may live with COPD for decades, this knowledge is important in understanding the need to continue treatment.

In conclusion, the exacerbation benefits observed in the VA trial and the UPLIFT trial support labeling revisions for tiotropium HandiHaler® to add the reduction of COPD

exacerbations to the Indication section and to insert the applicable data from both trials into the Clinical Studies section. Additionally, the updated safety data provides substantial evidence that tiotropium HandiHaler is not associated with an increased risk for fatal events or cardiovascular morbidity including stroke.

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17. APPENDICES

17.1 APPENDIX: ADVERSE EVENT COLLAPSING RULES FOR SECLECTED CARDIOVASCULAR AND LOWER RESPIRATORY EVENTS

Clinical endpoint	MedDRA PT included
Angina	Angina pectoris
Angina	Angina unstable
Angina/Ischemia (no MI)	Angina pectoris
Angina/Ischemia (no MI)	Angina unstable
Angina/Ischemia (no MI)	Arteriospasm coronary
Angina/Ischemia (no MI)	Coronary artery disease
Angina/Ischemia (no MI)	Coronary artery dissection
Angina/Ischemia (no MI)	Coronary artery insufficiency
Angina/Ischemia (no MI)	Coronary artery occlusion
Angina/Ischemia (no MI)	Coronary artery reocclusion
Angina/Ischemia (no MI)	Coronary artery stenosis
Angina/Ischemia (no MI)	Coronary artery thrombosis
Angina/Ischemia (no MI)	ECG signs of myocardial ischaemia
Angina/Ischemia (no MI)	Electrocardiogram ST segment depression
Angina/Ischemia (no MI)	Electrocardiogram T wave inversion
Angina/Ischemia (no MI)	Ischaemic cardiomyopathy
Angina/Ischemia (no MI)	Myocardial ischaemia
Angina/Ischemia (no MI)	Myocardial reperfusion injury
Angina/Ischemia (no MI)	Postinfarction angina
Angina/Ischemia (no MI)	Prinzmetal angina
Angina/Ischemia (no MI)	Subendocardial ischaemia
Atrial fibrillation/flutter	Atrial fibrillation
Atrial fibrillation/flutter	Atrial flutter
Cardiac arrest	AV dissociation
Cardiac arrest	Cardiac arrest
Cardiac arrest	Cardiac death
Cardiac arrest	Cardiac massage
Cardiac arrest	Cardiogenic shock
Cardiac arrest	Cardio-respiratory arrest
Cardiac arrest	Electromechanical dissociation
Cardiac arrest	Resuscitation
Cardiac arrest/Sudden death	AV dissociation
Cardiac arrest/Sudden death	Cardiac arrest
Cardiac arrest/Sudden death	Cardiac death
Cardiac arrest/Sudden death	Cardiac massage
Cardiac arrest/Sudden death	Cardiogenic shock
Cardiac arrest/Sudden death	Cardio-respiratory arrest
Cardiac arrest/Sudden death	Electromechanical dissociation
Cardiac arrest/Sudden death	Resuscitation
Cardiac arrest/Sudden death	Sudden cardiac death
Cardiac arrest/Sudden death	Sudden death
Cardiac failure	Acute left ventricular failure
Cardiac failure	Acute pulmonary oedema

Clinical endpoint	MedDRA PT included
Cardiac failure	Acute right ventricular failure
Cardiac failure	Cardiac cirrhosis
Cardiac failure	Cardiac failure
Cardiac failure	Cardiac failure acute
Cardiac failure	Cardiac failure chronic
Cardiac failure	Cardiac failure congestive
Cardiac failure	Cardiac failure high output
Cardiac failure	Cardiogenic shock
Cardiac failure	Cardiopulmonary failure
Cardiac failure	Cardiorenal syndrome
Cardiac failure	Chronic left ventricular failure
Cardiac failure	Chronic right ventricular failure
Cardiac failure	Congestive cardiomyopathy
Cardiac failure	Cor pulmonale
Cardiac failure	Cor pulmonale acute
Cardiac failure	Cor pulmonale chronic
Cardiac failure	Left ventricular failure
Cardiac failure	Low cardiac output syndrome
Cardiac failure	Pulmonary congestion
Cardiac failure	Pulmonary oedema
Cardiac failure	Right ventricular failure
Cardiac failure	Ventricular failure
Cardiac failure (narrow)	Cardiac failure
Cardiac failure (narrow)	Cardiac failure acute
Cardiac failure (narrow)	Cardiac failure chronic
Cardiac failure (narrow)	Cardiac failure congestive
Cardiac failure (narrow)	Ventricular failure
Cardiac failure – left ventricular	Acute left ventricular failure
Cardiac failure – left ventricular	Acute pulmonary oedema
Cardiac failure – left ventricular	Chronic left ventricular failure
Cardiac failure – left ventricular	Congestive cardiomyopathy
Cardiac failure – left ventricular	Left ventricular failure
Cardiac failure – left ventricular	Low cardiac output syndrome
Cardiac failure – left ventricular	Pulmonary congestion
Cardiac failure – left ventricular	Pulmonary oedema
Cardiac failure – right ventricular	Acute right ventricular failure
Cardiac failure – right ventricular	Chronic right ventricular failure
Cardiac failure – right ventricular	Cor pulmonale
Cardiac failure – right ventricular	Cor pulmonale acute
Cardiac failure – right ventricular	Cor pulmonale chronic
Cardiac failure – right ventricular	Right ventricular failure
Myocardial infarction	Acute myocardial infarction
Myocardial infarction	Myocardial infarction
Myocardial infarction	Papillary muscle infarction
Myocardial infarction	Silent myocardial infarction
Other arrhythmias	Adams-Stokes syndrome
Other arrhythmias	Agonal rhythm
Other arrhythmias	Anomalous atrioventricular excitation
Other arrhythmias	Arrhythmia
Other arrhythmias	Arrhythmia supraventricular

Clinical endpoint	MedDRA PT included
Other arrhythmias	Atrial conduction time prolongation
Other arrhythmias	Atrioventricular block
Other arrhythmias	Atrioventricular block complete
Other arrhythmias	Atrioventricular block first degree
Other arrhythmias	Atrioventricular block second degree
Other arrhythmias	Atrioventricular conduction time shortened
Other arrhythmias	Bifascicular block
Other arrhythmias	Bradycardia
Other arrhythmias	Brugada syndrome
Other arrhythmias	Bundle branch block
Other arrhythmias	Bundle branch block bilateral
Other arrhythmias	Bundle branch block left
Other arrhythmias	Bundle branch block right
Other arrhythmias	Cardiac fibrillation
Other arrhythmias	Cardiac flutter
Other arrhythmias	Conduction disorder
Other arrhythmias	Extrasystoles
Other arrhythmias	Heart alternation
Other arrhythmias	Heart block congenital
Other arrhythmias	Heart rate abnormal
Other arrhythmias	Heart rate decreased
Other arrhythmias	Heart rate irregular
Other arrhythmias	Long QT syndrome
Other arrhythmias	Long QT syndrome congenital
Other arrhythmias	Lown-Ganong-Levine syndrome
Other arrhythmias	Sick sinus syndrome
Other arrhythmias	Sinoatrial block
Other arrhythmias	Sinus arrest
Other arrhythmias	Sinus arrhythmia
Other arrhythmias	Sinus bradycardia
Other arrhythmias	Supraventricular extrasystoles
Other arrhythmias	Trifascicular block
Other arrhythmias	Wandering pacemaker
Palpitations	Extrasystoles
Palpitations	Palpitations
Palpitations	Supraventricular extrasystoles
Palpitations	Ventricular extrasystoles
Supraventricular tachycardia	Atrial tachycardia
Supraventricular tachycardia	Postural orthostatic tachycardia syndrome
Supraventricular tachycardia	Sinus tachycardia
Supraventricular tachycardia	Supraventricular tachycardia
Supraventricular tachycardia	Tachycardia paroxysmal
Tachycardia	Heart rate increased
Tachycardia	Sinus tachycardia
Tachycardia	Tachycardia
Ventricular arrhythmias	Accelerated idioventricular rhythm
Ventricular arrhythmias	Rhythm idioventricular
Ventricular arrhythmias	Torsade de pointes
Ventricular arrhythmias	Ventricular arrhythmia
Ventricular arrhythmias	Ventricular asystole

Clinical endpoint	MedDRA PT included
Ventricular arrhythmias	Ventricular extrasystoles
Ventricular arrhythmias	Ventricular fibrillation
Ventricular arrhythmias	Ventricular flutter
Ventricular arrhythmias	Ventricular pre-excitation
Ventricular arrhythmias	Ventricular tachycardia
Ventricular arrhythmias	Wolff-Parkinson-White syndrome
Ventricular arrhythmias	Wolff-Parkinson-White syndrome congenital
Ventricular tachycardia / fibrillation	Ventricular fibrillation
Ventricular tachycardia / fibrillation	Ventricular tachycardia

Vascular Disorder System Organ Class	
Aneurysm	Aneurysm
Aneurysm	Aneurysm arteriovenous
Aneurysm	Aneurysm ruptured
Aneurysm	Aortic aneurysm
Aneurysm	Aortic aneurysm rupture
Aneurysm	Aortic aneurysm syphilitic
Aneurysm	Aortic dissection
Aneurysm	Aortic dissection rupture
Aneurysm	Aortic intramural haematoma
Aneurysm	Artery dissection
Aneurysm	Cardiac aneurysm
Aneurysm	Carotid aneurysm rupture
Aneurysm	Cerebral aneurysm ruptured syphilitic
Aneurysm	Charcot-Bouchard microaneurysms
Aneurysm	Coronary artery aneurysm
Aneurysm	Coronary artery dissection
Aneurysm	Dissecting coronary artery aneurysm
Aneurysm	Femoral artery aneurysm
Aneurysm	Femoral artery dissection
Aneurysm	Haemorrhage coronary artery
Aneurysm	Hepatic artery aneurysm
Aneurysm	Infective aneurysm
Aneurysm	Intracranial aneurysm
Aneurysm	Mycotic aneurysm
Aneurysm	Peripheral artery aneurysm
Aneurysm	Peripheral artery dissection
Aneurysm	Pulmonary artery aneurysm
Aneurysm	Renal aneurysm
Aneurysm	Renal artery dissection
Aneurysm	Retinal aneurysm
Aneurysm	Ruptured cerebral aneurysm
Aneurysm	Splenic artery aneurysm
Aneurysm	Subclavian artery aneurysm
Aneurysm	Venous aneurysm

Vascular Disorder System Organ Class	
Hypertension	Accelerated hypertension
Hypertension	Blood pressure ambulatory increased
Hypertension	Blood pressure diastolic increased
Hypertension	Blood pressure inadequately controlled
Hypertension	Blood pressure increased
Hypertension	Blood pressure orthostatic increased
Hypertension	Blood pressure systolic increased
Hypertension	Diastolic hypertension
Hypertension	Essential hypertension
Hypertension	Hypertension
Hypertension	Hypertensive angiopathy
Hypertension	Hypertensive cardiomegaly
Hypertension	Hypertensive cardiomyopathy
Hypertension	Hypertensive crisis
Hypertension	Hypertensive emergency
Hypertension	Hypertensive encephalopathy
Hypertension	Hypertensive heart disease
Hypertension	Hypertensive nephropathy
Hypertension	Labile hypertension
Hypertension	Liddle's syndrome
Hypertension	Malignant hypertension
Hypertension	Malignant hypertensive heart disease
Hypertension	Malignant renal hypertension
Hypertension	Mean arterial pressure increased
Hypertension	Neurogenic hypertension
Hypertension	Paradoxical pressor response
Hypertension	Procedural hypertension
Hypertension	Renal hypertension
Hypertension	Renovascular hypertension
Hypertension	Secondary hypertension
Hypertension	Systolic hypertension
Stroke	Amaurosis fugax
Stroke	Basal ganglia haemorrhage
Stroke	Basilar artery occlusion
Stroke	Basilar artery thrombosis
Stroke	Brain stem haemorrhage
Stroke	Brain stem infarction
Stroke	Brain stem ischaemia
Stroke	Brain stem stroke
Stroke	Brain stem thrombosis
Stroke	Carotid aneurysm rupture
Stroke	Carotid arterial embolus
Stroke	Carotid artery occlusion

Vascular Disorder System Organ Class	
Stroke	Carotid artery thrombosis
Stroke	Cerebellar artery occlusion
Stroke	Cerebellar artery thrombosis
Stroke	Cerebellar embolism
Stroke	Cerebellar haematoma
Stroke	Cerebellar haemorrhage
Stroke	Cerebellar infarction
Stroke	Cerebellar ischaemia
Stroke	Cerebral arteriovenous malformation haemorrhagic
Stroke	Cerebral artery embolism
Stroke	Cerebral artery occlusion
Stroke	Cerebral artery thrombosis
Stroke	Cerebral haematoma
Stroke	Cerebral haemorrhage
Stroke	Cerebral haemorrhage foetal
Stroke	Cerebral haemorrhage neonatal
Stroke	Cerebral infarction
Stroke	Cerebral infarction foetal
Stroke	Cerebral ischaemia
Stroke	Cerebral thrombosis
Stroke	Cerebrovascular accident
Stroke	Embolic cerebral infarction
Stroke	Embolic stroke
Stroke	Haemorrhage intracranial
Stroke	Haemorrhagic cerebral infarction
Stroke	Haemorrhagic stroke
Stroke	Haemorrhagic transformation stroke
Stroke	Intracranial haematoma
Stroke	Intracranial tumour haemorrhage
Stroke	Intraoperative cerebral artery occlusion
Stroke	Intraventricular haemorrhage
Stroke	Intraventricular haemorrhage neonatal
Stroke	Ischaemic cerebral infarction
Stroke	Ischaemic stroke
Stroke	Lacunar infarction
Stroke	Lateral medullary syndrome
Stroke	Pituitary haemorrhage
Stroke	Pituitary infarction
Stroke	Post procedural stroke
Stroke	Precerebral artery occlusion
Stroke	Putamen haemorrhage
Stroke	Reversible ischaemic neurological deficit

Vascular Disorder System Organ Class	
Stroke	Ruptured cerebral aneurysm
Stroke	Stroke in evolution
Stroke	Subarachnoid haemorrhage
Stroke	Subarachnoid haemorrhage neonatal
Stroke	Subdural haemorrhage neonatal
Stroke	Thalamic infarction
Stroke	Thalamus haemorrhage
Stroke	Thrombotic cerebral infarction
Stroke	Thrombotic stroke
Stroke	Transient ischaemic attack
Stroke	Vertebral artery occlusion
Stroke	Vertebral artery thrombosis

Lower Respiratory System Disorders

Pooled (collapsed) Term	**Preferred Term**
Asthma	Analgesic asthma syndrome
Asthma	Asthma
Asthma	Asthma late onset
Bronchitis	Allergic bronchitis
Bronchitis	Bronchitis
Bronchitis	Bronchitis bacterial
Bronchitis	Bronchitis chronic
Bronchitis	Bronchitis fungal
Bronchitis	Bronchitis haemophilus
Bronchitis	Bronchitis moraxella
Bronchitis	Bronchitis pneumococcal
Bronchitis	Bronchitis viral
Bronchitis	Fibrinous bronchitis
Bronchitis	Noninfective bronchitis
Bronchitis	Sinobronchitis
Bronchitis	Tracheobronchitis
COPD exacerbation	Chronic obstructive pulmonary disease
COPD exacerbation	Infective exacerbation of chronic obstructive airways disease
COPD exacerbation	Obstructive airways disorder
COPD exacerbation (broad)	Allergic bronchitis
COPD exacerbation (broad)	Bronchitis
COPD exacerbation (broad)	Bronchitis bacterial
COPD exacerbation (broad)	Bronchitis chronic
COPD exacerbation (broad)	Bronchitis fungal
COPD exacerbation (broad)	Bronchitis haemophilus
COPD exacerbation (broad)	Bronchitis moraxella
COPD exacerbation (broad)	Bronchitis pneumococcal

Pooled (collapsed) Term	Preferred Term
COPD exacerbation (broad)	Bronchitis viral
COPD exacerbation (broad)	Chronic obstructive pulmonary disease
COPD exacerbation (broad)	Fibrinous bronchitis
COPD exacerbation (broad)	Increased bronchial secretion
COPD exacerbation (broad)	Increased viscosity of bronchial secretion
COPD exacerbation (broad)	Infective exacerbation of chronic obstructive airways disease
COPD exacerbation (broad)	Lower respiratory tract infection
COPD exacerbation (broad)	Lung infection
COPD exacerbation (broad)	Lung infection pseudomonal
COPD exacerbation (broad)	Noninfective bronchitis
COPD exacerbation (broad)	Obstructive airways disorder
COPD exacerbation (broad)	Respiratory tract infection
COPD exacerbation (broad)	Respiratory tract infection viral
COPD exacerbation (broad)	Sinobronchitis
COPD exacerbation (broad)	Sputum discoloured
COPD exacerbation (broad)	Sputum purulent
COPD exacerbation (broad)	Tracheobronchitis
COPD exacerbation (broad) with pneumonia	Allergic bronchitis
COPD exacerbation (broad) with pneumonia	Bronchitis
COPD exacerbation (broad) with pneumonia	Bronchitis bacterial
COPD exacerbation (broad) with pneumonia	Bronchitis chronic
COPD exacerbation (broad) with pneumonia	Bronchitis fungal
COPD exacerbation (broad) with pneumonia	Bronchitis haemophilus
COPD exacerbation (broad) with pneumonia	Bronchitis moraxella
COPD exacerbation (broad) with pneumonia	Bronchitis pneumococcal
COPD exacerbation (broad) with pneumonia	Bronchitis viral
COPD exacerbation (broad) with pneumonia	Bronchopneumonia
COPD exacerbation (broad) with pneumonia	Chronic obstructive pulmonary disease
COPD exacerbation (broad) with pneumonia	Congenital pneumonia
COPD exacerbation (broad) with pneumonia	Embolic pneumonia
COPD exacerbation (broad) with pneumonia	Enterobacter pneumonia
COPD exacerbation (broad) with pneumonia	Fibrinous bronchitis
COPD exacerbation (broad) with pneumonia	Increased bronchial secretion
COPD exacerbation (broad) with pneumonia	Increased viscosity of bronchial secretion
COPD exacerbation (broad) with pneumonia	Infective exacerbation of chronic obstructive airways disease
COPD exacerbation (broad) with pneumonia	Lobar pneumonia
COPD exacerbation (broad) with pneumonia	Lower respiratory tract infection
COPD exacerbation (broad) with pneumonia	Lung infection
COPD exacerbation (broad) with pneumonia	Lung infection pseudomonal
COPD exacerbation (broad) with pneumonia	Miliary pneumonia

Pooled (collapsed) Term	Preferred Term
COPD exacerbation (broad) with pneumonia	Mycobacterium kansasii pneumonia
COPD exacerbation (broad) with pneumonia	Neonatal pneumonia
COPD exacerbation (broad) with pneumonia	Noninfective bronchitis
COPD exacerbation (broad) with pneumonia	Obstructive airways disorder
COPD exacerbation (broad) with pneumonia	Pneumonia
COPD exacerbation (broad) with pneumonia	Pneumonia adenoviral
COPD exacerbation (broad) with pneumonia	Pneumonia anthrax
COPD exacerbation (broad) with pneumonia	Pneumonia bacterial
COPD exacerbation (broad) with pneumonia	Pneumonia blastomyces
COPD exacerbation (broad) with pneumonia	Pneumonia bordetella
COPD exacerbation (broad) with pneumonia	Pneumonia chlamydial
COPD exacerbation (broad) with pneumonia	Pneumonia cryptococcal
COPD exacerbation (broad) with pneumonia	Pneumonia cytomegaloviral
COPD exacerbation (broad) with pneumonia	Pneumonia escherichia
COPD exacerbation (broad) with pneumonia	Pneumonia fungal
COPD exacerbation (broad) with pneumonia	Pneumonia haemophilus
COPD exacerbation (broad) with pneumonia	Pneumonia helminthic
COPD exacerbation (broad) with pneumonia	Pneumonia herpes viral
COPD exacerbation (broad) with pneumonia	Pneumonia influenzal
COPD exacerbation (broad) with pneumonia	Pneumonia klebsiella
COPD exacerbation (broad) with pneumonia	Pneumonia legionella
COPD exacerbation (broad) with pneumonia	Pneumonia measles
COPD exacerbation (broad) with pneumonia	Pneumonia moraxella
COPD exacerbation (broad) with pneumonia	Pneumonia mycoplasmal
COPD exacerbation (broad) with pneumonia	Pneumonia necrotising
COPD exacerbation (broad) with pneumonia	Pneumonia parainfluenzae viral
COPD exacerbation (broad) with pneumonia	Pneumonia pneumococcal
COPD exacerbation (broad) with pneumonia	Pneumonia primary atypical
COPD exacerbation (broad) with pneumonia	Pneumonia respiratory syncytial viral
COPD exacerbation (broad) with pneumonia	Pneumonia salmonella
COPD exacerbation (broad) with pneumonia	Pneumonia staphylococcal
COPD exacerbation (broad) with pneumonia	Pneumonia streptococcal
COPD exacerbation (broad) with pneumonia	Pneumonia toxoplasmal
COPD exacerbation (broad) with pneumonia	Pneumonia tularaemia
COPD exacerbation (broad) with pneumonia	Pneumonia viral
COPD exacerbation (broad) with pneumonia	Post procedural pneumonia
COPD exacerbation (broad) with pneumonia	Respiratory tract infection
COPD exacerbation (broad) with pneumonia	Respiratory tract infection viral
COPD exacerbation (broad) with pneumonia	Sinobronchitis
COPD exacerbation (broad) with pneumonia	Sputum discoloured
COPD exacerbation (broad) with pneumonia	Sputum purulent
COPD exacerbation (broad) with pneumonia	Tracheobronchitis
Cystic fibrosis	Cystic fibrosis

Pooled (collapsed) Term	Preferred Term
Cystic fibrosis	Cystic fibrosis lung
Dyspnoea	Dyspnoea
Dyspnoea	Dyspnoea at rest
Dyspnoea	Dyspnoea exertional
Dyspnoea	Dyspnoea paroxysmal nocturnal
Dyspnoea	Nocturnal dyspnoea
Dyspnoea	Orthopnoea
Dyspnoea	Platypnoea
Lower respiratory tract infection	Actinomycotic pulmonary infection
Lower respiratory tract infection	Acute interstitial pneumonitis
Lower respiratory tract infection	Acute pulmonary histoplasmosis
Lower respiratory tract infection	Amoebic lung abscess
Lower respiratory tract infection	Aspergilloma
Lower respiratory tract infection	Bronchiectasis
Lower respiratory tract infection	Bronchitis
Lower respiratory tract infection	Bronchitis bacterial
Lower respiratory tract infection	Bronchitis fungal
Lower respiratory tract infection	Bronchitis haemophilus
Lower respiratory tract infection	Bronchitis moraxella
Lower respiratory tract infection	Bronchitis pneumococcal
Lower respiratory tract infection	Bronchitis viral
Lower respiratory tract infection	Bronchopneumonia
Lower respiratory tract infection	Bronchopulmonary aspergillosis
Lower respiratory tract infection	Bronchopulmonary aspergillosis allergic
Lower respiratory tract infection	Chronic pulmonary histoplasmosis
Lower respiratory tract infection	Coccidioidomycosis
Lower respiratory tract infection	Congenital pneumonia
Lower respiratory tract infection	Embolic pneumonia
Lower respiratory tract infection	Enterobacter pneumonia
Lower respiratory tract infection	Hantavirus pulmonary infection
Lower respiratory tract infection	Infective exacerbation of chronic obstructive airways disease
Lower respiratory tract infection	Lobar pneumonia
Lower respiratory tract infection	Lower respiratory tract infection
Lower respiratory tract infection	Lower respiratory tract infection bacterial
Lower respiratory tract infection	Lower respiratory tract infection fungal
Lower respiratory tract infection	Lower respiratory tract infection viral
Lower respiratory tract infection	Lung abscess
Lower respiratory tract infection	Lung infection
Lower respiratory tract infection	Lung infection pseudomonal
Lower respiratory tract infection	Mediastinal abscess

Pooled (collapsed) Term	Preferred Term
Lower respiratory tract infection	Metapneumovirus infection
Lower respiratory tract infection	Miliary pneumonia
Lower respiratory tract infection	Mycobacterium kansasii pneumonia
Lower respiratory tract infection	Neonatal pneumonia
Lower respiratory tract infection	Paragonimiasis
Lower respiratory tract infection	Pleural infection
Lower respiratory tract infection	Pleural infection bacterial
Lower respiratory tract infection	Pneumocystis jiroveci pneumonia
Lower respiratory tract infection	Pneumonia
Lower respiratory tract infection	Pneumonia adenoviral
Lower respiratory tract infection	Pneumonia anthrax
Lower respiratory tract infection	Pneumonia bacterial
Lower respiratory tract infection	Pneumonia blastomyces
Lower respiratory tract infection	Pneumonia bordetella
Lower respiratory tract infection	Pneumonia chlamydial
Lower respiratory tract infection	Pneumonia cryptococcal
Lower respiratory tract infection	Pneumonia cytomegaloviral
Lower respiratory tract infection	Pneumonia escherichia
Lower respiratory tract infection	Pneumonia fungal
Lower respiratory tract infection	Pneumonia haemophilus
Lower respiratory tract infection	Pneumonia helminthic
Lower respiratory tract infection	Pneumonia herpes viral
Lower respiratory tract infection	Pneumonia influenzal
Lower respiratory tract infection	Pneumonia klebsiella
Lower respiratory tract infection	Pneumonia legionella
Lower respiratory tract infection	Pneumonia measles
Lower respiratory tract infection	Pneumonia moraxella
Lower respiratory tract infection	Pneumonia mycoplasmal
Lower respiratory tract infection	Pneumonia necrotising
Lower respiratory tract infection	Pneumonia parainfluenzae viral
Lower respiratory tract infection	Pneumonia pneumococcal
Lower respiratory tract infection	Pneumonia primary atypical
Lower respiratory tract infection	Pneumonia respiratory syncytial viral
Lower respiratory tract infection	Pneumonia salmonella
Lower respiratory tract infection	Pneumonia staphylococcal
Lower respiratory tract infection	Pneumonia streptococcal
Lower respiratory tract infection	Pneumonia toxoplasmal
Lower respiratory tract infection	Pneumonia tularaemia
Lower respiratory tract infection	Pneumonia viral
Lower respiratory tract infection	Post procedural pneumonia
Lower respiratory tract infection	Pseudomonas bronchitis
Lower respiratory tract infection	Pulmonary echinococciasis
Lower respiratory tract infection	Pulmonary mycosis

Pooled (collapsed) Term	Preferred Term
Lower respiratory tract infection	Pulmonary sepsis
Lower respiratory tract infection	Pulmonary syphilis
Lower respiratory tract infection	Pulmonary trichosporonosis
Lower respiratory tract infection	Pulmonary tuberculoma
Lower respiratory tract infection	Pulmonary tuberculosis
Lower respiratory tract infection	Pyopneumothorax
Lower respiratory tract infection	Pyothorax
Lower respiratory tract infection	Respiratory moniliasis
Lower respiratory tract infection	Respiratory syncytial virus bronchiolitis
Lower respiratory tract infection	Severe acute respiratory syndrome
Lower respiratory tract infection	Sputum purulent
Lower respiratory tract infection	Young's syndrome
Pneumonia	Bronchopneumonia
Pneumonia	Congenital pneumonia
Pneumonia	Embolic pneumonia
Pneumonia	Enterobacter pneumonia
Pneumonia	Lobar pneumonia
Pneumonia	Miliary pneumonia
Pneumonia	Mycobacterium kansasii pneumonia
Pneumonia	Neonatal pneumonia
Pneumonia	Pneumonia
Pneumonia	Pneumonia adenoviral
Pneumonia	Pneumonia anthrax
Pneumonia	Pneumonia bacterial
Pneumonia	Pneumonia blastomyces
Pneumonia	Pneumonia bordetella
Pneumonia	Pneumonia chlamydial
Pneumonia	Pneumonia cryptococcal
Pneumonia	Pneumonia cytomegaloviral
Pneumonia	Pneumonia escherichia
Pneumonia	Pneumonia fungal
Pneumonia	Pneumonia haemophilus
Pneumonia	Pneumonia helminthic
Pneumonia	Pneumonia herpes viral
Pneumonia	Pneumonia influenzal
Pneumonia	Pneumonia klebsiella
Pneumonia	Pneumonia legionella
Pneumonia	Pneumonia measles
Pneumonia	Pneumonia moraxella
Pneumonia	Pneumonia mycoplasmal
Pneumonia	Pneumonia necrotising
Pneumonia	Pneumonia parainfluenzae viral

Pooled (collapsed) Term	Preferred Term
Pneumonia	Pneumonia pneumococcal
Pneumonia	Pneumonia primary atypical
Pneumonia	Pneumonia respiratory syncytial viral
Pneumonia	Pneumonia salmonella
Pneumonia	Pneumonia staphylococcal
Pneumonia	Pneumonia streptococcal
Pneumonia	Pneumonia toxoplasmal
Pneumonia	Pneumonia tularaemia
Pneumonia	Pneumonia viral
Pneumonia	Post procedural pneumonia
Pulmonary edema	Acute pulmonary oedema
Pulmonary edema	Acute respiratory distress syndrome
Pulmonary edema	Non-cardiogenic pulmonary oedema
Pulmonary edema	Pulmonary congestion
Pulmonary edema	Pulmonary oedema
Pulmonary edema	Pulmonary oedema post fume inhalation
Respiratory failure	Acute respiratory failure
Respiratory failure	Cardiopulmonary failure
Respiratory failure	Chronic respiratory failure
Respiratory failure	Hypoxia
Respiratory failure	Respiratory acidosis
Respiratory failure	Respiratory failure
Respiratory failure	Respiratory paralysis
Respiratory failure (broad)	Acute respiratory failure
Respiratory failure (broad)	Cardiopulmonary failure
Respiratory failure (broad)	Cardio-respiratory distress
Respiratory failure (broad)	Chronic respiratory failure
Respiratory failure (broad)	Hypoxia
Respiratory failure (broad)	Postoperative respiratory distress
Respiratory failure (broad)	Respiratory acidosis
Respiratory failure (broad)	Respiratory distress
Respiratory failure (broad)	Respiratory failure
Respiratory failure (broad)	Respiratory fatigue
Respiratory failure (broad)	Respiratory paralysis
Sputum purulent	Sputum discoloured
Sputum purulent	Sputum purulent

17.2 APPENDIX: ESTIMATED MEAN LUNG FUNCTION OVER TIME DURING THE UPLIFT TRIAL

Table 17.2: 1 Estimated mean FEV_1 over time during the UPLIFT trial

		Placebo	Tiotropium	Tiotropium - Placebo
	Time point	**Mean (SE) [L]**	**Mean (SE) [L]**	**Mean (CI)**
Day 1	Pre-BD	1.116	1.116	
	Post-BD	1.347	1.347	
Month 1	Pre-BD	1.134 (0.004)	1.221 (0.004)	0.087 (0.077, 0.098)
	Post-BD	1.372 (0.004)	1.418 (0.004)	0.047 (0.037, 0.057)
Month 6	Pre-BD	1.126 (0.004)	1.225 (0.004)	0.099 (0.087, 0.111)
	Post-BD	1.365 (0.004)	1.423 (0.004)	0.058 (0.047, 0.069)
Month 12	Pre-BD	1.111 (0.004)	1.213 (0.004)	0.103 (0.091, 0.115)
	Post-BD	1.345 (0.004)	1.398 (0.004)	0.054 (0.042, 0.065)
Month 18	Pre-BD	1.101 (0.005)	1.192 (0.005)	0.091 (0.078, 0.104)
	Post-BD	1.326 (0.005)	1.379 (0.005)	0.053 (0.040, 0.066)
Month 24	Pre-BD	1.079 (0.005)	1.173 (0.005)	0.094 (0.081, 0.107)
	Post-BD	1.294 (0.005)	1.356 (0.005)	0.062 (0.049, 0.075)
Month 30	Pre-BD	1.061 (0.005)	1.156 (0.005)	0.095 (0.081, 0.109)
	Post-BD	1.274 (0.005)	1.335 (0.005)	0.061 (0.047, 0.075)
Month 36	Pre-BD	1.045 (0.005)	1.144 (0.005)	0.099 (0.085, 0.114)
	Post-BD	1.250 (0.005)	1.315 (0.005)	0.065 (0.051, 0.080)
Month 42	Pre-BD	1.034 (0.005)	1.129 (0.005)	0.095 (0.080, 0.110)
	Post-BD	1.236 (0.006)	1.297 (0.005)	0.061 (0.045, 0.076)
Month 48	Pre-BD	1.024 (0.006)	1.112 (0.005)	0.088 (0.073, 0.103)
	Post-BD	1.219 (0.006)	1.268 (0.006)	0.049 (0.033, 0.065)

Day 1 (baseline) values are observed overall mean values.
Source data: see U08-3718-04, Table 15.2.1: 12

Table 17.2: 2 Estimated mean FVC over time during the UPLIFT trial

		Placebo	Tiotropium	Tiotropium - Placebo
	Time point	**Mean (SE) [L]**	**Mean (SE) [L]**	**Mean (CI)**
Day 1	Pre-BD	2.652	2.652	
	Post-BD	3.119	3.119	
Month 1	Pre-BD	2.667 (0.008)	2.856 (0.008)	0.190 (0.168, 0.211)
	Post-BD	3.149 (0.007)	3.204 (0.006)	0.055 (0.037, 0.073)
Month 6	Pre-BD	2.658 (0.009)	2.862 (0.008)	0.204 (0.180, 0.228)
	Post-BD	3.137 (0.008)	3.193 (0.007)	0.054 (0.034, 0.076)
Month 12	Pre-BD	2.640 (0.009)	2.838 (0.009)	0.198 (0.173, 0.222)
	Post-BD	3.110 (0.008)	3.158 (0.008)	0.048 (0.026, 0.070)
Month 18	Pre-BD	2.622 (0.010)	2.816 (0.010)	0.194 (0.167, 0.221)
	Post-BD	3.075 (0.009)	3.126 (0.009)	0.050 (0.026, 0.074)
Month 24	Pre-BD	2.597 (0.010)	2.785 (0.010)	0.189 (0.161, 0.216)
	Post-BD	3.036 (0.009)	3.095 (0.009)	0.059 (0.035, 0.084)
Month 30	Pre-BD	2.572 (0.010)	2.757 (0.010)	0.185 (0.157, 0.213)
	Post-BD	3.010 (0.010)	3.057 (0.009)	0.047 (0.021, 0.074)
Month 36	Pre-BD	2.553 (0.011)	2.753 (0.010)	0.200 (0.170, 0.229)
	Post-BD	2.973 (0.010)	3.038 (0.010)	0.065 (0.038, 0.093)
Month 42	Pre-BD	2.540 (0.011)	2.724 (0.011)	0.184 (0.154, 0.215)
	Post-BD	2.959 (0.011)	3.005 (0.010)	0.046 (0.017, 0.076)
Month 48	Pre-BD	2.532 (0.011)	2.702 (0.011)	0.170 (0.139, 0.201)
	Post-BD	2.929 (0.011)	2.961 (0.010)	0.032 (0.002, 0.061)

Day 1 (baseline) values are observed overall mean values.
Source data: see U08-3718-04, Table 15.2.2: 5

17.3 APPENDIX: EXACERBATION DATA FROM OTHER CLINICAL TRIALS

17.3.1 MISTRAL (205.214)

17.3.1.1 Study design

The one year trial in France (205.214/U04-1252-01) was a randomized, double-blind, parallel group, placebo-controlled study of tiotropium 18 mcg once daily in patients with COPD. The primary outcome was morning peak expiratory flow rates (PEFR) with exacerbations of COPD being a secondary outcome. Patients were required to have had a history of at least one exacerbation in the preceding year.

Exacerbations of COPD were defined as follows:

A change in therapy such as:
- increase beta agonist dose *or*
- prescription of an antibiotic *or*
- prescription or increase of corticosteroid *or*
  - prescription or increase of bronchodilators (theophylline, nebulized bronchodilators, etc)

and at least one of the following symptoms during at least the past 24 hours:
- worsening of dyspnea *or*
- worsening of cough (frequency or severity) *or*
  - worsening of sputum production *or*
- development of purulent sputum *or*
- fever > 38° C *or*
- development of a new chest x-ray abnormality

The severity of severity of an exacerbation was defined as follows:

Mild:
- Therapeutic modification with less than three of the above clinical symptoms.

Severe:
- Exacerbations requiring a hospitalisation,
  or associated with a decline in FEV_1 drop or PEFR at least 30% of baseline values on at least two consecutive days
  or a decline of $PaO_2 \geq 10$ mmHg *or* $PaO_2 \leq 60$ mmHg
  or an increase of $PaCO_2 \geq 5$ mmHg *or* $PaCO_2 \geq 45$ mmHg.

Moderate:
- Exacerbations that was neither mild nor severe.

The study began in October 2000 with the last patient being completed in October 2003. A total of 1,010 patients were randomized.

In trial 205.214, patients were issued a Personal Best peak-flow meter and a diary. Patients recorded morning PEFR measurements each day in the diary. Measurements were performed

immediately upon arising after the patient had cleared out mucus and before administration of test drug. The best of three PEFR readings were recorded. The patients also recorded their use of rescue medication and recorded their response to the question: "How do you feel today from a respiratory point of view?" The answer to this question was documented according to a 0 to 10 scale with 0 meaning "very badly" and 10 meaning "very well". Patients were instructed to contact the investigator immediately if they experienced an exacerbation of COPD or changes in their respiratory status. Clinic visits were scheduled at 6, 12, 24, 36 and 48 weeks following randomization. In addition, there was a follow-up visit scheduled two weeks after completing randomized treatment.

17.3.1.2 Data analysis

The efficacy of tiotropium was determined by the changes in the mean weekly morning PEFRs measured between screening visit and week 48 in comparison to placebo. The statistical model for the mean weekly morning PEFR was a one-way analysis of covariance (ANCOVA). The baseline measurement obtained during the last week of the screening period was used as the covariate.

The proportion of patients with at least one exacerbation was analyzed using the Fisher's Exact test (two-sided). Time to first COPD exacerbation was compared between treatment groups using log-rank test. The number exacerbations and number of days of COPD exacerbations were calculated per day of extent of exposure for each patient, the treatment groups were compared by the Wilcoxon-Mann-Whitney test. The number of COPD exacerbations as well as number of exacerbation days were summarized by counting all COPD exacerbations for a treatment group and dividing this number by the sum of extent of exposure for all patients in that treatment group. Finally, these numbers were multiplied by 36,525 to express the data in units of 100 patient years for ease of interpretation. There is no well-accepted estimate of uncertainty for ratio estimator (bootstrap estimates offer some choice but are controversial); hence statistical inference is not possible based on this method.

17.3.1.3 Study population

A total of 1,010 COPD patients (mean FEV_1 1.37 L, 47.6% predicted; age 64.8 years; 88% men) with a history of at least one exacerbation in the previous year were randomized. A total of 71.2% of placebo and 76.6% of tiotropium patients completed the trial. Withdrawal due to an adverse event occurred in 14.9% of placebo and 7.4% of tiotropium treated patients U04-1252, Table 15.1.1: 2). The demographics of the population are as follows:

Table 17.3.1.3:1 Baseline Characteristics of patients in trial 205.214

	Tiotropium	**Placebo**	**Total**
N	500	510	1010
Males (%)	88.8	86.9	87.8
Age (mean [range], years)	64.5 [35-88] ±9.1	65.0 [39-88] ±9.5	64.8 [35-88] ±9.3
Smoking history (pack years)	43.1±20.9	43.0±19.9	43.1±20.4
Ex-smokers (%)	73.2	75.9	74.6
COPD duration (y.) (mean ±SD)	8.2±7.8	8.5±7.7	8.3±7.8
FEV_1 (L) (mean ±SD)	1.38±0.45	1.36±0.44	1.37±0.45
FEV_1 % predicted (median)	48.3%	47.1%	47.6%
FVC (L) (mean ±SD)	2.57±0.75	2.54±0.77	2.56±0.76
a.m. PEFR (L/min)	261±96	258±96	260±96

Source data: see U04-1252, Tables 15.1.4:6, 15.1.4:1, 15.1.4:8

17.3.1.4 Exacerbation outcomes

The exacerbation results were as follows:

Table 17.3.1.4: 1 Exacerbation results in trial 205.214

	Placebo	**Tiotropium**	**Difference**	**p-value**
N	506	497		
Mild, moderate and severe Exacerbations				
% patients with ≥1 exacerbation	60.3	49.9	-10.4	0.0010[1]
Number of exacerbations per 100 pt−yrs	152.5	114.5	-38.0	0.0008[2]
Number of exacerbation days per 100 pt−yrs	2184.1	1500.9	-683.2	0.0004[2]
Moderate to severe exacerbations				
% patients with ≥1 exacerbation	43.7	30.6	-13.1	<0.0001[1]
Number of exacerbations per 100 pt−yrs	101.4	69.1	-32.3	<0.0001[2]
Number of exacerbation days per 100 pt−yrs	1577.8	991.1	-586.6	<0.0001[2]

[1]Fischer's exact test for patients with at least one exacerbation; [2]Wilcoxon-Mann-Whitney test for mean number of events per day of extent of exposure.
Source data: see U04-1252, Table 11.4.1.2.1: 1 and 15.2.3: 1

The time to the first exacerbation was significantly reduced with tiotropium (p<0.001, CTR U04-1252, Appendix 16.1.9.2 STATDOC 6.9.9).

17.3.1.5 Other relevant outcomes

For the primary outcome, tiotropium significantly improved morning PEFR compared to placebo (average difference of 25 L/minute) and this effect was maintained over the 48-week treatment period.

Improvements were observed in patient-reported data such as daily use of short-acting beta-agonists as rescue medication and on the respiratory condition scale. Tiotropium significantly improved trough FEV_1, FVC, SVC and IC compared to placebo and these effects were maintained over the 48-week treatment period

17.3.2 Sputum study 205.270

17.3.2.1 Study design

The sputum study was a 1-year, single-centre, double-blind, randomized, placebo-controlled trial to assess the effect of tiotropium on sputum inflammatory markers and exacerbation frequency. The primary end-point was the concentration of interleukin (IL)-6 in sputum. Secondary end-points included sputum IL-8 and myeloperoxidase (MPO) levels, serum IL-6 and C-reactive protein (CRP) levels, sputum bacterial colonization, FEV_1 and exacerbation frequency.

Patients were provided with diary cards for recording daily symptoms, morning peak flow and drug compliance, and baseline sputum and blood samples were collected. Patients were seen at weeks 4, 16, 32 and 52 after randomization. During clinic visits, spirometry was performed, a sputum sample obtained and diaries were examined. Additionally, at weeks 32 and 52, serum samples were collected and patients asked about any change in sputum production. Patients at least 40 years of age with a diagnosis of COPD (FEV_1 < 80% of the predicted value and FEV_1/FVC < 70%) and a minimum 10-pack-yr smoking history were recruited from primary care or the outpatients department of the London Chest Hospital (London, United Kingdom). Patients with a history of asthma or atopy were excluded, as were those on long-term oxygen therapy or with another clinically significant disease. Anticholinergics other than the study drug were not permitted during the course of the study.

The diagnosis of an exacerbation was based upon symptomatic criteria previously published by the East London COPD Study Group (London, UK). The lead investigator of the East London COPD Study Group was the principal investigator for trial 205.270. An exacerbation was defined as the presence, for 2 days consecutively, of an increase in any two major symptoms (dyspnea, sputum purulence and sputum volume) or in one major and one minor symptom (wheeze, sore throat, cough and symptoms of a common cold). The definition permitted the inclusion of mild exacerbations that did not necessarily require an intervention with an antibiotic or systemic steroid.

17.3.2.2 Data analysis

Analyses were carried out using all randomized treated patients with efficacy data to compare treatments, using ANCOVA that adjusted for smoking status and exacerbation history over the previous year (<3 or >=3 exacerbations). For sputum markers, the area under the curve (AUC) was calculated for each patient, with missing data replaced by interpolation or the last observation carried forward. The model also included baseline inflammatory marker levels as a covariate. AUCs for IL-6 and MPO were skewed and therefore log10-transformed. Change from baseline for serum IL-6 were analysed using a Wilcoxon test.

The effect of tiotropium on individual COPD exacerbation annual rates (number of exacerbations adjusted for 365 days on drug) and number of exacerbation days (per year) was tested using a Wilcoxon test. The number of patients with no exacerbations was compared using the Chi-square-test. Analysis of time to first exacerbation is based on Kaplan-Meier estimates and log-rank test.

17.3.2.3 Study population

One hundred and forty two patients met the protocol specification and were randomized (69 patients on tiotropium and 73 on placebo). During the study 21/69 (30.4%) of patients on tiotropium withdrew before one year compared to 21/73 (28.8%) patients on placebo. Seven (10.1%) patients on tiotropium and 14 (19.2%) patients on placebo withdrew due to an adverse event (U06-1607, Table 10.1:1).

The baseline characteristics of the study population are outlined in table 17.3.2.3: 1.

Table 17.3.2.3: 1 Baseline characteristics of patients in trial 205.270*

	Placebo N=73	**Tiotropium N=69**
Male (%)	56.2%	69.6%
>=3 exacerbations last year (%)	30.1%	30.4%
Current smoking (%)	57.5%	59.4%
Age (years) mean (SD)	66.4 (9.8)	66.3 (8.1)
Smoking (pack-years) mean (SD)	55.7 (28.0)	54.6 (25.5)
FEV_1 (L)	1.23 (0.51)	1.35 (0.47)
FEV_1% predicted (%)	49.2 (15.6)	50.9 (14.8)
FVC (L)	2.16 (0.79)	2.29 (0.75)

*mean (SD) unless otherwise specified
Source data: see U06-1607, Tables 15.1.4:10, 15.1.4:11, 15.1.4:2, 15.1.4:1

17.3.2.4 Exacerbation outcomes

The patients in the tiotropium treated group experienced 60 exacerbations compared to 134 in the placebo arm. Tiotropium was associated with a 52% reduction in exacerbation rate (1.17 vs.2.46 per year, $p<0.01$). A total of 43% of patients on tiotropium experienced at least one exacerbation compared to 64% on placebo ($p=0.01$). Time to first exacerbation was increased with tiotropium (236 vs. 157 days, $p<0.01$) and total exacerbation days reduced compared to placebo (17.3 vs. 34.5, $p<0.01$). Two patients (3.3%) who experienced exacerbations on tiotropium were hospitalized compared to 3 patients (2.2%) on placebo.

Table 17.3.2.4: 1 Exacerbation outcomes in the tiotropium and placebo groups in trial 205.270

	Placebo N=73	**Tiotropium N=69**	**p-value**
Exacerbation rate (per year)	2.46 (3.82)	1.17 (2.25)	0.001[1]
Treated exacerbation rate (per year)	1.73 (2.46)	0.75 (1.52)	0.007[1]
Patients with no exacerbations over study period	35.6%	56.5%	0.012[2]
Time to 1st exacerbation (days)	157 (124)	236 (143)	0.009[3]
Number of exacerbation days (per year)	34.5 (47.5)	17.3 (33.6)	0.002[1]

[1]Wilcoxon test; [2] Chi-square-test; [3]log-rank test.
Source data: see U06-1607, Tables 15.2.3:1, 15.2.3:2

17.3.2.5 Other relevant results

Using analysis of covariance there was no difference in area under the curve for sputum IL-6 (p=0.32) or MPO (p=0.08) between the groups but sputum IL-8 was increased in the tiotropium arm (p=0.043). There was no difference between the two groups in change from baseline for serum IL-6 (p=0.69).

17.3.3 Canadian SAFE 205.259

17.3.3.1 Study design

Trial (205.259) was a one-year parallel group, double-blind, randomized, placebo-controlled study conducted in Canada assessing the effect of tiotropium 18 mcg once daily on FEV_1 in patients with COPD. A 2:1 (tiotropium:placebo) randomization was used. Exacerbations were captured as both efficacy (secondary endpoint) and safety on separate case record forms. The efficacy capture was based on fulfilment of the prespecified definition; whereas safety was simply coded from the reported verbatim.

17.3.3.2 Data analysis

FEV_1 (primary outcome) and the St. George's Respiratory Questionnaire scores were analyzed using an ANCOVA model with treatment as a factor and baseline as a covariate. The number (percent) of patients with at least one COPD exacerbation was compared across treatment groups using the Fisher's Exact test (two-sided). The number of COPD exacerbations and the number of COPD exacerbation days was compared across treatment groups using Poisson regression with extent of exposure (minus the duration of events) as the offset.

17.3.3.3 Study population

There were 305 patients in the placebo group and 608 in the tiotropium group. A total of 72.5% of placebo and 77.8% of tiotropium patients completed the trial. Withdrawal due to an

adverse event occurred in 12.8% of placebo and 12.0% of tiotropium treated patients (U05-3345, Table 15.1.1: 1). The baseline characteristics are listed in Table 17.3.3.3: 1.

Table 17.3.3.3: 1 Baseline characteristics of patients in trial 205.259*

	Placebo N=305	**Tiotropium N=608**
Male (%)	60.7%	59.4%
Current smoking (%)	30.2%	32.1%
Age (years)	66.9 (9.1)	66.8 (8.7)
Smoking (pack-years)	51.0 (26.3)	50.2 (22.6)
FEV_1 (L)	0.96 (0.38)	0.97 (0.39)
FEV_1% predicted (%)	39.28 (13.61)	39.36 (13.41)
FVC (L)	2.11 (0.73)	2.11 (0.76)

*means (SD) unless otherwise specified.
Source data: see U05-3345, Tables 15.1.4:1, 15.1.4:2 and 15.1.4:4

17.3.3.4 Exacerbation outcomes

There were no statistically significant differences for exacerbation variables between treatment groups. The results from the efficacy analysis of exacerbations are as follows:

Table 17.3.3.4: 1 Exacerbation outcomes in the tiotropium and placebo group in trial 205.259

	Placebo (N=305)	**Tiotropium (n=608)**
Mean number of exacerbations*	0.92	0.88[2]
Mean number of exacerbation days*	16.2	16.1[2]
% of patients with exacerbations	41.0	44.1[1]
Mean number of hospitalizations due to an exacerbation*	0.15	0.13[2]
Mean number of hospitalization days due to an exacerbation*	1.16	1.14[2]
% of patients with hospitalization due to an exacerbation	8.2	8.4[1]

*per patient year
[1]Fisher's Exact test (two-sided); [2] Poisson regression with extent of exposure as the offset.
Source data: U05-3345, Tables 15.2.5:1, 15.2.5:2, 15.2.6:1, 15.2.6:2

17.3.3.5 Other relevant outcomes

Tiotropium resulted in statistically significant improvements in FEV_1 (primary outcome) and improved the St. George's Respiratory Questionnaire scores relative to placebo.

17.3.4 TIPHON trial 205.256

17.3.4.1 Study design

Trial 205.256 was a 9-month double-blind, randomized, placebo controlled, parallel group study performed in France evaluating the effect of tiotropium 18 mcg once daily on health related quality of life in patients with COPD. Exacerbations of COPD were reported as adverse events.

17.3.4.2 Data analysis

The primary endpoint, proportion of patients achieving a reduction of at least 4 units in the SGRQ total score at study end (Month 9), was analyzed using the Cochran-Mantel-Haenszel test, stratified by center. Analysis of covariance with terms for treatment was used for all the HRQoL and spirometric endpoints, with baseline data as covariates.

The proportion of patients with at least one exacerbation was analyzed using the Fisher's Exact test (two-sided). The number exacerbations and number of days of COPD exacerbations were calculated per day of extent of exposure for each patient, the treatment groups were compared by the Wilcoxon-Mann-Whitney test. The number of COPD exacerbations as well as number of exacerbation days were summarized by counting all COPD exacerbations for a treatment group and dividing this number by the sum of extent of exposure for all patients in that treatment group. Finally, these numbers were multiplied by 36,525 to express the data in units of 100 patient years for ease of interpretation. There is no well-accepted estimate of uncertainty for ratio estimator (bootstrap estimates offer some choice but are controversial); hence statistical inference is not possible based on this method.

17.3.4.3 Study population

There were 288 patients in the placebo group and 266 in the tiotropium group. A total of 74.3% of placebo and 85.3% of tiotropium patients completed the trial. Withdrawal due to an adverse event occurred in 10.8% of placebo and 4.9% of tiotropium treated patients (U05-1961, Table 15.1.1: 2). The baseline characteristics are listed in Table 17.3.4.3: 1.

Table 17.3.4.3: 1 Baseline characteristics of patients in trial 205.256*

	Placebo N=288	**Tiotropium N=266**
Male (%)	85.4%	86.8%
Current smoking (%)	30.2%	23.7%
Age (years)	63.5 (10.1)	64.9 (9.7)
Smoking (pack-years)	43.0 (22.5)	44.4 (21.3)
FEV_1 (L)	1.35 (0.46)	1.38 (0.44)
FEV_1% predicted (%)	46.2 (12.4)	47.5 (13.3)
FVC (L)	2.49 (0.75)	2.50 (0.68)

*means (SD) unless otherwise indicated. Baseline is defined as time before randomisation date.
Source data: see U05-1961, Tables 15.1.4:1, 15.1.4: 3 and 15.1.4: 5

17.3.4.4 Exacerbation outcomes

The exacerbation data are displayed in Table 17.3.4.4: 1 below. There were no statistically significant differences between treatment groups for proportion of patients with at least one exacerbation, but number of exacerbations and exacerbation days per 100 pt−yrs were significantly different.

Table 17.3.4.4: 1 Exacerbation outcomes from trial 205.256

	Placebo (n=288)	Tiotropium (n=266)	Difference	p-value
% patients with ≥1 exacerbation	45.1	38	7.2	0.101[1]
Number of exacerbations per 100 pt−yrs	137.1	94.4	42.7	0.029[2]
Number of exacerbation days per 100 pt−yrs	1586.5	1001.8	584.7	0.021[2]

[1]Fischer's exact test for patients with at least one exacerbation; [2]Wilcoxon-Mann-Whitney test for mean number of events per day of extent of exposure.
Source data: see U05-1961, Table 15.2.5:2

17.3.4.5 Other relevant outcomes

The primary efficacy endpoint was the proportion of patients achieving a reduction of at least 4 units in the SGRQ total score at study end (month 9). Mean ± SD baseline SGRQ total score was 47.4±17.4 (U05-1961, Table 15.1.4: 6). Significantly more tiotropium-treated patients achieved a reduction of at least 4 units in the SGRQ score vs. placebo at study end (59.1% vs. 48.2%, respectively; p = 0.029, U05-1961, Table 11.4.1.1: 1). The mean (SE) improvement in the SGRQ total score at the end of the trial (tiotropium – placebo) was -4.19 (1.27)($p<0.001$). Tiotropium significantly improved FEV_1 (adjusted means±SE: 0.11±0.02 L vs. 0.01±0.02 L, difference=0.10±0.03 L, p=0.0001) (U05-1961, Table 15.2.3: 1).

17.3.5 Pulmonary rehabilitation trial 205.230

17.3.5.1 Study design

Trial 205.230 was a randomized, double-blind, placebo-controlled 24-week trial to compare the effect of tiotropium 18 mcg once daily on exercise tolerance in patients with COPD participating in 8 weeks of pulmonary rehabilitation. Exacerbations of COPD were reported as adverse events.

17.3.5.2 Data analysis

Exercise tolerance was analyzed using an ANCOVA model with treatment and center as factors and baseline as a covariate. The frequency of COPD exacerbations and the COPD exacerbations leading to hospitalizations were summarized numerically only.

17.3.5.3 Study population

A total of 108 patients were randomized. A total of 64.2% of placebo and 67.3% of tiotropium patients completed the trial. Withdrawal due to an adverse event occurred in

17.0% of placebo and 16.4% of tiotropium treated patients (U03-3251, Table 10.1:1). The baseline characteristics are listed in Table 17.3.5.3: 1.

Table 17.3.5.3: 1 Baseline characteristics of patients in trial 205.230*

	Placebo N=53	**Tiotropium N=55**
Male (%)	58.5%	54.5%
Current smoking (%)	18.9%	29.1%
Age (years)	67.3 (6.9)	65.9 (8.8)
Smoking (pack-years)	58.8 (31.4)	58.6 (34.6)
FEV_1 (L)	0.94 (0.40)	0.82 (0.31)
FEV_1% predicted (%)	36.2 (12.2)	32.6 (12.4)
FVC (L)	2.14 (0.85)	2.01 (0.68)

*means (SD) unless otherwise indicated.
Source data: see U03-3251, Tables 11.2: 1, 11.2: 2, 11.2: 3

17.3.5.4 Exacerbation outcomes

There were 10 patients who were reported to experience exacerbations in both the tiotropium and placebo groups.

17.3.5.5 Other relevant results

For the primary endpoint (after 13 weeks on treatment (Test Day 92) including eight weeks of rehabilitation program), patients receiving tiotropium showed significantly longer exercise endurance time compared to patients on the placebo. The mean difference was 5.35 minutes (p=0.025).

17.3.6 Summary

The non-pivotal controlled clinical trials outlined provide additional data that, in general, indicate positive effects on exacerbations. No benefit was observed in trial 205.259 and the smaller trial 205.230 (n=108); however, both trials 205.214, 205.256 and 205.270 included exacerbations as objectives and indicated significant improvements with tiotropium. In addition, the improvements were observed despite quite different approaches to the exacerbation definition, which attests to the robustness of the effect of tiotropium.

17.4 APPENDIX: ADVERSE EVENTS FROM SPONTANEOUS AND HEALTH AUTHORITY SOURCES

The following section represents a summary of adverse events from spontaneous and health authority sources. Details are presented for fatal events, cardiovascular events, stroke and lower respiratory events. The summaries are presented from the global database and limited to the United States.

GLOBAL SPONTANEOUS AND HEALTH AUTHORITY ADVERSE EVENTS

All adverse events

Individual case safety reports from spontaneous and health authority sources contained in the Boehringer Ingelheim Global Drug Safety database where tiotropium was considered a suspect drug that were reported to Boehringer Ingelheim between 09 October 2001 (date of first international registration) and 31 January 2009 were selected for analysis.

A total of 21,787 individual Spiriva case reports have been reported to the company since October 2001. The data includes both formulations; however as tiotropium Respimat® has recently been approved and marketed, only 209 adverse event reports have been reported (including 2 fatal cases). The data presented refers to both formulations; however, the United States specific data only includes reports from the HandiHaler® formulation. It is relevant to note that the number of events in several of the tables displayed in this section may exceed the absolute number of patients as an individual patient may have multiple events reported.

Sixty percent of cases were reported to the company by a health care professional. Where gender was reported, 52% of reports involved female patients and 48% involved male patients. The gender was not reported in 17% of cases. Where age was reported, 68% of patients were greater than 65 years old at the time of the adverse event; 90% were greater than 55 years old. The age of the patient was not reported in 51% of cases.

Table 17.4: 1 Demographic distribution of case reports for all spontaneous adverse events

Age (Years)	Gender		
	Female	Male	Not Reported
	No. of cases	No. of Cases	No. of Cases
<= 35 yrs	39	21	1
36 - 45 yrs	128	79	4
46 - 55 yrs	471	353	6
56 - 65 yrs	1166	1128	27
66 - 75 yrs	1849	2074	27
> 75 yrs	1594	1768	33
not available	4059	3247	3713
All	9306	8670	3811

The cumulative, global exposure during this same time period (including samples) is estimated to be 14,001,446 patient years, assuming that all capsules distributed were consumed by patients. There were a total of 35,113 adverse events reported from

Spontaneous and Health Authority sources during this time period. Serious adverse events constituted 10.5% (3,693) of the total adverse events.

A review of the total adverse events (serious plus non-serious) reported reveals that the ten most common System Organ Class (SOC) categories include the following SOCs: (1) Respiratory, thoracic and mediastinal disorders (6,012 [17.12%]); (2) Injury, poisoning and procedural complications (4,845 [13.80%]); (3) Gastrointestinal disorders (4,831 [13.76%]); (4) General disorders and administration site conditions (4,752 [13.53%]); (5) Nervous system disorders (2,439 [6.95%]); (6) Skin and subcutaneous tissue disorders (2,185 [6.22%]); (7) Eye disorders (2,068 [5.89%]); (8) Renal and urinary disorders (1,518 [4.32%]); (9) Cardiac disorders (1,265 [3.60%]); and (10) Infections and Infestations (1,189 [3.39]). This distribution of total adverse event SOCs is most consistent with either the underlying illness being treated (Chronic Obstructive Pulmonary Disease [COPD]), medical complications associated with COPD, or the expected pharmacologic effects of an anti-muscarinic agent. In one other situation, the large number of "Incorrect route of drug administration" events (3070) which elevates the SOC of "Injury, poisoning and procedural complications" is due to the large number of non serious reports of accidental oral ingestion of the tiotropium capsules. Oral ingestion of tiotropium capsules is unlikely to lead to symptoms or signs indicated an adverse drug reasction due to low bioavailability. Boehringer Ingelheim has strengthened the patient instructions for use to indicate that capsules should not be swallowed.

The ten most common adverse event preferred terms were: (1) Incorrect route of drug administration (3070); (2) Drug ineffective (1927); (3) Dyspnea (1798); (4) Dry mouth (1576); (5) Cough (796); (6) Medication error (743); (7) Urinary retention (683); (8) Vision blurred (617); (9) Dysphonia (569); and (10) Rash (504). Again, these most common individual preferred terms can generally be considered to be consistent with the generic difficulties of administering medications as well as allergic reactions, the underlying disease of COPD or its complications, and the effects consistent with an anti-muscarinic agent.

For serious adverse events, the ten most common System Organ Class (SOC) categories were: (1) Respiratory, thoracic and mediastinal disorders (794 [21.5%]); (2) General disorders and administration site conditions (433 [11.72]); (3) Cardiac disorders (424 [11.48%]); (4) Gastrointestinal disorders (308 [8.34%]); (5) Infections and infestations (253 [6.85%]); (6) Nervous system disorders (245 [6.63]}; (7) Renal and Urinary disorders (171 [4.63%]); (8) Skin and subcutaneous tissue disorders (166 [4.49]); (9) Neoplasms benign, malignant and unspecified (including cysts and polyps) (148 [4.01%]); and (10) Eye disorders (139 [3.76%]). This distribution of Serious adverse event SOCs is again most consistent with either the underlying illness being treated (Chronic Obstructive Pulmonary Disease [COPD]), medical complications associated with COPD, or the expected pharmacologic effects of an anti-muscarinic agent. One major difference from the list of SOCs associated with the total adverse events is that the SOC "Injury, poisoning and procedural complications" is not present. This is due to the fact the most of the adverse events associated with the oral ingestion of Spiriva capsules and medication errors were non-serious adverse events.

When looking at the serious adverse events, the ten most common individual Preferred terms included the following: (1) Dyspnea (235); (2) Death (147); (3) Chronic Obstructive Pulmonary Disease (129); (4) Urinary retention (114); (5) Pneumonia (110); (6) Atrial fibrillation (65); (7) Myocardial infarction (60); (8) Respiratory failure (48); (9) Chest pain (44); and (10) Lung neoplasm malignant (42).

Spontaneous Reports with a Fatal Outcome

Four-hundred and fifty-six case reports were identified as including an adverse event with an outcome of death. One duplicate was identified therefore the analysis is based on 455 cases. Seventy-seven percent of cases were reported to the company by a health care professional. Where gender was reported, 32% of patients in the group were female and 68% male. The patient gender was not reported in 15% of cases. Where age was reported, 77% of patients within the group were greater than 65 years old, 96% of patients were greater than 55 years old. The age was not reported in 40% of cases.

Table 17.4: 2 Demographic distribution of case reports with a fatal outcome

Age (Years)	**Gender**		
	Female	**Male**	**Not Reported**
	No. of cases	**No. of Cases**	**No. of Cases**
<= 35 yrs	0	1	0
36 - 45 yrs	0	1	0
46 - 55 yrs	2	8	0
56 - 65 yrs	17	29	4
66 - 75 yrs	28	71	1
> 75 yrs	28	80	2
not available	49	74	60
All	124	264	67

A review of the demographic distribution of fatal cases reveals that, when patient's age was provided, there was a progressive increase in fatal cases associated with age with the largest increase occurring in patients over 65 years of age.

Time to onset of death after the initiation of tiotropium was reviewed. This time was provided in 185/455 fatal cases. There were 38 cases (21%) in which the fatal event occurred during the first week of Spiriva therapy and 15 cases (8%) in which the fatal event occurred during the second week of Spiriva therapy.

There were 590 fatal adverse events reported in the 455 fatal case reports. When looking at the cause of death, the most common SOCs were: General disorders and administration site conditions – 178; Respiratory, thoracic and mediastinal disorders – 152; Cardiac disorders – 109; Infections and Infestations – 48; and Neoplasms, benign, malignant and unspecified (incl cysts and polyps) – 42. The most common Preferred terms were: Death – 144; Respiratory failure – 39; COPD – 37; Myocardial infarction – 27; Pneumonia – 22; Cardiac failure – 18; Lung neoplasm malignant – 18; Cardiac arrest – 16; Respiratory arrest – 13; Sudden death – 11; and Acute respiratory failure – 11.

Table 17.4: 3 Summary of fatal events by MedDRA system organ class and preferred term

MedDRA System Organ Class	Preferred Term	No. of Events
Blood and lymphatic system disorders	Disseminated intravascular coagulation	1
Cardiac disorders	Acute myocardial infarction	7
	Arrhythmia	4
	Arteriosclerosis coronary artery	1
	Atrial fibrillation	2
	Atrioventricular block	1
	Bradycardia	1
	Cardiac arrest	16
	Cardiac disorder	5
	Cardiac failure	18
	Cardiac failure congestive	4
	Cardio-respiratory arrest	5
	Cardiogenic shock	1
	Cardiopulmonary failure	1
	Congestive cardiomyopathy	1
	Cor pulmonale	2
	Coronary artery disease	1
	Cyanosis	2
	Left ventricular failure	1
	Myocardial infarction	27
	Myocardial ischaemia	1
	Tachycardia	1
	Torsade de pointes	1
	Ventricular arrhythmia	1
	Ventricular fibrillation	5
Gastrointestinal disorders	Abdominal pain	1
	Diarrhoea	1
	Dyspepsia	1
	Gastrointestinal haemorrhage	2
	Intestinal infarction	2
	Odynophagia	1
	Pancreatitis acute	1
	Peritonitis	1
General disorders and administration site conditions	Asthenia	1
	Cardiac death	2
	Chest discomfort	1
	Chest pain	2
	Condition aggravated	1
	Death	144
	Disease progression	1
	Drug ineffective	3
	Drug interaction	1
	Fatigue	1
	Foaming at the mouth	1
	General physical health deterioration	1
	Malaise	1
	Multi-organ failure	5
	Organ failure	1

Table 17.4: 3 (continued) Summary of fatal events by MedDRA system organ class and preferred term (Page 2 of 4)

MedDRA System Organ Class	Preferred Term	No. of Events
	Sudden death	11
	Swelling	1
Infections and infestations	Bronchopneumonia	4
	Cellulitis	1
	Infection	3
	Infective exacerbation of chronic obstructive airways disease	1
	Influenza	1
	Lobar pneumonia	1
	Lower respiratory tract infection	3
	Lung infection	2
	Meningitis	1
	Pneumonia	22
	Pneumonia bacterial	1
	Pulmonary tuberculosis	1
	Respiratory tract infection	4
	Sepsis	1
	Septic shock	2
Injury, poisoning and procedural complications	Accident	1
	Asbestosis	1
	Device misuse	1
	Drug toxicity	1
	Post procedural complication	1
	Road traffic accident	1
Investigations	Biopsy liver	1
Metabolism and nutrition disorders	Acidosis	1
	Diabetes mellitus	1
	Fluid retention	1
	Metabolic acidosis	1
Musculoskeletal and connective tissue disorders	Intervertebral disc compression	1
	Muscle fatigue	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder cancer	2
	Cervix carcinoma	1
	Colon cancer	2
	Hepatic neoplasm malignant	2
	Lung cancer metastatic	1
	Lung neoplasm malignant	18
	Lymphangiosis carcinomatosa	1
	Malignant pleural effusion	1
	Metastases to central nervous system	2
	Metastases to kidney	1
	Metastases to lung	1
	Metastases	1
	Metastatic bronchial carcinoma	2
	Multiple myeloma	1
	Neoplasm malignant	1

Table 17.4: 3 (continued) Summary of fatal events by MedDRA system organ class and preferred term (Page 3 of 4)

MedDRA System Organ Class	Preferred Term	No. of Events
	Non-Hodgkin's lymphoma	1
	Oesophageal carcinoma	1
	Renal cancer	2
	Small cell lung cancer stage unspecified	1
Nervous system disorders	Cerebral haemorrhage	2
	Cerebrovascular accident	4
	Coma	1
	Dizziness	1
	Haemorrhagic stroke	1
	Lethargy	1
	Ruptured cerebral aneurysm	1
	Subarachnoid haemorrhage	1
	Syncope	1
Psychiatric disorders	Anxiety	1
	Suicide attempt	1
Renal and urinary disorders	Dysuria	1
	Renal failure	4
	Renal failure acute	2
	Renal tubular necrosis	1
Respiratory, thoracic and mediastinal disorder	Acute pulmonary oedema	1
	Acute respiratory failure	11
	Apnoea	1
	Asphyxia	2
	Aspiration	1
	Asthma	4
	Bronchospasm	1
	Chronic obstructive pulmonary disease	37
	Cough	1
	Dyspnoea	9
	Emphysema	9
	Hypercapnia	1
	Hyperoxia	1
	Hypocapnia	1
	Hypoventilation	1
	Hypoxia	2
	Lung disorder	3
	Obstructive airway disorder	1
	Pharyngeal haemorrhage	1
	Pneumothorax	2
	Pulmonary embolism	3
	Pulmonary fibrosis	1
	Pulmonary infarction	3
	Pulmonary oedema	1
	Respiratory arrest	13
	Respiratory disorder	2
	Respiratory failure	39
	Rhinorrhoea	1
	Wheezing	1

Table 17.4: 3 (continued) Summary of fatal events by MedDRA system organ class and preferred term (Page 4 of 4)

MedDRA System Organ Class	Preferred Term	No. of Events
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis	1
Vascular disorders	Aortic aneurysm	1
	Aortic aneurysm rupture	1
	Aortic dissection	1
	Circulatory collapse	5
	Haemorrhage	1
	Hypertension	1
	Shock	1
Total events		590

Narratives from the fatal cases were reviewed. Most patients had multiple concomitant illnesses and receiving multiple concomitant medications. In some of these patients the pulmonary medications were changed or discontinued at the same time that tiotropium was begun. In these patients it may be postulated that the patient's condition had been deteriorating leading to the physician initiating a change in the medication. In these cases the death of the patient could be considered to have been related to a deterioration of the underlying condition.

Table 17.4: 4 Time to onset of the fatal adverse event after the start of Spiriva therapy was calculated for these cases. The results are noted below

Time to Onset of Fatal Event	Number of Cases
Less than 1 Day	9
1 – 2 Days	12
3 – 7 Days	17
8 -14 Days	15
Greater than 15 Days	132
Unknown	270
Total	455

Cardiovascular adverse events

A summary of serious and non-serious cardiac adverse events are presented in Tables 17.4: 5 and 17.4: 6.

Table 17.4: 5 Summary of spontaneous serious and non-serious cardiovascular adverse events occurring at a preferred term frequency of 0.1% of all adverse events.

System Organ Class (SOC)	Number of Events	% Total Events within SOC	Adverse Event (AE) Preferred Term	Number of AEs
Cardiac disorders	1265	3.60	Palpitations	303
			Tachycardia Palpitations	302
			Atrial fibrillation	141
			Arrhythmia	80
			Myocardial infarction	61
			Cardiac failure	42
			Angina pectoris	42
Vascular disorders	252	0.73		
			Hypertension	54

Table 17.4: 6 Summary of spontaneous serious cardiovascular adverse events occurring at a preferred term frequency of 0.1% of all serious adverse events

System Organ Class (SOC)	Number of Events	% Total Events within SOC	Adverse Event (AE) Preferred Term	Number of AEs
Cardiac disorders	424	11.5		
			Atrial fibrillation	65
			Myocardial infarction	60
			Tachycardia	39
			Cardiac failure	33
			Cardiac failure congestive	24
			Arrhythmia	21
			Palpitations	19
			Cardiac disorder	18
			Cardiac arrest	17
			Angina pectoris	13
			Supraventricular tachycardia	11
			Acute myocardial infarction	10
			Atrial flutter	9
			Cardio-respiratory arrest	6
			Ventricular fibrillation	6
			Tachyarrhythmia	5
			Ventricular tachycardia	5
			Cyanosis	4
			Coronary artery occlusion	4
			Coronary artery disease	4
			Cor pulmonale	4
			Ventricular extrasystoles	4
			Extrasystoles	4
Vascular disorders	76	2.05		
			Circulatory collapse	10
			Hypertension	8
			Hypotension	8
			Aortic aneurysm	6
			Haemorrhage	5
			Thrombosis	4

Stroke

Adverse events from the individual reports were grouped according to the combined preferred term of stroke defined in the pooled analysis of clinical data. The definition of the pooled term of stroke is listed in Appendix 17.1.

Sixty case reports are included in combined endpoint of stroke. Sixty-two percent of cases were reported to the company by a health care professional. Where gender was reported, 44% of patients in this group were female and 56% male. The patient gender was not

reported in 8% of cases. Where the age of the patient was reported, 64% of patients were greater than 65 years old at the time of the adverse event; 85% were greater than 55 years old. The age of the patient was not reported in 35% of cases.

Table 17.4: 7 Demographic distribution of case reports with stroke

Age (Years)	Gender		
	Female	Male	Not Reported
	No. of cases	No. of Cases	No. of Cases
36 - 45 yrs	0	1	0
46 - 55 yrs	3	2	0
56 - 65 yrs	4	4	0
66 - 75 yrs	4	8	0
> 75 yrs	8	5	0
not available	5	11	5
All	24	31	5

The most common adverse events associated with Strokes included "Stroke" in 56 cases and "Ischemic cerebrovascular" conditions in 55 cases. The most common Serious adverse events included "Stroke" in 48 cases and "Ischemic cerebrovascular conditions" in 46 cases. The most common Fatal adverse events associated with Stroke were "Stroke" in eight cases and "Hemorrhagic cerebrovascular conditions" in eight cases.

Table 17.4: 8 Individual case reports for the combined term stroke.

	All Cases		SAEs Cases		Fatal Cases	
	N	reporting rate[1]	N	reporting rate[1]	N	reporting rate[1]
Stroke	56	0.40	48	0.34	8	0.06

[1] – individual case reports per 100,000 patient years of exposure to marketed drug and samples, estimated from cumulative ex-factory sales. Total exposure is estimated to be 14,000,000 patient-years through January 2009.

Narratives of cases in which the event was found under the heading of "Stroke" were reviewed. In evaluating the time to onset of the "Stroke" event, the number of stroke events did not seem to correlate with the length of time the patient was receiving tiotropium which could indicate that there was not a relationship between strokes and the use of tiotropium.

Table 17.4: 9 Time to onset of the stroke adverse event after the start of tiotropium therapy was calculated for these cases. The results are noted below.

Time to Onset of Fatal Event	Number of Cases
Less than 1 Day	2
1 – 2 Days	1
3 – 7 Days	1
8 -14 Days	1
Greater than 15 Days	23
Unknown	23
Total	51

Respiratory

Respiratory events are included in different MedDRA SOCs. The most commonly reported serious and non-serious respiratory adverse events categorized by the associated SOC are summarized in Tables 17.4: 10 and 11.

Table 17.4: 10 Summary of spontaneous serious and non-serious respiratory adverse events occurring at a preferred term frequency of 0.1% or greater of all adverse events

System Organ Class (SOC)	Number of Events	% Total Events within SOC	Adverse Event (AE) Preferred Term	Number of AEs
Infections and infestations	1189	3.39		
			Pneumonia	162
			Oral candidiasis	102
			Bronchitis	79
			Laryngitis	72
			Candidiasis	72
			Sinusitis	62
			Nasopharyngitis	53
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	166	0.47		
			Lung neoplasm malignant	42
Respiratory, thoracic and mediastinal disorders	5924	17.07		
			Dyspnoea	1798
			Cough	796
			Dysphonia	569
			Oropharyngeal pain	289
			Throat irritation	254
			Epistaxis	200
			Chronic obstructive pulmonary disease	186
			Dry throat	179
			Wheezing	137
			Productive cough	123
			Bronchospasm	110
			Increased upper airway secretion	77
			Asthma	75
			Pharyngeal oedema	72
			Rhinorrhoea	57
			Haemoptysis	56
			Dyspnoea exertional	54
			Nasal congestion	54
			Respiratory failure	54
			Throat tightness	51
			Lung disorder	39
			Choking	38
			Nasal dryness	37

Table 17.4: 11 Summary of spontaneous serious respiratory adverse events occurring at a preferred term frequency of 0.1% or greater of all serious adverse events

System Organ Class (SOC)	Number of Events	% Total Events within SOC	Adverse Event (AE) Preferred Term	Number of AEs
			Pulmonary congestion	34
			Sputum discoloured	33
Infections and infestations	253	6.85		
			Pneumonia	110
			Lung infection	17
			Bronchitis	13
			Lower respiratory tract infection	9
			Respiratory tract infection	7
			Bronchopneumonia	7
			Staphylococcal infection	5
			Infection	5
			Sepsis	4
			Upper respiratory tract infection	4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	148	4.01		
			Lung neoplasm malignant	42
			Lung neoplasm	6
			Small cell lung cancer stage unspecified	4
Respiratory, thoracic and mediastinal disorders	794	21.50		
			Dyspnoea	235
			Chronic obstructive pulmonary disease	129
			Respiratory failure	48
			Bronchospasm	31
			Cough	25
			Asthma	23
			Emphysema	20
			Acute respiratory failure	19
			Lung disorder	17
			Respiratory arrest	16
			Wheezing	13
			Dysphonia	12
			Throat tightness	11
			Pharyngeal oedema	10
			Pulmonary embolism	10
			Epistaxis	10
			Pulmonary oedema	9
			Haemoptysis	9
			Hypoxia	8
			Oropharyngeal pain	8
			Respiratory distress	8

Table 17.4: 11 (continued) Summary of spontaneous serious respiratory adverse events occurring at a preferred term frequency of 0.1% or greater of all serious adverse events (Page 2 of 2)

System Organ Class (SOC)	Number of Events	% Total Events within SOC	Adverse Event (AE) Preferred Term	Number of AEs
Respiratory, thoracic and mediastinal disorders (continued)	794	21.50		
			Pneumothorax	6
			Pulmonary hypertension	6
			Respiratory disorder	6
			Bronchial secretion retention	5
			Interstitial lung disease	5
			Pleural effusion	5
			Oropharyngeal blistering	4

COPD Exacerbations

Adverse events from the individual reports were grouped according to the combined preferred terms defined in the pooled analysis of clinical data. The definition of terms is listed in Appendix 17.1.

Four-hundred-eleven case reports are included in combined endpoint of exacerbations. Fifty-nine percent of cases were reported to the company by a health care professional. Where gender was reported, 50% of patients in this group were female and 50% male. The patient gender was not reported in 4% of cases. Where the age of the patient was reported, 64% of patients were greater than 65 years old at the time of the adverse event; 90% were greater than 55 years old. The age of the patient was not reported in 40% of cases.

Table 17.4: 12 Individual case reports for the combined terms representing exacerbations

	All Cases		SAEs Cases		Fatal Cases	
	N	reporting rate[1]	N	reporting rate[1]	N	reporting rate[1]
COPD exacerbations	206	1.47	134	0.96	39	0.28
COPD exacerbations (broad)	411	2.94	175	1.25	46	0.33

[1] – individual case reports per 100,000 patient years of exposure to marketed drug and samples, estimated from cumulative ex-factory sales. Total exposure is estimated to be 14,000,000 patient-years through January 2009.

Pneumonia

Adverse events from the individual reports were grouped according to the pooled preferred terms defined in the pooled analysis of clinical data. The definition of terms is listed in Appendix 17.1.

One-hundred-seventy-eight case reports are included in combined endpoint of pneumonia. Thirty percent of cases were reported to the company by a health care professional. Where gender was reported, 53% of patients in this group were female and 47% male. The patient gender was not reported in 4% of cases. Where the age of the patient was reported, 70% of patients were greater than 65 years old at the time of the adverse event; 92% were greater than 55 years old. The age of the patient was not reported in 26% of cases.

Table 17.4: 13 Individual case reports for the pooled term representing pneumonia.

	All Cases		SAEs Cases		Fatal Cases	
	N	reporting rate[1]	N	reporting rate[1]	N	reporting rate[1]
Pneumonia	178	1.27	122	0.87	27	0.19

[1] – individual case reports per 100,000 patient years of exposure to marketed drug and samples, estimated from cumulative ex-factory sales. Total exposure is estimated to be 14,000,000 patient-years through January 2009.

Respiratory Failure

Adverse events from the individual reports were grouped according to the pooled preferred terms defined in the pooled analysis of clinical data. The definition of terms is listed in Appendix 17.1.

One-hundred case reports are included in combined endpoint of respiratory failure. Eighty-five percent of cases were reported to the company by a health care professional. Where gender was reported, 50% of patients in this group were female and 50% male. The patient gender was not reported in 14% of cases. Where the age of the patient was reported, 67% of patients were greater than 65 years old at the time of the adverse event; 89% were greater than 55 years old. The age of the patient was not reported in 33% of cases.

The two most common causes of acute respiratory failure are acute exacerbations of asthma and COPD. Respiratory failure is the third most common serious adverse event in the SOC of Respiratory, thoracic and mediastinal disorders.

Table 17.4: 14 Individual case reports for the pooled terms representing respiratory failure.

	All Cases		SAEs Cases		Fatal Cases	
	N	reporting rate[1]	N	reporting rate[1]	N	reporting rate[1]
Respiratory failure	85	0.61	76	0.54	50	0.36
Respiratory failure (broad)	100	0.71	83	0.59	49	0.35

[1] – individual case reports per 100,000 patient years of exposure to marketed drug and samples, estimated from cumulative ex-factory sales. Total exposure is estimated to be 14,000,000 patient-years through January 2009.

ADVERSE EVENTS ORIGINATING IN THE UNITED STATES

All adverse events

Individual case safety reports from spontaneous and health authority sources contained in the Boehringer Ingelheim Global Drug Safety database where tiotropium was considered a suspect drug, the event occurred in the United States and the report was received by the company between 30 January 2004 (date of US approval) and 31 January 2009 were selected for analysis.

A total of 10,412 US domestic individual tiotropium case reports have been reported to the company since 30 January 2004. Thirty-Six percent of cases were reported to the company by a health care professional. Where gender was reported, 64% of reports involved female patients and 36% involved male patients. The gender was not reported in 19% of cases. Where the age of the patient was reported, 69% of patients were greater than 65 years old at the time of the adverse event; 89% were greater than 55 years old. The age of the patient was not reported in 58% of cases.

Table 17.4: 15 Demographic distribution of case reports for all spontaneous adverse events

Age (Years)	Gender		
	Female	Male	Not Reported
	No. of cases	No. of Cases	No. of Cases
<= 35 yrs	16	7	0
36 - 45 yrs	47	26	1
46 - 55 yrs	242	109	0
56 - 65 yrs	592	296	4
66 - 75 yrs	997	592	6
> 75 yrs	899	499	9
not available	2623	1495	1952
All	5416	3024	1972

The 15 most common adverse event preferred terms were: (1) Incorrect route of drug administration (2441); (2) Dyspnoea (1191); (3) Drug ineffective (1150); (4) Dry mouth (701); (5) Cough (410); (6) Vision blurred (358); (7) Dysphonia (293); (8) Dizziness (225); (9) Urinary retention (220); (10) Constipation (217); (11) Headache (205); (12) Rash (196); (13) Ageusia (186); (14) Oropharyngeal pain (158); (15) Nausea (151).

The 15 most common serious adverse event preferred terms were: (1) Dyspnoea (132); (2) Pneumonia (81); (3) Death (46); (4) COPD (43); (5) Myocardial infection (25); (6) Chest pain (24); (7) Lung neoplasm malignant (23); (8) Atrial fibrillation (17); (9) Chest discomfort (17); (10) Cerebrovascular accident (16); (11) Cardiac failure congestive (16); (12) Swollen tongue (13); (13) Heart rate increased (13); (14) Prostate cancer (13); (15) Oedema peripheral (12); (16) Lung infection (12); (17) Fall (12); (18) Emphysema (12); (19) Lung disorder (12).

Adverse events with a fatal outcome

Eighty-two case reports contained an event with a fatal outcome. Thirty-three percent of cases were reported to the company by a health care professional. Where gender was reported, 45% of patients in this group were female and 55% male. The patient gender was not reported in 9% of cases. Where the age of the patient was reported, 67% of patients were greater than 65 years old at the time of the adverse event; 91% were greater than 55 years old. The age of the patient was not reported in 60% of cases.

Table 17.4: 16 Demographic distribution of case reports with a fatal outcome

Age (Years)	Gender		
	Female	Male	Not Reported
	No. of cases	No. of Cases	No. of Cases
<= 35 yrs	0	1	0
36 - 45 yrs	0	0	0
46 - 55 yrs	0	2	0
56 - 65 yrs	3	4	1
66 - 75 yrs	3	6	0
> 75 yrs	5	8	0
not available	20	17	12
All	31	38	13

There were a total of 103 fatal adverse events reported in the US data base. The most common SOCs were: (1) General disorders and administration site conditions – 47; (2) Respiratory, thoracic and mediastinal disorders – 21; (3) Neoplasms benign, malignant and unspecified (incl cysts and polyps) – 11; (4) Cardiac disorders – 7; and (5) Infections and Infestations – 4. The most common preferred terms included: (1) Death – 46; (2) COPD – 5; (3) Respiratory failure (5); (4) Myocardial infarction – 4; (5) Lung neoplasm malignant – 4; (6) Pneumonia – 3; (7) Dyspnoea – 3; (8) Renal cancer - 2; (9) Emphysema – 2: and (10) Lung disorder – 2.

This frequency and distribution of fatal adverse events seen in the United States spontaneous safety data with tiotropium is consistent with COPD, medical complications of COPD, illnesses associated with prolonged tobacco use (e.g. cancer and cardiovascular disease), the increased age of patients with COPD, the expected pharmacologic effects of an anti-cholinergic agent, and adverse effects that may be associated with the multiple co-medications commonly used in this patient population.. The frequency of the nonspecific preferred term of "Death" is due to the relatively large number of reports with limited medical information that are received from either Sales Representatives or information received from marketing programs in the form of returned mailings.

Table 17.4: 17 Summary of fatal events by MedDRA System Organ Class and Preferred Term

MedDRA System Organ Class	Preferred Term	No. of Events
Cardiac disorders	Cardiac arrest	1
	Cardiac failure	1
	Cardio-respiratory arrest	1
	Myocardial infarction	4
General disorders and administration site conditions	Asthenia	1
	Death	46
	Swelling	1
Infections and infestations	Infection	1
	Pneumonia	3
Injury, poisoning and procedural complications	Post procedural complication	1
	Road traffic accident	1
Metabolism and nutrition disorders	Fluid retention	1
	Metabolic acidosis	1
Musculoskeletal and connective tissue disorders	Intervertebral disc compression	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder cancer	1
	Cervix carcinoma	1
	Colon cancer	1
	Lung neoplasm malignant	4
	Metastases to central nervous system	1
	Oesophageal carcinoma	1
	Renal cancer	2
Nervous system disorders	Dizziness	1
	Lethargy	1
	Syncope	1
Renal and urinary disorders	Dysuria	1
	Renal failure	1
	Renal tubular necrosis	1
Respiratory, thoracic and mediastinal disorder	Chronic obstructive pulmonary disease	5
	Cough	1
	Dyspnoea	3
	Emphysema	2
	Hypoventilation	1
	Lung disorder	2
	Pharyngeal haemorrhage	1
	Respiratory arrest	1
	Respiratory failure	5
Vascular disorders	Shock	1
Total events		103

Cardiovascular adverse events

A summary of spontaneous serious and non-serious cardiovascular adverse events is presented in Tables 17.4: 18 and 17.4: 19.

Table 17.4: 18 Summary of spontaneous serious and non-serious cardiovascular adverse events occurring at a preferred term frequency of 0.1% or greater of all adverse events

System Organ Class (SOC)	Number of Events	% Total Events within SOC	Adverse Event (AE) Preferred Term	Number of AEs
Cardiac disorders	317	1.8		
			Palpitations	77
			Tachycardia	62
			Atrial fibrillation	39
			Myocardial infarction	26
			Cardiac failure congestive	18
Vascular disorders	111	0.6		
			Hypertension	27

Table 17.4: 19 Summary of spontaneous cardiovascular serious adverse events occurring at a preferred term frequency of 0.1% or greater of all serious adverse events

System Organ Class (SOC)	Number of Events	% Total Events within SOC	Adverse Event (AE) Preferred Term	Number of AEs
Cardiac disorders	122	8.1		
			Myocardial infarction	25
			Atrial fibrillation	17
			Cardiac failure congestive	16
			Tachycardia	9
			Cardiac disorder	8
			Arrhythmia	6
			Palpitations	5
			Coronary artery occlusion	4
			Supraventricular tachycardia	4
			Atrial flutter	3
			Cardiac failure	3
			Coronary artery disease	3
			Extrasystoles	2
			Pericardial effusion	2
			Sinus tachycardia	2
			Ventricular extrasystoles	2
Vascular disorders	32	2.1		
			Hypertension	6
			Aortic aneurysm	5
			Thrombosis	4
			Hypotension	3
			Haemorrhage	2

Stroke

Adverse events from the individual reports were grouped according to the combined preferred term of stroke defined in the pooled analysis of clinical data. The definition of the pooled term of stroke is listed in Appendix 17.1.

Thirty-five case reports are included in combined endpoint of stroke. Forty-three percent of cases were reported to the company by a health care professional. Where gender was reported, 52% of patients in this group were female and 48% male. The patient gender was not reported in 11% of cases. Where the age of the patient was reported, 67% of patients were greater than 65 years old at the time of the adverse event; 81% were greater than 55 years old. The age of the patient was not reported in 40% of cases.

Table 17.4: 20 Demographic distribution of case reports with stroke.

Age (Years)	Gender		
	Female	Male	Not Reported
	No. of cases	No. of Cases	No. of Cases
46 - 55 yrs	3	1	0
56 - 65 yrs	2	1	0
66 - 75 yrs	4	3	0
> 75 yrs	5	2	0
not available	2	8	4
All	16	15	4

Table 17.4: 21 Individual case reports for the combined term stroke.

	All Cases		SAEs Cases		Fatal Cases	
	N	reporting rate[1]	N	reporting rate[1]	N	reporting rate[1]
Stroke	32	0.90	25	0.71	0	0

[1] – individual case reports per 100,000 patient years of exposure to marketed drug and samples, estimated from cumulative ex-factory sales. Total exposure in the United States is estimated to be 3,536,571 patient-years through January 2009.

Respiratory

Respiratory events are included in different MedDRA SOCs. The most commonly reported serious and non-serious respiratory adverse events categorized by the associated SOC are summarized in Tables 17.4:22 and 17.4:23.

Table 17.4: 22 Summary of spontaneous serious and non-serious adverse events occurring at a preferred term frequency of 0.1% of all adverse events

System Organ Class (SOC)	Number of Events	% Total Events within SOC	Adverse Event (AE) Preferred Term	Number of AEs
Infections and infestations	750	4.2		
			Pneumonia	123
			Bronchitis	64
			Laryngitis	62
			Candidiasis	47
			Nasopharyngitis	43
			Upper respiratory tract infection	29
			Oral candidiasis	27
			Sinusitis	27
			Lung infection	23
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	99	0.6		
			Lung neoplasm malignant	23
Respiratory, thoracic and mediastinal disorders	3304	18.3		
			Dyspnoea	1191
			Cough	410
			Dysphonia	293
			Oropharyngeal pain	158
			Throat irritation	110
			Wheezing	96
			Productive cough	78
			Dry throat	75
			Increased upper airway secretion	61
			Epistaxis	60
			Chronic obstructive pulmonary disease	58
			Dyspnoea exertional	49
			Pharyngeal oedema	47
			Throat tightness	39
			Asthma	38
			Rhinorrhoea	37
			Nasal congestion	33
			Lung disorder	30
			Pulmonary congestion	30
			Choking	29
			Bronchospasm	27
			Haemoptysis	24
			Nasal dryness	20
			Emphysema	19
			Sputum discoloured	19

Table 17.4: 23 Summary of spontaneous serious respiratory adverse events occurring at a preferred term frequency of 0.1% of all serious adverse events

System Organ Class (SOC)	Number of Events	% Total Events within SOC	Adverse Event (AE) Preferred Term	Number of AEs
Infections and infestations	158	10.5		
			Pneumonia	81
			Lung infection	12
			Bronchitis	11
			Upper respiratory tract infection	4
			Candidiasis	3
			Bronchopneumonia	2
			Pneumonia bacterial	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	88	5.9		
			Lung neoplasm malignant	23
			Lung neoplasm	6
			Neoplasm malignant	4
			Small cell lung cancer stage unspecified	3
Respiratory, thoracic and mediastinal disorders	329	21.9		
			Dyspnoea	132
			Chronic obstructive pulmonary disease	43
			Emphysema	12
			Lung disorder	12
			Cough	11
			Respiratory failure	11
			Throat tightness	10
			Dysphonia	6
			Respiratory distress	6
			Hypoxia	5
			Pharyngeal oedema	5
			Pulmonary hypertension	5
			Asthma	5
			Bronchospasm	5
			Pulmonary embolism	4
			Respiratory arrest	4
			Wheezing	4
			Epistaxis	3
			Pulmonary oedema	3
			Throat irritation	3
			Choking	2
			Haemoptysis	2

Table 17.4: 23 (continued) Summary of spontaneous serious respiratory adverse events occurring at a preferred term frequency of 0.1% of all serious adverse events (Page 2 of 2)

System Organ Class (SOC)	Number of Events	% Total Events within SOC	Adverse Event (AE) Preferred Term	Number of AEs
Respiratory, thoracic and mediastinal disorders (continued)	329	21.9		
			Hypoventilation	2
			Laryngospasm	2
			Obstructive airways disorder	2
			Oropharyngeal pain	2
			Productive cough	2
			Acute respiratory failure	2
			Bronchial secretion retention	2
			Bronchospasm paradoxical	2

Exacerbations

Adverse events from the individual reports were grouped according to the combined preferred terms defined in the pooled analysis of clinical data. The definition of terms is listed in Appendix 17.1.

One-hundred-eighty-six case reports are included in combined endpoint of exacerbations. Thirty-two percent of cases were reported to the company by a health care professional. Where gender was reported, 68% percent of patients in this group were female and 32% male. The patient gender was not reported in 16% of cases. Where the age of the patient was reported, 57% of patients were greater than 65 years old at the time of the adverse event; 88% were greater than 55 years old. The age of the patient was not reported in 36% of cases.

Table 17.4: 24 Individual case reports for the combined terms representing exacerbations.

	All Cases		SAEs Cases		Fatal Cases	
	N	reporting rate[1]	N	reporting rate[1]	N	reporting rate[1]
COPD exacerbations	65	1.84	45	1.27	5	0.14
COPD exacerbations (broad)	186	5.26	67	1.89	5	0.14

[1] – individual case reports per 100,000 patient years of exposure to marketed drug and samples, estimated from cumulative ex-factory sales. Total exposure in the United States is estimated to be 3,536,571 patient-years through January 2009.

Pneumonia

Adverse events from the individual reports were grouped according to the combined preferred terms defined in the pooled analysis of clinical data. The definition of terms is listed in Appendix 17.1.

One-hundred-thirty-one case reports are included in combined endpoint of pneumonia. Thirteen percent of cases were reported to the company by a health care professional. Where gender was reported, 59% of patients in this group were female and 41% male. The patient gender was not reported in less than 2% of cases. Where the age of the patient was reported, 69% of patients were greater than 65 years old at the time of the adverse event; 89% of patients were greater than 55 years old. The age of the patient was not reported in 28% of cases.

Table 17.4: 25 Individual case reports for the combined terms representing pneumonia.

	All Cases		SAEs Cases		Fatal Cases	
	N	reporting rate[1]	N	reporting rate[1]	N	reporting rate[1]
Pneumonia	131	3.70	85	2.40	3	0.08

[1] – individual case reports per 100,000 patient years of exposure to marketed drug and samples, estimated from cumulative ex-factory sales. Total exposure in the United States is estimated to be 3,536,571 patient-years through January 2009.

Respiratory Failure

Adverse events from the individual reports were grouped according to the combined preferred terms defined in the pooled analysis of clinical data. The definition of terms is listed in Appendix 17.1.

Twenty-nine case reports are included in combined endpoint of respiratory failure. Sixty-six percent of cases were reported to the company by a health care professional. Where gender was reported, 69% of patients in this group were female and 31% male. The patient gender was not reported in 10% of cases. Where the age of the patient was reported, 47% of patients were greater than 65 years old at the time of the adverse event; 88% were greater than 55 years old. The age of the patient was not reported in 41% of cases.

Table 17.4: 26 Individual case reports for the combined terms representing respiratory failure.

	All Cases		SAEs Cases		Fatal Cases	
	N	reporting rate[1]	N	reporting rate[1]	N	reporting rate[1]
Respiratory failure	18	0.51	17	0.48	5	0.14
Respiratory failure (broad)	29	0.82	23	0.65	5	0.14

[1] individual case reports per 100,000 patient years of exposure to marketed drug and samples, estimated from cumulative ex-factory sales. Total exposure in the United States is estimated to be 3,536,571 patient-years through January 2009.

Conclusion

The frequency and distribution of fatal events, cardiovascular adverse events, stroke and respiratory events seen in the spontaneous safety data with tiotropium are consistent with what would be expected in the population of patients where tiotropium would be prescribed.

The events are expected in patients with COPD given the increased age of patients, medical complications associated with COPD, illnesses often associated with prolonged tobacco use (cardiovascular and neoplastic) and the common use of concomitant medications. However, the lack of a reliable denominator, expected reporting frequency and reference data limit definitive conclusions based on spontaneous data. Nevertheless, it can be generally concluded that there are no new safety signals that have emerged from the post-marketing spontaneous reports.

17.5 APPENDIX: PUBLICATIONS

17.5.1 Publications with descriptions of adverse events or discontinuations associated with studies involving tiotropium

A total of 38 studies were published with a mention of adverse events (AEs), discontinuations due to adverse events or other reasons, or exacerbations as study endpoints. Six publications (P07-11657, P08-15244, P05-02765, P-05-02766, P06-08976, P06-09375) stated that there were no adverse events or discontinuations. One of the publications was a health economic study that mentioned AEs (P08-16085). Health outcome reports where exacerbations of COPD were studied are not included in the reporting of adverse events.

Of the 38 publications, the abstracts and full publications of three meta-analyses (P07-13230, P06-11072, and P08-12019) and four database studies (P07-13582, P07-07347, P08-10308, P08-15645) are included in Appendix 2 for completeness, but are not discussed.

Of the remaining 31 publications discussed in detail below, only one study (P09-00584) compared tiotropium with placebo, while five publications (P07-10204, P07-11657, P07-11820, P08-02598, P08-02593) are based on controlled, double-blind studies with an active-drug comparator arm. In the remaining 25 trials, tiotropium was studied with an open-label study design.

Publications mentioning adverse events, discontinuations, or exacerbations as study end-points are described below.

P09-00584 describes a 24 week, randomized, partially-blinded, placebo-controlled trial studying the clinical efficacy and safety of formoterol, tiotropium, and the combination in patients with COPD. A total of 847 patients with COPD were randomized to receive one of the following four treatments for 24 weeks: formoterol 10 mcg bid plus tiotropium 18 mcg od; formoterol 10 mcg bid; tiotropium 18 mcg od, or placebo. The study was partially blinded (formoterol and placebo; tio open-label). The overall incidence of adverse events was similar with all active treatments, although COPD-related adverse events were more common with tiotropium. 13.1% of patients in the tio only group and 12.1% of patients in the tio + formoterol group discontinued the study. 5.9% and 3.9% discontinued due to adverse events, respectively. There were no deaths in either group. There were no indications of safety concerns affecting particular organ systems, including cardiac disorders. Most adverse events (87–92% of events in the active treatment groups) were mild or moderate in severity. Of the serious adverse events, reported by 8–10 patients in each active treatment group, three were thought to be related to treatment: two cases of COPD exacerbation (one tiotropium and one combined treatment) and one case of tremor with formoterol. Data was also collected for 'all COPD-related events', including additional related events such as cough, dyspnoea and bronchospasm. COPD-related events were most common with placebo (38 subjects; 18.2%), followed by tiotropium (32 subjects; 14.5%), formoterol (24 subjects; 11.4%) and combined treatment (23 subjects; 11.1%). Such events were serious or led to premature discontinuation from the study in 7 (3.3%) subjects taking placebo, 9 (4.1%) taking tiotropium, 4 (1.9%) taking combined treatment and 4 (1.9%) taking formoterol. Laboratory values and vital signs showed no statistically significant or clinically relevant changes with treatment; only isolated

individual abnormal values or changes were seen. Results for serum potassium showed no significant differences between treatments at the end of the study: compared with placebo, differences were 0.02, 0.00 and 0.07 mmol/L for the formoterol, tiotropium and combined treatments, respectively. There was an unexpected shift to above-normal plasma potassium levels in 4–5% of subjects receiving formoterol (with or without tiotropium). ECG measurements showed no differences in QTc interval between groups in mean values; abnormal values or changes occurred with similar frequencies in the active treatment groups and were not more frequent with combination treatment.

P07-10204 describes a 12-week, randomized, double-blind, double-dummy parallel group study comparing salmeterol/fluticasone propionate 50/500 (FSC) twice daily to tiotropium 18 mcg once daily and to both together in 90 patients with COPD. The number of patients experiencing an adverse event were: 13 patients (43.3%) in tiotropium group, 8 patients (26.7%) in FSC group, and 15 patients (50.0%) in tiotropium + FSC group. The most common adverse events seen in patients receiving tiotropium were dry mouth, headache, and cough, whereas patients receiving FSC experienced irritation, hoarseness/dysphonia, headaches, and candidiasis of the mouth and throat. No patient experienced a serious adverse event.

P07-11657 describes a single dose, randomized, double-blind, double-dummy, placebo-controlled, cross-over study conducted in 11 healthy volunteers. It is noted that there were no adverse side effects such as palpitations, tremor, headache and rhythm disturbances observed.

P07-11820 describes a 2-year, randomized, double-blind, double-dummy, multi-center controlled trial aiming to compare the relative efficacy of the combination or salmeterol/fluticasone propionate 50/500 mcg bid and tiotropium 18 mcg qd in preventing exacerbations and related outcomes in moderate-severe COPD. A total of 1323 patients entered a 2-week run-in period during which they discontinued all existing COPD maintenance medications and received oral prednisolone 30 mg/day and inhaled salmeterol 50 mcg twice daily to standardize their clinical condition prior to randomization. Patients were then randomized to inhaled salmeterol 50 mcg plus fluticasone propionate 500 mcg combination twice daily by Diskus/Accuhaler or tiotropium bromide 18 mcg once daily by Handihaler. A total of 232 (35.3%) SFC patients and 279 (42%) tiotropium patients withdrew from the study of which 67/66 were due to adverse events and 37/51 were due to COPD exacerbations. Mortality was significantly lower in the salmeterol/fluticasone propionate group; 21 (3 %) of patients in this group died compared to 38 (6 %) in the tiotropium group. More cases of pneumonia were reported in the salmeterol/fluticasone propionate group relative to tiotropium. Cardiac disorders recorded by the investigator were associated with death in 9 (1%) SFC-treated and 19 (3%) tiotropium-treated patients. Among those with concurrent medical disorders, there were 15 (3%) deaths on treatment among patients randomized to SFC and 27 (6%) among patients randomized to tiotropium. In those subjects with baseline cardiovascular disease, there were 9 deaths (3%) in SFC patients and 24 (8%) for tiotropium patients. No more than 2% of patients in either treatment group had clinically significant ECG abnormalities at any time point in the study. The frequency of adverse events was 66% of patients on SFC and 62% of those receiving tiotropium reporting some adverse event, the most frequent of which was a COPD exacerbation. Pneumonia was

reported during treatment in 8 and 4% of patients, respectively, and the hazard ratio for time to reported pneumonia was 1.94 (95% CI, 1.19–3.17; *P* = 0.008) for SFC compared with tiotropium over the 2 years. The number of reported pneumonias that overlapped with an exacerbation treated with antibiotics was 55% in the SFC group and 48% in the tiotropium group (i.e., the other episodes were not given antibiotic treatment despite the report of pneumonia). A total of 14 patients were withdrawn from the study due to pneumonia (9 SFC, 5 tiotropium). Serious adverse events were reported during treatment by 30% of SFC-treated and 24% of tiotropium-treated patients. Other adverse events (e.g., fractures, bruising, candidiasis) were infrequent.

P08-02598 describes a randomized, double-blind, double-dummy, 3-way cross-over study comparing the effects of the combination of salmeterol and fluticasone propionate 50/500 mcg bid plus tiotropium bromide 18 mcg qd with the individual treatments alone. A total of 41 COPD patients participated in this 13-week study including 2-week wash-out periods between treatments. Four patients discontinued the study due to adverse events in the SFC+ Tio and 4 in the Tio alone arm, of which one was due to an exacerbation. The mean blood pressure and pulse rate were comparable between the treatment groups at baseline and at the end of the study (data not shown in article).

P08-02593 describes a randomized, double-blind, placebo-controlled, parallel-group trial evaluating the efficacy and safety of formoterol fumarate inhalation solution in subjects receiving tiotropium as a maintenance treatment for COPD. The study was preceded by a 7 - 14-day screening period when 129 COPD (>/= 25 % to < 65 % predicted FEV1) patients received only tiotropium 18 mcg once daily. Subjects were subsequently randomized to receive 20 mcg formoterol fumarate inhalation solution (FFIS) twice daily for nebulization plus tiotropium or nebulized placebo twice daily plus tiotropium (placebo/tiotropium) for 6 weeks. More placebo/tiotropium (PLA/TIO)- than formoterol fumarate inhalation solution/tiotropium (FFIS/TIO)-treated subjects experienced AEs (39.7 % vs. 22.9 %). A total of 40% in the PLA/TIO group reported at least one AE compared with 24% of FFIS/TIO-treated subjects; 13% and 6% were assessed as drug-related, respectively. The following AEs were reported: cough, pulmonary congestion, nasopharyngitis, diarrhea, vomiting, insomnia, bronchitis, psychomotor hyperactivity, abnormally frequent urination. COPD exacerbations occurred in 7.9% and 4.5% of PLA/TIO and FFIS/TIO -treated subjects, respectively. Those with exacerbations lasting at least 3 days and/or requiring oral corticosteroids and/or antibiotics were discontinued from the study (6/8) with one (FFIS/TIO) considered to be a serious adverse event (SAE). Other reasons for discontinuation included dyspnea exacerbations (*n*=1, PLA/TIO), chest pain (*n*=1, FFIS/TIO subject also with COPD exacerbation), acute bronchitis (*n*=1, FFIS/TIO), insomnia/psychomotor hyperactivity (*n*=1, PLA/TIO), and insomnia/abnormally frequent urination (*n*=1, PLA/TIO). Serious AEs occurred in 3.2 % vs. 1.5 % of PLA/TIO and FFIS/TIO -treated subjects, respectively. Two PLA/TIO-treated subjects experienced SAEs, one with cellulitis and one with pneumonia. None of the SAEs were considered drug-related, and all resolved without sequelae. Most laboratory measures were within normal range at screening and Week 6. One FFIS/TIO-treated subject experienced a decrease in serum potassium to 3.1 mmol/L. Electrocardiogram mean heart rate changes at Week 6 for the post-dose ECG were 0.2 bpm (FFIS/TIO) and 1.5 bpm (PLA/TIO). Mean post-dose changes in the QTcB interval were 6.2 ms (FFIS/TIO)

and 0.6 ms (PLA/TIO). Two FFIS/TIO-treated subjects and one subject in the PLA/TIO group had maximum changes in QTcB interval ≥60 ms. Changes in PR interval, RR interval, and QRS duration were unremarkable.

P05-02158 describes a prospective, open-label intervention study in which 24 patients with COPD were assessed three months after switching from ipratropium bromide to tiotropium bromide. Adverse events reported were dry mouth in four patients and headache in one patient.

P06-10713 describes the outcome of an open label trial in which 50 patients were started on tiotropium for six weeks and then half were started on a pulmonary rehabilitation program while the rest remained on tiotropium alone. Patents were then followed for 3 months. It was noted that nine patients discontinued from the study and the reasons for discontinuation included increase in sputum, dry mouth, "heart pain" and worsening of shortness of breath.

P06-07921 describes a randomized, open-label cross-over study in 38 COPD patients comparing formoterol 12 mcg twice daily to tiotropium 18 mcg once daily. The drugs were administered for 7 days in each period. During formoterol, 3 adverse events occurred and during tiotropium 6 adverse events occurred. The most common event was headache. One serious adverse event occurred during treatment with tiotropium. A patient with a history of hypertension and aortic insufficiency experienced apoplexy and terminated the study prematurely.

P07-05941 describes a 1-year randomized, double blind study comparing salmeterol to fluticasone/salmeterol and to placebo in patients also receiving tiotropium. It was noted that 4 patients died in the tiotropium plus placebo group and 6 in each of the other groups. There were 10 serious adverse events (SAEs) in the tiotropium plus placebo group, and 9 in each of the other groups.

P07-09043 describes a report of 19 patients with stable COPD (5 females, mean age 69.2 +/- 10.7 years) who were studied to evaluate the efficacy and safety of once-daily tiotropium bromide. Tiotropium was administered in addition to prior medication except for short-acting anticholinergic drugs. Patients inhaled 18 mcg of tiotropium daily for 4 - 5 weeks. Adverse events reported were mild including dry mouth in 2 cases and irritant feeling of tongue in another 2 cases. These 4 patients discontinued tiotropium.

P07-10915 describes a retrospective study comparing 84 patients treated for at least one month with tiotropium prior to surgery after January 1, 2004 to 82 patients treated for at least one month with oxitropium before December 31.2003. Three patients in the tiotropium group complained of dry mouth and none in the oxitropium group. No severe side effects were observed.

P08-01391 describes a randomized, prospective, open label study to compare the efficacy of tiotropium alone and tiotropium plus budesonide in patients with chronic obstructive pulmonary disease. The study subjects received either tiotropium 18 mcg once daily with or without budesonide 200 g twice daily for 6 week. The proportions of patients who

experienced mouth dryness were similar in the two groups (the tiotropium group, 5.0%; the tiotropium/budesonide group, 4.8%).

P08-00577 describes an open label comparison of tiotropium 18 mcg to the tulobuterol patch 2 mg in 27 COPD patients in each group. It was noted that one patient receiving tiotropium complained of mild dyspnea and stopped treatment.

P08-05706 describes a 12-week open-label study investigating whether bronchodilator response to tiotropium is influenced by beta2 adrenergic receptor genotype in patients with COPD who show poor responsiveness to inhaled beta2-agonists. Forty-four patients completed the study and 2 withdrew prematurely. The reasons for withdrawal were an adverse reaction (excessive thirst) and an exacerbation of COPD during the treatment period.

P09-00874 describes and 8-week study analyzing the effect of tiotropium on the frequency of dysuria in COPD patients with benign prostatic hyperplasia. Authors measured changes in the pre- and post-treatment conditions of the patients using International Prostate Symptom Score (I-PSS),which was administered to 241 consecutive male COPD patients. All subjects inhaled tiotropium 18 mcg every day and the occurrence of dysuria during the first 8 weeks was examined. In total ten patients withdrew from the study, of which two patients in the tio group discontinued treatment due to dysuria during the follow-up period.

P09-00540 describes a randomized (not double-blinded), 12-week study investigating the anti-inflammatory effects of salmeterol/fluticasone, tiotropium/fluticasone and tiotropium alone on the inflammatory cells and mediators in sputum induced from 99 COPD patients. Subjects were either newly diagnosed or had not taken any medication for 3 months prior to the study. After randomization patients received either salmeterol/fluticasone (SFC; 100/1000 mcg daily), tiotropium + fluticasone (TIO/FC; 18 mcg/1000 mcg daily) or tiotropium (TIO; 18 mcg daily) for 12 weeks. Three patients discontinued the trial in the TIO arm (1 due to patient's perception of worsening of COPD, 2 due to AEs), 4 patients discontinued the trial in the TIO/FC arm (2 due to patient's perception of worsening of COPD, 2 due to AEs). There was 1 death in each study group.

P08-15244 describes a three-day cross-over study, in which authors examined the influence of higher than conventional doses of salbutamol ipratropium bromide on bronchodilation induced by a regular treatment tiotropium 18 mcg/day in 30 patients with stable COPD. On 3 separate days, a dose-response curve to inhaled salbutamol (100 mcg puff-1), ipratropium bromide (20 mcg puff-1) or placebo was constructed 3 hours after inhalation of the last dose of tiotropium, using 1 puff, 1 puff, 2 puffs and 2 puffs, for a total cumulative dose of 600 mcg salbutamol or 120 mcg ipratropium bromide. Doses were given at 30-min intervals and measurements made 15 min after each dose. Neither drug affected heart rate and SpO2. None of the patients complained of adverse symptoms, such as dry mouth or tremor.

P08-14437 describes a randomized, blind, crossover study in 80 patients with stable COPD (40 moderate and 40 severe) who received 5 different bronchodilator 30-day treatments in a random order. Treatments were: treatment 1: tiotropium 18 mcg once-daily (8 a.m.); treatment 2: tiotropium 18 mcg (8 a.m.) + formoterol 12 mcg (8 p.m.); treatment 3: formoterol 12 mcg twice-daily (8 am and 8 pm); treatment 4: tiotropium 18 mcg (8 a.m.) +

formoterol 12 mcg twice-daily (8 a.m. and 8 p.m.); treatment 5: formoterol 12 mcg twice-daily (8 a.m. and 8 p.m.) + tiotropium 18 mcg (8 p.m.). Sixty-eight patients completed all the treatments. Twelve patients prematurely discontinued the study: 8 patients because of exacerbations (2 with moderate and 6 with severe COPD) and four patients with severe COPD because unavailability at follow-up. The publication did not specify at what period of the study or from which treatment arm patients dropped out due to the exacerbations. Authors stated that there were no notable side-effects.

P08-14037 describes a study comparing the effects of a combination therapy of tiotropium and theophylline with theophylline alone in COPD patients. 61 COPD patients completed this 12-week, open-labelled, parallel-group randomized trial. During the eight-week treatment period two patients dropped out of the combination group (one for dry mouth, one for non-complete case report). No subject in either group experienced disease exacerbation from baseline to 8 weeks.

P09-00737 describes a three-month open-label, prospective pilot study conducted to analyze the effect of tiotropium on lower urinary tract functions in 25 male COPD patients with benign prostatic hyperplasia. Patients were given tiotropium once a day for 3 months. Two patients discontinued the study after one month due to dry mouth. Acute urinary retention was not observed in any patients. The authors concluded that tiotropium did not adversely affect lower urinary tract functions in COPD patients with benign prostatic hyperplasia, suggesting the possibility that tiotropium can be safely given to those patients.

P04-02052 describes a double-blind, double-dummy, cross-over, randomized, pilot study to compare the acute bronchodilator efficacy of a single dose of formoterol with that of tiotropium in patients with stable COPD. A total of 20 outpatients with stable COPD were enrolled. Single doses of 12 mcg formoterol, 18 mcg tiotropium, and 12 mcg formoterol + 18 mcg tiotropium were given. Pulse rate and changes in SpO2 were detected. Modifications were small and without clinical significance. The differences between treatments were always non-significant ($p>0.05$).

P05-00110 describes a double-blind, double-dummy, crossover, randomized, pilot study exploring the acute effects of adding salmeterol and tiotropium in patients with stable COPD. A total of 20 outpatients with stable COPD were enrolled. Single doses of 18-mcg tiotropium, 50-mcg salmeterol, and 18-mcg tiotropium + 50-mcg salmeterol were given. No statistically significant modifications from baseline in pulse rate and SpO2 were detected. The differences between treatments were always non-significant ($p>0.05$).

P05-02765 describes a study with the aim to quantify the early protection of a single dose of inhaled tiotropium against methacholine induced bronchoconstriction in asthmatic patients with airway hyperresponsiveness. A total of 10 subjects (7 male, 3 female), with a history of asthma were enrolled in the study. Each subject performed 3 methacholine challenge tests with a time of 72 hours between each challenge: test A (methacholine challenge test), and successively, at random, test B (methacholine 30 minutes after inhaled tiotropium) and test C (methacholine 30 minutes after inhaled placebo). Inhaled tiotropium bromide 18 mcg has shown a protective effect against methacholine-induced bronchoconstriction in asthmatic

patients, with mild-moderate airways hyperresponsiveness, already 30 minutes after its administration. Authors reported that there were no AEs.

P05-02766 describes a cross-over trial aimed to determine whether the combination of salmeterol and tiotropium improved lung function in COPD patients more than either of them alone. A total of 22 patients (20 men) diagnosed with COPD were enrolled. There were no notable side effects.

P06-04230 describes a double-blind, placebo-controlled, 4-way cross-over study in 30 healthy subjects comparing the ability of spirometry, plethysmography and impulse oscillometry to assess the effects of long- and short-acting anticholinergic agents. Single doses of tiotropium bromide 54 and 18 mcg, ipratropium bromide 40 mcg and placebo were administered. Authors reported one discontinuation in the ipratriopium arm but the reason was unspecified.

P06-08976 describes a study assessing whether alveolar-capillary membrane permeability testing can be used as an early alternative test method to identify whether patients with COPD would benefit from long term inhaled corticosteroids. A total of 14 patients with severe and symptomatic moderate COPD (group S) were prescribed an inhaled steroid 800 mcg/day for 3 months. Before inhalation and 4 weeks after inhalation therapy, FEV1 and alveolar-capillary membrane permeability using 99mTc-DTPA were performed. Another 10 patients with COPD of comparable severity (group B) prescribed tiotropium were examined and studied as controls. Authors stated that there were no acute exacerbations during the study period.

P06-09375 describes a study investigating the additive benefit of tiotropium in severe COPD and aiming to establish whether the improvement in lung function in these patients can be predicted from their acute bronchodilator response to ipratropium or salbutamol. 46 patients with severe COPD treated with inhaled long-acting beta2 agonists and corticosteroids were enrolled. Tiotropium (18 mcg, once daily) was added via a dry-powder inhaler device. After a month of treatment, tiotropium was stopped but their previous medication was continued. Patients were reassessed a month later. Authors stated in their report that there were no acute exacerbations or withdrawals during the study.

P07-03007 describes a study to compare the short-term efficacy of tiotropium bromide with that of oxitropium bromide in improving pulmonary function in patients with COPD. A total of 80 patients were randomized either to continue oxitropium 800 mcg/day or to receive tiotropium 18 mcg/day with 76 (39 in the tiotropium and 37 in the oxitropium group) completing the study. One patient in the tiotropium group withdrew consent for reasons unspecified by authors and 3 oxitropium subjects discontinued (2 withdrew consent, 1 non-compliant with the protocol due to family problems).

P07-07893 describes a double-blind, randomized, placebo-controlled, crossover study designed to evaluate the effects of halving inhaled steroid dosage plus salmeterol, or salmeterol and tiotropium. A total of 18 life-long non-smoking severe asthmatics had a 4 week run-in period on HFA fluticasone propionate 1000 mcg daily, and were subsequently randomized to 4 weeks of either HFA-fluticasone propionate 500 mcg BD/salmeterol 100

mcg BD/HFA-tiotropium bromide 18 mcg od; or fluticasone propionate 500 mcg BD/salmeterol 100 mcg BD matched placebo. Measurements of spirometry and body plethysmography were made. Authors reported 8 discontinuations but did not state the reason for study withdrawal.

P07-13821 describes a study aimed to compare the bronchodilator effects of a single dose of 18 mcg of tiotropium administered via a pressurized MDI and spacer with the currently available dry powder inhaler form through Rotahaler in patients with COPD. A randomized, double-blind, double-dummy, 3-period, placebo-controlled, crossover, single-center study was conducted in 19 patients with stable COPD. Single doses of tiotropium (18 mcg) or placebo were administered on 3 separate study days (4 - 7 days apart) through a Rotahaler and pressurized MDI with a non-static spacer (Zerostat). The authors reported one discontinuation due to non-compliance.

P08-14038 describes a study seeking to evaluate the effectiveness of treatment with tiotropium bromide (18 mcg once daily) on the small airway impairment in 2 groups of COPD patients, divided according to frequency of exacerbations (n =37 per group). Baseline mean number of exacerbations was 3.6/year and 1.38/year in frequent and in infrequent exacerbators, respectively. During the 3-month period of the study the mean number of exacerbations was 0.66 in frequent and 0.12 in infrequent exacerbators. Two patients discontinued the study for reasons not stated by the authors. FTreatment with tiotropium in COPD subjects with frequent exacerbations proved to be effective in improving small airway impairment.

P08-15229 describes a study with the objective to elucidate efficacy of a combination almitrine + tiotropium bromide + pulmonary rehabilitation in COPD Stage II - III complicated with chronic respiratory failure. Efficacy of therapy was compared in 2 groups of patients: group 1 (n = 22) received tiotropium bromide in a dose 18 mcg/day for 1 year, almitrine in a dose 10 mg/kg/day for 3 months and an 8-week course of pulmonary rehabilitation. Group 2 (n = 17) received tiotropium bromide and pulmonary rehabilitation. The treatment efficacy was determined by spirometric parameters of external respiration function, blood gases, dyspnea indices, exercise tolerance assessed by 6-min walk test, quality of life (SGRQ). Group 1 patients had a decreased exacerbation rate per 1 patient a year (by 25 %). The full-text article is in Russian.

P08-16085 describes a study examining whether the addition of tiotropium to a respiratory-therapist-directed bronchodilator protocol affects bronchodilator costs for patients hospitalized for COPD exacerbation. The authors retrospectively analyzed data on the number and type of bronchodilator treatments administered to all patients admitted for COPD exacerbation during the 3-month period (January through March 2006) after tiotropium was added to their bronchodilator protocol, and compared that data to a historical control period (January through March 2004) before tiotropium was available in their hospital (and ipratropium bromide was a component of therapy). The costs of bronchodilator treatments, baseline patient characteristics, comorbidities, and concomitant medications, length of stay, adverse events, and in-hospital deaths were compared. There were no adverse events related to tiotropium. Pulmonary-related in-hospital deaths were not significantly different between the 2 periods.

17.5.2 Publication details

Publications with Mention of Adverse Events (Abstracts)

P05-02158

Jaen Diaz JI; Castro Mesa C de; Cordero Garcia B; Garcia-Salamanca MJG; Callejas Perez S; Lopez de Castro F. **Effectiveness of treatment with tiotropium in patients who suffer from COPD.** Med Clin (Barc). 2005;124(1):1-3.

The authors assessed the clinical and functional changes taking place in patients diagnosed of COPD who have been treated with ipratropium bromide, 3 months after this medicament was replaced by the new tiotropium bromide. A prospective intervention survey was carried out in a primary health-care area in patients who suffered from COPD who fulfilled the inclusion criteria. Before changing the treatment and 3 months after changing it, the authors carried out the following procedures: spirometry, 6 minutes walking test with pulsioximetry before and after the exercise, St. George Respiratory Questionnaire and assessment of: patient's chronic dyspnea, degree of patient's compliance, adverse effects and degree of satisfaction with the new drug. 24 Patients (22 males and 2 females) with a mean age of 68.54 years participated in the survey. The FVC improved 4.92 % and the FEV1, 14.16 %. The degree of compliance rose from 67.54 % to 96.73 %, the degree of dyspnea decreased from 4.63 to 3.89, the 6 minutes walking test increased 23.79 m and the global mark of the St. George Respiratory Questionnaire decreased (improved) 13.35 points. There were adverse effects in 5 cases (mouth dryness in 4 patients and headache in 1 of them) and 15 patients said the new drug was better. In conclusion, most analyzed parameters had positive changes 3 months after changing the treatment. Tiotropium may be a valid alternative in the treatment of patients suffering from COPD in a stable stage. (Full-text article in Spanish).

P06-10713

Lindsay M; Lee A; Chan K; Poon P; Han LK; Wong WCW; Wong S. **Does pulmonary rehabilitation give additional benefit over tiotropium therapy in primary care management of chronic obstructive pulmonary disease? Randomized controlled clinical trial in Hong Kong Chinese.** J Clin Pharm Ther. 2005;30(6):567-573.
The aim of the study was to evaluate whether multidisciplinary pulmonary rehabilitation program provides additional benefit over tiotropium therapy in managing COPD in primary care. A randomized controlled trial to analyze the difference in outcomes of COPD patients (male, female; mean age 60 - 80 years) receiving tiotropium (18 mcg, once) plus pulmonary rehabilitation program vs. tiotropium treatment alone was done. Patients were recruited from 2 primary care teaching clinics affiliated with a university. 50 Primary care COPD patients were included. 50 Subjects underwent spirometry and their status of COPD was confirmed by using the vitalograph gold standard. They were then assessed by the 6-min walking distance, peak Visual Analogue Scale and Chronic Respiratory Disease Questionnaire. All subjects were given tiotropium to optimize their treatment. After a 6-week period, half were randomized to the intervention group (i.e. receiving pulmonary rehabilitation program), whereas the rest were randomized to control group which received only medication. Spirometry, 6-min walking distance, peak Visual Analogue Scale and

Chronic Respiratory Disease Questionnaire were performed in both groups at 6 weeks, 12 weeks and 3 months. Significant improvement was seen in 6-min walking distance, symptoms of dyspnea measured by peak Visual Analogue Scale and the Chronic Respiratory Disease Questionnaire. The improvement was sustained at 3-month follow-up. However, no additional significant improvement was seen in the intervention group when compared with control. In conclusion, tiotropium therapy has improved health outcomes in COPD patients in primary care settings. A 6 weekly pulmonary rehabilitation program did not give any additional benefits in patients already given tiotropium.

P06-07921

Richter K; Stenglein S; Muecke M; Sieder C; Schmidtmann S; Harnest U; Weidinger G; Magnussen H. **Onset and duration of action of formoterol and tiotropium in patients with moderate to severe COPD**. Respiration. 2006;73(4):414-419.
The objective was to compare the onset and duration of action of formoterol and tiotropium in patients with COPD. This randomized, multicenter, open-label crossover study in 38 patients with COPD (mean age 64 years; mean FEV1 55 % predicted) assessed the effect of 7 days of treatment with formoterol (12 mcg bid via Foradil Aerolizer) vs. tiotropium (18 mcg od via Spiriva HandiHaler) on lung function measured over a period of 12 h after the first dose on day 1 and the last dose on day 8. The primary efficacy variable, FEV1-AUC during the first 2 h post-dose (FEV1-AUC10-120 min), was significantly higher for formoterol compared with tiotropium, with between-treatment differences of 124 mL after the first dose and 80 mL after 7 days' treatment in favor of formoterol. FEV1 measured 12 h after inhalation did not differ statistically significantly between treatments. Adverse events occurred in 2 patients after treatment with formoterol and in 5 patients after treatment with tiotropium. In conclusion, this study demonstrates faster onset of action and greater bronchodilation of formoterol vs. tiotropium for bronchodilation within the first 2 h of inhalation (FEV1 AUC10-120 min) and comparable bronchodilation 12 h post-inhalation in patients with moderate to severe COPD.

P08-01391

Um SW; Yoo CG; Kim YW; Han SK; Shim YS. **The combination of tiotropium and budesonide in the treatment of chronic obstructive pulmonary disease.** J Korean Med Sci. 2007;22(5): 839-845.

A study was performed to compare the efficacy of tiotropium alone and tiotropium plus budesonide in patients with chronic obstructive pulmonary disease. The study subjects were randomized to receive either tiotropium 18 mcg once daily with or without budesonide 200 mcg twice daily for 6 weeks. The efficacy variables were changes in trough FEV1, St. George's Respiratory Questionnaire (SGRQ), 6-minute walk distance, and use of rescue medication. One hundred patients were randomized and 81 completed the study. The mean age was 64.0 years, and the mean FEV1 was 39.7 % predicted. Compared with tiotropium alone (n = 40), the tiotropium/budesonide combination (n = 41) was related to an improvement in the SGRQ total score. The 6-Minute walk distance was improved by 13.5 minutes (m) in the tiotropium group and by 22.5 m in the tiotropium/budesonide group. Changes in trough FEV_1 and the use of rescue medication were similar between the two

groups. In conclusion, compared with tiotropium alone, the tiotropium/budesonide combination was associated with an improved health related quality of life. These data support that low-dose budesonide may enhance the efficacy of tiotropium.

P07-10204

Cazzola M; Ando F; Santus P; Ruggeri P; Marco F di; Sanduzzi A; D'Amato M. **A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD.** Pulm Pharmacol Ther. 2007;20(5):556-561.

The aim of this pilot study was to explore the relative efficacy in terms of improvement in symptoms and lung function of combining fluticasone propionate/salmeterol combination and tiotropium in patients with severe-to-very severe stable COPD. 90 Patients were randomized to receive 3 months of treatment in one of 3 treatment groups: fluticasone propionate/salmeterol combination 500/50 mcg Diskus, 1 inhalation twice daily + placebo HandiHaler 1 inhalation once-daily daily; tiotropium 18 mcg HandiHaler, 1 inhalation once daily + placebo Diskus, 1 inhalation twice daily; fluticasone propionate/salmeterol combination 500/50 mcg Diskus, 1 inhalation twice daily + tiotropium 18 mcg HandiHaler, 1 inhalation once-daily daily. Patients attended the clinic before and after 1 month, 2 months, and 3 months of treatment for evaluations of pulmonary function, and dyspnea, which was assessed using a visual analog scale (VAS). Also the supplemental salbutamol use was measured. A total of 81 patients completed the 3-month treatment period: 26 patients receiving fluticasone propionate/salmeterol combination, 26 patients receiving tiotropium, and 29 patients receiving fluticasone propionate/salmeterol combination + tiotropium. Patients were withdrawn for COPD exacerbation. Improvements in trough FEV_1 with all treatment medications were observed by the first month when trough FEV_1 had improved significantly above baseline by 74 mL in the tiotropium group, by 117 mL in the fluticasone propionate/salmeterol combination group and by 115 mL in fluticasone propionate/salmeterol combination + tiotropium group. At the end of the study, trough FEV_1 had improved significantly above baseline by 141 mL in the tiotropium group, by 140 mL in the fluticasone propionate/salmeterol combination group and by 186 mL in fluticasone propionate/salmeterol combination + tiotropium group. The difference between fluticasone propionate/salmeterol combination and tiotropium appeared to decrease, that between fluticasone propionate/salmeterol combination and fluticasone propionate/salmeterol combination + tiotropium appeared to increase and that between tiotropium and fluticasone propionate/salmeterol combination + tiotropium remained almost similar with study duration.These results suggest that adding fluticasone propionate/salmeterol combination and tiotropium may provide benefits in symptomatic patients with severe-to-very severe stable COPD.

P07-09043

Asamoto H; Iwasaki A. **Clinical effects of tiotropium bromide (Spiriva) in the stable COPD.** Ther Res. 2007;28(6):1183-1189.

A total of 19 patients with stable COPD (5 females, mean age 69.2 +/- 10.7 years) were studied to evaluate the efficacy and safety of once-daily tiotropium bromide (Spiriva). Tiotropium was administered in addition to prior medication except for short-acting anticholinergic drugs. Patients subsequently inhaled 18 mcg of tiotropium daily for 4 - 5 weeks. Adverse events reported were mild including dry mouth in 2 cases and irritant feeling of tongue in another 2 cases. These 4 patients discontinued tiotropium.

P07-05941

Aaron SD; et al; Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. **Tiotropium in combination with placebo, salmeterol, or fluticasonesalmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial.** Ann Intern Med. 2007;146(8):545-555.

The objective of this study was to determine whether combining tiotropium with salmeterol or fluticasone-salmeterol improves clinical outcomes in adults with moderate to severe COPD compared with tiotropium alone. A randomized, double-blind, placebo-controlled trial has been conducted from October 2003 to January 2006 in 27 academic and community medical centers in Canada. 449 Patients with moderate or severe COPD have been randomly assigned to 1 of 3 treatment groups for 52 weeks: tiotropium (Spiriva), 18 mcg once daily, plus placebo inhaler, 2 puffs twice daily; tiotropium, 18 mcg once daily, plus salmeterol (Serevent), 25 mcg/puff, 2 puffs twice daily; or tiotropium, 18 mcg once daily, plus fluticasone-salmeterol (Adavir), 250/25 mcg/puff, 2 puffs twice daily. The primary end point was the proportion of patients who experienced an exacerbation of COPD that required treatment with systemic steroids or antibiotics. The proportion of patients in the tiotropium plus placebo group who experienced an exacerbation (62.8 %) did not differ from that in the tiotropium plus salmeterol group (64.8 %) or in the tiotropium plus fluticasone-salmeterol group (60.0 %). In sensitivity analyses, the point estimates and 95 % confidence bounds shifted in the direction favoring tiotropium plus salmeterol and tiotropium plus fluticasone salmeterol. Tiotropium plus fluticasone-salmeterol improved lung function and disease specific quality of life and reduced the number of hospitalizations for COPD exacerbation and all-cause hospitalizations compared with tiotropium plus placebo. In contrast, tiotropium plus salmeterol did not statistically improve lung function or hospitalization rates compared with tiotropium plus placebo. More than 40 % of patients who received tiotropium plus placebo and tiotropium plus salmeterol discontinued therapy prematurely, and many crossed over to treatment with open-label inhaled steroids or long-acting beta-agonists. It is concluded that addition of fluticasone-salmeterol to tiotropium therapy did not statistically influence rates of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates in patients with moderate to severe COPD.

P07-11820

Wedzicha JA; Calverley PMA; Seemungal TA; Hagan G; Ansari Z; Stockley RA; INSPIRE Investigators. **The prevention of COPD exacerbations by salmeterol/fluticasone propionate or tiotropium bromide.** Am J Respir Crit Care Med. 2008; 177(1):19-26.

INSPIRE is a 2-year, double-blind, double-dummy, multicenter controlled trial aiming to compare the relative efficacy of the long-acting inhaled bronchodilator/anti-inflammatory combination (salmeterol/fluticasone propionate) 50/500 mcg bd and the long-acting bronchodilator (tiotropium) 18 mcg od in preventing exacerbations and related outcomes in moderate-severe chronic obstructive pulmonary disease. Patients were recruited between June 2003 and February 2004 in 179 centers from 20 countries. Patients entered a 2-week run-in period during which they discontinued all existing COPD maintenance medications and received oral prednisolone 30 mg/day and inhaled salmeterol 50 mcg twice daily to standardize their clinical condition prior to randomization. Patients were then randomized to inhaled salmeterol 50 mcg plus fluticasone propionate 500 mcg combination twice daily by Diskus/Accuhaler or tiotropium bromide 18 mcg once daily by Handihaler. Subjects randomized to salmeterol 50 mcg plus fluticasone propionate 500 mcg combination received a once daily placebo inhalation by Handihaler and subjects randomized to tiotropium received a twice daily placebo inhalation by Diskus/Accuhaler. 1323 Patients (mean age 64 years, forced expiratory volume in 1 sec 39 % predicted) were randomized (tiotropium, 665 patients, 84 % males). Primary endpoint was healthcare utilization exacerbation rate. Other endpoints included health status measured by St. Georges Respiratory Questionnaire, mortality, adverse events and study withdrawal. Probability of withdrawing from the study was 29 % greater with tiotropium than salmeterol/fluticasone propionate. The modeled annual exacerbation rate was 1.28 in the salmeterol/fluticasone propionate group and 1.32 in the tiotropium group. The St. Georges Respiratory Questionnaire total score was statistically significantly lower at 2 years on salmeterol/fluticasone propionate versus tiotropium. Mortality was significantly lower in the salmeterol/fluticasone propionate group; 21 (3 %) of patients in this group died compared to 38 (6 %) in the tiotropium group. More pneumonias were reported in the salmeterol/fluticasone propionate group relative to tiotropium. In conclusion, no difference in exacerbation rate between salmeterol/fluticasone propionate and tiotropium was found. More patients failed to complete the study receiving tiotropium. A small statistically significant beneficial effect was found on health status, with an unexpected finding of lower deaths in salmeterol/fluticasone propionate treated patients.

P08-00577

Inoue T; Suzuki N. **Comparison of efficacy between tiotropium inhalation and tulobuterol patch for mild to moderate chronic obstructive pulmonary disease.** Ther Res. 2007;28(11):2259-2265.

The use of long-acting inhaled anticholinergics and long-acting beta-2 agonists are recommended by the guidelines for controlling stable COPD. This study was conducted to evaluate the effect on pulmonary function and the clinical effect of tiotropium bromide hydrate (hereinafter tiotropium) and tulobuterol patch (hereinafter tulobuterol) in 24 patients with mild COPD and 30 patients with moderate COPD, totally 54 patients. After examination

of the above endpoints, instructions on the use of drugs were given by the off-site pharmacist to each 27 patients (15 moderate and 12 mild) assigned to tiotropium inhalation capsules 18 mcg and tulobuterol patch 2 mg. Then, treatment with tiotropium once daily qm or tulobuterol once daily hs was initiated. Both drugs significantly improved dyspnea and peak flow in patients with moderate COPD. Pulmonary function markedly improved in the group treated with tiotropium (Spiriva) but no improvement was observed in the group treated with tulobuterol (Hokunalin Tape). For mild COPD, pulmonary function, dyspnea and peak flow values significantly improved patients given tiotropium; however, there was no significant improvement in those given tulobuterol. One of the patients given tiotropium complained of mild dyspnea and stopped treatment. As compared with tulobuterol, tiotropium was highly effective for improving pulmonary function and clinical symptoms. Tiotropium can be considered as a first-line therapy for improving mild as well as more severe COPD. (Full text in Japanese).

P07-10915

Matsuyama W; Mitsuyama H; Koreeda Y; Higashimoto I; Osame M; Arimura K. **Use of tiotropium bromide for pre-operative treatment in chronic obstructive pulmonary disease patients: comparison with oxitropium bromide.** Intern Med (Tokyo). 2007; 46 (17):1373-1379.

In this study the authors compared the incidence of post-operative complications between COPD patients who received tiotropium bromide and those who did not. For 1 month before surgery the authors examined 84 and 82 patients treated with tiotropium bromide (tiotropium group) and oxitropium bromide (oxitropium group), respectively, in combination with other medications. Oxitropium bromide was administered 3 times daily (600 mcg/day) using inhalers and a holding chamber with a mouthpiece. Tiotropium bromide was administered once daily (18 mcg/day) using a dry-powder inhaler device (HandiHaler). The authors performed a statistical comparison of clinical features, pulmonary functions, and postoperative complications between the 2 groups. The improvements in clinical symptoms and FEV1 were better in the tiotropium group than in the oxitropium group. The incidence of post-operative pulmonary complications (refractory bronchospasm, pulmonary infection, and acute respiratory failure) was significantly lower in the tiotropium group than in the oxitropium group. 3 Patients in the tiotropium group complained of dry mouth; however, the symptoms could be controlled. The incidence of post-operative non-pulmonary complications was not significantly different between the 2 groups. In conclusion, the authors propose that tiotropium bromide might be a safe and useful drug for pre-operative treatment of COPD patients.

P08-05706

Umeda N; Yoshikawa T; Kanazawa H; Hirata K; Fujimoto S. **Association of beta2-adrenoreceptor genotypes with bronchodilatory effect of tiotropium in COPD.** Respirology 2008; 13: 346-352.

Recently, there has been interest in interactions of beta2 adrenergic receptors and muscarinic acetylcholine receptors, which share intracellular signal transduction systems. The aim of the

present study was to investigate whether bronchodilator response to tiotropium is influenced by beta2 adrenergic receptor genotype in patients with COPD who show poor responsiveness to inhaled beta2-agonists. After a 4-week run-in period, patients with COPD were treated with inhaled tiotropium bromide (18 mcg once daily; via a dry powder inhalation device) for 8 weeks. Spirometric measurements and reversibility testing with inhaled beta2 adrenergic receptor agonists were performed and health-related quality of life was assessed using the St George's respiratory questionnaire (SGRQ) before and after treatment. Genomic DNA was prepared from peripheral blood and individual genotypes at amino acid 16 of the beta2 adrenergic receptor were examined. Of the 48 patients recruited, 46 were eligible and participated in the study. 44 Completed the study and 2 withdrew prematurely. The reasons for withdrawal were an adverse reaction (excessive thirst) and an exacerbation of COPD during the treatment period. COPD patients with the Arg/Arg genotype (n = 22) had a significant increase in FEV1 during treatment compared with those without the Arg/Arg genotype (n = 22). While all component and total scores on the SGRQ improved significantly in both genetic groups, changes in impact and total scores were significantly greater in patients with Arg/Arg compared with those without. In conclusion, these findings indicate that the homozygous Arg/Arg genotype at amino acid 16 of the beta2 adrenergic receptors could affect bronchodilator response to tiotropium in patients with COPD with significant effects on health-related quality of life.

P08-02598

Singh D; Brooks J; Hagan G; Cahn T; O'Connor B. **Triple therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD.** Thorax 2008; 63(7): 592-598.

The combination of salmeterol and fluticasone propionate and tiotropium bromide are commonly used treatments in COPD but there is little data on their effectiveness when used together. The effects of combination of salmeterol and fluticasone propionate 50/500 mcg bd plus tiotropium bromide 18 mcg od were compared with the individual treatments alone. 41 COPD patients participated in a randomized, double-blind, double-dummy, 3-way cross-over study with 2-week wash-out periods between treatments. Lung function assessment included plethysmography and spirometry. The primary endpoint was post-dose specific airways conductance area-under the curve (AUC0-4hr) on day 14. AUC0-4hr specific airways conductance was significantly higher on day 14 after combination of salmeterol and fluticasone propionate + tiotropium bromide compared to tiotropium bromide (22 %) or combination of salmeterol and fluticasone propionate alone (27 %). Combination of salmeterol and fluticasone propionate + tiotropium bromide significantly improved trough FEV1 compared with tiotropium bromide alone (212 mL) and combination of salmeterol and fluticasone propionate alone (110 mL) on day 14. Inspiratory capacity measurements also showed significant benefits for triple therapy over individual components on day 14. Subjects receiving combination of salmeterol and fluticasone propionate + tiotropium bromide had clinically relevant improvements in TDI total score of 2.2 compared with tiotropium bromide alone (but not combination of salmeterol and fluticasone propionate alone, 0.7) and used significantly less rescue medication (1.0 occasion less daily than tiotropium bromide and 0.6 less than combination of salmeterol and fluticasone propionate). In conclusion, combination

of salmeterol and fluticasone propionate +tiotropium bromide triple therapy led to greater improvements in bronchodilation compared with tiotropium bromide and combination of salmeterol and fluticasone propionate alone. The advantages of triple therapy are observed across a range of physiologically important parameters, including airway conductance and lung volumes. Triple therapy also led to patient-related benefits by improving TDI and use of rescue medication.

P08-02593

Tashkin DP; Littner M; Andrews CP; Tomlinson L; Rinehart M; Denis-Mize K. **Concomitant treatment with nebulized formoterol and tiotropium in subjects with COPD: a placebo-controlled trial.** Respir Med 2008; 102 (4) ; 479-487.

Adding a long-acting beta2-agonist by dry powder inhaler to tiotropium provides significantly increased and sustained bronchodilation in chronic obstructive pulmonary disease patients over either product alone. To demonstrate similar benefits with a nebulized long-acting beta2-agonist, a placebo-controlled trial was conducted to evaluate the efficacy and safety of formoterol fumarate inhalation solution in subjects receiving tiotropium as a maintenance treatment for COPD. After a 7 - 14-day screening period using tiotropium 18 mcg once daily, subjects with diagnosed COPD (>/= 25 % to < 65 % predicted FEV1) were randomized to receive 20 mcg formoterol fumarate inhalation solution twice daily for nebulization plus tiotropium or nebulized placebo twice daily plus tiotropium (placebo/tiotropium) for 6 weeks. Efficacy was assessed with spirometry at each visit (day 1, week 1, 3, 6), the transition dyspnea index, and St. George's Respiratory Questionnaire. Baseline characteristics were comparable, including mean FEV1 % predicted. At week 6, FEV1 AUC0-3 was 1.52 l for formoterol fumarate inhalation solution/tiotropium-treated subjects vs. 1.34 l for placebo/tiotropium-treated subjects. The mean transition dyspnea index scores in the formoterol fumarate inhalation solution/tiotropium and placebo/tiotropium groups were 2.30 and 0.16, respectively. St. George's Respiratory Questionnaire did not change significantly with 6 weeks treatment, with the exception of formoterol fumarate inhalation solution/tiotropium improvements in symptom score vs. placebo/tiotropium. More placebo/tiotropium- than formoterol fumarate inhalation solution/tiotropium-treated subjects experienced AEs (39.7 % vs. 22.9 %), COPD exacerbations (7.9 % vs. 4.5 %), and serious AEs (3.2 % vs. 1.5 %). The following AEs were reported: cough, pulmonary congestion, nasopharyngitis, diarrhea, vomiting, insomnia, bronchitis, psychomotor hyperactivity, abnormally frequent urination. In conclusion, nebulized formoterol fumarate in combination with tiotropium provided statistically and clinically significant improvements in bronchodilation and symptom control over tiotropium alone and demonstrated good tolerability.

P09-00874

Kato M; Soda S; Kobyashi T; Hamamoto H; Yonemoto C; Furhshita Y; Tanabe N; Miura K; Goto S; Kawashima M. **Tiotropium for COPD complicated by prostatic diseases: a study on 241 consecutive patients.**

In the present study in which tiotropium was administered to 241 consecutive men with COPD, the authors evaluated frequency of dysuria and examined changes in the pre- and posttreatment conditions of the patients using International Prostate Symptom Score (I-PSS), which is an index to calculate the severity of dysuria associated with benign prostatic hyperplasia, in order to investigate the safety of administration of the drug. Subjects were 241 consecutive of 276 outpatients with COPD who visited the department of thoracic surgery, Kishiwada City Hospital, and received tiotropium for the first time. All subjects inhaled tiotropium 18 mcg every day and the occurrence of dysuria during the first 8 weeks was examined. Analysis of age distribution showed that most of the patients receiving tiotropium were aged 60 or older. 5 Patients started dysuria treatment during the period between initiation of tiotropium and 12 weeks after initiation.

P09-00540

Perng DW; Tao CW; Su KC; Tsai CC; Liu LY; Lee YC. **Anti-inflammatory effects of salmeterol/fluticasone, tiotropium/fluticasone or tiotropium on COPD.** Eur Respir J 2009, Express. Published on January 7, 2009 as doi: 10.1183/09031936.00115308

The authors investigated the anti-inflammatory effects of salmeterol/fluticasone, tiotropium/fluticasone and tiotropium alone on the inflammatory cells and mediators in sputum induced from COPD patients. Subjects were either newly diagnosed or had not taken any medication for 3 months prior to the study. Subjects (n = 99) were randomized (not double blinded) and received either salmeterol/fluticasone (100/1000 mcg daily), tiotropium + fluticasone (18 mcg/1000 mcg daily) or tiotropium (18 mcg daily) for 12 weeks. Tiotropium was administered once daily by Handihaler. Induced sputum and serum C-reactive protein were analyzed prior to and at the end of treatment. The results showed that treatment with salmeterol/fluticasone caused a significant reduction in IL-8 and matrix metalloprotease-9 in induced sputum as compared with treatment with tiotropium alone. There were no treatment differences between the salmeterol/fluticasone and tiotropium + fluticasone groups in decreasing IL-8 and metalloprotease-9 levels. The reduction in IL-8 showed significant association with the reduction in metalloprotease-9. All treatment groups failed to significantly reduce the numbers of total cells, neutrophils, macrophages and eosinophils in induced sputum; in addition, there were no treatment differences in terms of improvement of FEV1, FVC, C-reactive protein or quality of life between the 3 groups. There was 1 death in each study group. In conclusion, the anti-inflammatory effects of salmeterol/fluticasone likely contribute to the clinical benefits seen in COPD patients.

P08-15244

Cazzola M; Santus P; D'Adda A; Pizzolato S; Marco F di; Centanni S. **Acute effects of higher than standard doses of salbutamol and ipratropium on tiotropium-induced bronchodilation in patients with stable COPD.** Pulmonary Pharmacology and Therapeutics 2008; Article in Press.

In this trial, the authors examined the influence of higher than conventional doses of the short-acting inhaled beta2-adrenergic agent salbutamol and the short-acting anticholinergic drug ipratropium bromide on bronchodilation induced by a regular treatment with the long-

acting anticholinergic drug tiotropium 18 mcg/day in 30 patients with stable COPD. On 3 separate days, a dose-response curve to inhaled salbutamol (100 mcg puff-1), ipratropium bromide (20 mcg puff-1) or placebo was constructed 3 hours after inhalation of the last dose of tiotropium, using 1 puff, 1 puff, 2 puffs and 2 puffs, for a total cumulative dose of 600 mcg salbutamol or 120 mcg ipratropium bromide. Doses were given at 30-min intervals and measurements made 15 min after each dose. At the highest cumulative dose, salbutamol showed a trend to be more effective than ipratropium bromide in improving FEV1, and reducing sRaw, although the differences between the 2 treatments were always not significant, whereas there was no substantial difference between the 2 drugs in changing FVC, IC, TGV, TLC and RV. Both drugs did not affect heart rate and SpO2. In conclusion, the results indicate that there is not much difference in bronchodilation between adding higher than conventional doses of salbutamol or ipratropium bromide to tiotropium in patients with stable COPD. Effective improvement of the pulmonary function may be achieved in such a type of patients by adding salbutamol 600 mcg or ipratropium bromide 120 mcg to regular tiotropium.

P08-14437

Terzano C; Petroianni A; Conti V; Ceccarelli D; Graziani E; Sanduzzi A; D'Avelli S. **Rational timing of combination therapy with tiotropium and formoterol in moderate and severe COPD.** Respir Med 2008; 102, 1701-1707.

The aim of this study was to determine which timing of therapy with formoterol and/or tiotropium shows the greater and more continuous functional improvement during 24 h in patients with moderate to severe COPD. In this randomized, blind, crossover study 80 patients with stable COPD (40 moderate and 40 severe) received 5 different bronchodilator 30-day treatments in a random order. Treatments were: treatment 1: tiotropium 18 mcg once-daily (8 a.m.); treatment 2: tiotropium 18 mcg (8 a.m.) + formoterol 12 mcg (8 p.m.); treatment 3: formoterol 12 mcg twice-daily (8 am and 8 pm); treatment 4: tiotropium 18 mcg (8 a.m.) + formoterol 12 mcg twice-daily (8 a.m. and 8 p.m.); treatment 5: formoterol 12 mcg twice-daily (8 a.m. and 8 p.m.) + tiotropium 18 mcg (8 p.m.). Spirometries were performed during 24 h on day 1 and day 30. End-points were gain of FEV_1 (DeltaFEV_1) from baseline of the day 1 and day 30, AUC, Dyspnea Index, and as-needed use of salbutamol. 68 Patients completed all treatments. The greater and continuous daily functional improvement was shown during treatment 4 and treatment 5. Daily means of DeltaFEV1 were significantly different between single-drug treatments and combination therapy. Dyspnea was greater in single-drug treatments. Less use of rescue salbutamol was reported in treatment 4 and treatment 5. In conclusion, in patients with moderate to severe COPD, combination therapy with tiotropium administered in the morning (treatment 4) was the most effective; in patients with prevailing night-symptoms, treatment with tiotropium in the evening (treatment 5) reduced symptoms and use of salbutamol. Treatment 5 showed less variability of FEV_1 during the 24 h.

P08-14037

Kawayama T; Hoshino T; Ichiki M; Tsuda T; Kinoshita M; Takata S; Koga T; Iwanaga T; Aizawa H; Kurume COPD Study Group. **Effect of add-on therapy of tiotropium in COPD treated with theophylline.** Int J Chronic Obstruct Pulm Dis 2008; 3 (1): 137-147.

Although combination therapy with bronchodilators is recommended for COPD, there is insufficient evidence for the efficacy of some combinations of long-acting bronchodilators. The objective was to investigate the effects of a combination therapy with tiotropium and theophylline in COPD patients. In a 12-week, open-labeled, parallel-group randomized study, pulmonary functions and dyspnea scores were compared between the combination and theophylline alone therapy at baseline, and 4 and 8 weeks after randomization in COPD. 61 COPD patients completed the trial (31 combination therapy, 30 theophylline alone; mean age 70 years; 58 males; mean dyspnea score 2.0 and FEV1 1.5 l (62.5 % predicted). FEV1 in the combination group, but not in the theophylline alone group, was significantly increased at 4 and 8 weeks from the baseline. In the combination group, but not the theophylline alone group, the dyspnea score was significantly improved after 4 and 8 weeks compared with baseline. In 17 patients who did not receive theophylline at screening, treatment with 4 or 8 weeks of theophylline alone did not improve dyspnea score or FEV1. In conclusion, addition of tiotropium therapy to theophylline treatment can improve dyspnea and pulmonary function in COPD. Although this study did not assess whether there was any benefit of adding theophylline to patients treated with tiotropium, tiotropium can be a useful addition in COPD already treated with theophylline.

P09-00737

Miyazaki H; Suda T; Otsuka A; Nagata M; Ozono S; Hashimoto D; Nakamura Y; Inui N; Nakamura H; Chida K. **Tiotropium does not affect lower urinary tract functions in COPD patients with benign prostatic hyperplasia.** Pulm Pharmacol Ther 2008: 21 (6): 879-883.

The objective was to clarify the effect of tiotropium on lower urinary tract functions in COPD patients with benign prostatic hyperplasia. This prospective pilot study comprised 25 male COPD patients with benign prostatic hyperplasia as defined by the International Prostate Symptom Score, the QOL index, maximum flow rate in uroflowmetry, and prostate volume. Patients were given tiotropium once a day for 3 months. At baseline and after treatment, lower urinary tract functions were assessed symptomatically by the International Prostate Symptom Score and the QOL index, and objectively by urinary parameters, including maximum flow rate, average flow rate, postvoid residual urine volume, and bladder voiding efficiency. Acute urinary retention was not observed in any patients. Subjectively, no significant difference was found in the International Prostate Symptom Score or the QOL index between baseline and after tiotropium treatment. Additionally, tiotropium treatment did not change maximum flow rate, average flow rate, time to maximum flow rate, or overall flow time compared to baseline. No significant increase was found in postvoid residual urine volume or bladder voiding efficiency. In conclusion, in this preliminary study, tiotropium did not adversely affect lower urinary tract functions in COPD patients with benign prostatic hyperplasia, suggesting the possibility that tiotropium can be safely given to those patients.

P09-00584

Vogelmeier C; Kardos P; Harari S; Gans SJM; Stenglein S; Thirlwell J. **Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study.** Respir Med 2008; 102 (11): 1511-1520.

Although guidelines recommend combining long-acting bronchodilators in COPD, data are limited. The authors examined the clinical efficacy and safety of formoterol, tiotropium and the combination in patients with COPD. 847 Patients with COPD (mean FEV_1 52 % predicted; FEV_1/FVC 53 %) were randomized to receive one of the following four treatments for 24 weeks: formoterol 10 mcg bid plus tiotropium 18 mcg od; formoterol 10 mcg bid; tiotropium 18 mcg od, or placebo. The study was partially blinded (formoterol and placebo). For the primary endpoint, FEV_1 2 h post-dose after 24 weeks, there were small differences in favour of the combination therapy versus formoterol or tiotropium. All 3 treatments were superior to placebo. The combination was statistically superior to monotherapy for: the primary endpoint; FEV_1 5 min after the first dose and at 12 weeks; and peak expiratory flow averaged over the first 6 weeks. The 3 active treatments were significantly more effective than placebo for secondary endpoints: COPD-related 'bad days', symptoms, use of rescue medication and peak expiratory flow, and aspects of health-related quality of life. The overall incidence of adverse events was similar with all active treatments, although COPD-related adverse events were more common with tiotropium. Combined bronchodilator therapy may be a valuable treatment option for patients with COPD.

P05-02765

Terzano C; Petroianni A; Ricci A; D'Antoni L; Allegra L. **Early protective effects of tiotropium bromide in patients with airways hyperresponsiveness**. Eur Rev Med Pharmacol Sci. 2004;8(6):259-264.

Tiotropium is an anticholinergic drug for COPD patients, with a peak bronchodilator effect observed after 1.5 to 2 hours and a long duration of action. The aim of this study was to quantify the early protection of a single dose of inhaled tiotropium against methacholineinduced bronchoconstriction in asthmatic patients with airway hyperresponsiveness. 10 Subjects (7 male, 3 female), with history of asthma and a baseline FEV_1 (> 80 % of predicted, were enrolled in the study. Each subject performed 3 methacholine challenge tests, with a time of 72 hours between each challenge: test A (methacholine challenge test), and successively, at random, test B (methacholine 30 minutes after inhaled tiotropium) and test C (methacholine 30 minutes after inhaled placebo). Provocative dose causing a 20 % decrease in basal FEV_1 values was reached to assess airways responsiveness. All the subjects showed in test A and test C a mild-moderate airway hyperresponsiveness. In test B no provocative dose causing a 20 % decrease in basal FEV_1 value was reached at the inhaled maximum dose of methacholine (1600 mcg), FEV_1 before tiotropium was 88.6 % +/- 4.4, beginning test FEV_1 92.6 % +/- 4.3, end test FEV_1 85.7 % +/- 4.6. Inhaled tiotropium bromide 18 mcg has shown a protective effect against methacholine-induced bronchoconstriction in asthmatic patients, with mild-moderate airways hyperresponsiveness, already 30 minutes after its administration.

P05-02766

Baloira Villar A; Pombo CV. **Bronchodilator efficacy of combined salmeterol and tiotropium in patients with chronic obstructive pulmonary disease**. Arch Bronconeumol. 2005;41(3):130-134.

Bronchodilators are still the most effective drugs for controlling the symptoms of COPD. Tiotropium bromide, a long-acting anticholinergic drug, has recently been added to the therapeutic arsenal for the disease. To date, there have been no studies combining 2 long acting bronchodilators. The aim of the present trial was to determine whether the combination of salmeterol and tiotropium improved lung function in COPD patients more than either of them alone. 22 Patients (20 men) diagnosed with COPD, with a mean age of 64 years, were enrolled in this cross-over trial. Active smokers were excluded. Mean (SD) FEV_1 was 43 % (14 %) of predicted. All patients were experienced in the use of inhalers. The following 3 therapeutic combinations were randomly assigned to be administered for a 1-week period: fluticasone (500 mcg/12 h), salmeterol (50 mcg/12 h) and placebo; fluticasone, tiotropium (18 mcg/24 h), and placebo; and fluticasone, salmeterol, and tiotropium. At the end of each period, forced spirometry was performed before inhalation of the therapeutic combination (between 8:30 a.m. and 9:30 a.m.) and 2 hours after inhalation. Throughout the week, morning peak flow rates measured immediately before inhalation were recorded, and there was a 48-hour wash-out period between each therapeutic combination. All the patients completed the protocol. There were no significant differences in preinhalation or postinhalation FEV1 with salmeterol compared to tiotropium (preinhalation FEV_1, 1.17 [0.55] l compared to 1.19 [0.49] l; postinhalation FEV_1, 1.32 [0.65] l compared to 1.29 [0.61] l). In all cases postinhalation FEV_1 was significantly higher than preinhalation FEV1. The combination of fluticasone, salmeterol, and tiotropium proved superior to the other 2 combinations with respect to both preinhalation FEV1 and postinhalation FEV1 (preihalation FEV_1, 1.32 [0.56] l; postinhalation FEV_1, 1.49 [0.68] l). Peak flow rate was also significantly higher with the combination of the 2 bronchodilators (345 l/min compared to 291 l/min and 311 mL, respectively. There were no notable side effects. In conclusion, in terms of improvement in lung function, the combination of salmeterol and tiotropium together with fluticasone is more effective in patients with moderate-to-severe COPD than either of the bronchodilators administered alone.

P06-04230

Singh D; Tal-Singer R; Faiferman I; Lasenby S; Henderson A; Wessels D; Goosen A; Dallow N; Vessey R; Goldman M. Plethysmography and impulse oscillometry assessment of tiotropium and ipratropium bromide; a randomized, double-blind, placebo-controlled, cross-over study in healthy subjects. Br J Clin Pharmacol. 2006; 61(4):398-404.
Spirometry, plethysmography and impulse oscillometry measure different aspects of lung function. These methods have not been compared for their ability to assess long- and short acting anticholinergic agents. The authors therefore performed a double-blind, placebo controlled, 4-way cross-over study in 30 healthy subjects. Single doses of tiotropium bromide 54 and 18 mcg, ipratropium bromide 40 mcg and placebo were administered. Specific conductance (sGaw), TLC, inspiratory capacity and residual volume were measured using plethysmography, while impulse oscillometry measured resistance (R5 - 25) and reactance

(RF and X5). Pulmonary function was measured for 26 h post dose. Tiotropium bromide caused significant improvements in sGaw, FEV_1, MMEF and R5 - R25 at time points up to 26 h, with no clear differences between doses. Ipratropium bromide improved the same parameters, but only up to 8 h. The weighted mean change (0 - 24 h) caused by tiotropium bromide 54 mcg compared with placebo for FEV_1 was 240 mL, while for sGaw the ratio of geometric means (tiotropium bromide compared with placebo) was 1.35. Neither drug caused consistent statistically significant changes in RF, forced vital capacity, TLC or inspiratory capacity over 26 h. Residual volume was significantly improved from 8 to 24 h by tiotropium bromide 54 mcg only. In conclusion, in addition to spirometry, impulse oscillometry resistance measurements and sGaw can distinguish between the effects of long- and short acting anticholinergic effects in healthy subjects.

P06-08976

Chou SH; Chen YW; Chuang HY; Kao EL; Huang MF. **Alveolar-capillary membrane permeability for early prediction of response of inhaled steroid on patients with chronic obstructive pulmonary disease.** J Clin Pharm Ther. 2006;31(4):363-368.

This study assessed whether alveolar-capillary membrane permeability testing can be used as an early alternative test method to identify whether patients with COPD would benefit from long term inhaled corticosteroids. 14 Patients with severe and symptomatic moderate COPD (group S) were prescribed inhaled steroid 800 mcg/day for 3 months. Before inhalation and 4 weeks after inhalation therapy, FEV_1 and alveolar-capillary membrane permeability using 99mTc-DTPA were performed. FEV_1 was recorded again at the end of the 3rd month. Another 10 patients with COPD of comparable severity (group B) prescribed with inhaled bronchodilators were examined and studied as controls. In group S, the permeability decreased in 8 patients (group D) and increased in 6 patients (group I). No significant change was noted in FEV_1 at the end of the 1st month. However, 7 patients in group D showed significant improvement in FEV1 at the end of the 3rd month, whereas in patients in group I no significant changes were observed. In group B, no significant change in alveolar-capillary membrane permeability was observed, although the FEV_1 increased by 12 - 17 %. In conclusion, with steroid inhalation, the alveolar-capillary membrane permeability at 4 weeks predicts future changes in lung functions. Long-term inhaled corticosteroids are likely to be useful if permeability decreases. This test, which needs further validation, appears to provide much earlier prediction of response than glucocorticoid reversibility testing.

P06-09375

Perng DW; Wu CC; Su KC; Lee YC; Perng RP; Tao CW. **Additive benefits of tiotropium in COPD patients treated with long-acting beta2 agonists and corticosteroids.** Respirology. 2006;11(5):598-602.

The aim of this study was to investigate the additive benefit of tiotropium in severe COPD and to establish whether the improvement in lung function in these patients can be predicted from their acute bronchodilator response to ipratropium or salbutamol. 46 Patients with severe COPD treated with inhaled long-acting beta2 agonists and corticosteroids were

enrolled. Their prebronchodilator FEV_1 was less than 50 % of the predicted value. Tiotropium (18 mcg, once daily) was added via a dry-powder inhaler device. After a month of treatment, tiotropium was stopped but their previous medication was continued. Patients were reassessed a month later. Acute bronchodilator response to ipratropium and salbutamol was assessed prior to tiotropium treatment. Pulmonary function and health status were evaluated. Adding tiotropium significantly improved FVC, FEV_1 and inspiratory capacity. The increase in FVC was significantly associated with an increase in inspiratory capacity and a decrease in residual volume. Total scores of St. George Respiratory Questionnaire scores were significantly improved after adding tiotropium treatment ($P<0.001$). After tiotropium withdrawal, FVC, FEV_1 and inspiratory capacity decreased markedly. Bronchodilator response to ipratropium did not predict the tiotropium-mediated improvement in FEV_1 or FVC. In conclusion, adding tiotropium to inhaled long-acting beta2 agonists and corticosteroids can yield clinical benefits in lung function and improved quality of life in COPD patients, as both drugs act through separate yet complementary pathways to maintain airway calibre.

P07-03007

Incorvaia C; Riario-Sforza GG; Pravettoni C; Dugnani N; Paterniti F; Pessina L; Fumagalli M. **Effects of replacing oxitropium with tiotropium on pulmonary function in patients with COPD: a randomized study**. Respir Med. 2007;101(3): 476-480.

Inhaled bronchodilators are first line drugs in the treatment of COPD. Tiotropium bromide is a recently introduced long-acting anticholinergic agent able to reduce dyspnoea and COPD exacerbations and to improve pulmonary function and quality of life. The authors designed a study to compare the short-term efficacy of tiotropium bromide with that of oxitropium bromide in improving pulmonary function in patients with COPD. 80 Patients were randomized either to continue oxitropium 800 mcg/day or to receive tiotropium 18 mcg/day. 76 (39 in the tiotropium and 37 in the oxitropium group) completed the study. Plethysmography was performed at baseline and after 72 h in all patients. The changes in functional parameters in the 2 groups were compared by the Mann-Whitney U-test. There were no differences between the 2 groups regarding age (72.5 vs. 74.2 years), male/female ratio (25/14 vs. 23/14) and pulmonary function at baseline. The changes in spirometric parameters were significantly greater in tiotropium- than in oxitropium-treated patients: mean FEV1 increased significantly by 15 % vs. 3 %, mean FVC by 10.5 % vs. 2.2 %, and FEF 25, 50, and 75 by 34 % vs. 14 %, 33 % vs. 7 %, and 50 % vs. 6 %, respectively; mean FRC and RV decreased nonsignificantly by 7.5 % and 10 % with tiotropium vs. 4.3 % and 6.5 % with oxitropium, respectively. In conclusion, the replacement of oxitropium with tiotropium significantly increases pulmonary function in patients with COPD. The improvement involves also small airways that have not been investigated thus far.

P07-07893

Fardon T; Haggart K; Lee DKC; Lipworth BJ. **A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma.** Respir Med. 2007;101(6):1218-1228.

The aim of this double-blind, randomized, placebo-controlled, crossover study was to evaluate the effects of halving inhaled steroid dosage plus salmeterol, or salmeterol and tiotropium. 18 Life-long non-smoking severe asthmatics were run-in for 4 weeks on HFA fluticasone propionate 1000 mcg daily, and were subsequently randomized to 4 weeks of either HFA-fluticasone propionate 500 mcg BD/salmeterol 100 mcg BD/HFA-tiotropium bromide 18 mcg od; or fluticasone propionate 500 mcg BD/salmeterol 100 mcg BD matched placebo. Measurements of spirometry and body plethysmography were made. Adding salmeterol to half the dose of fluticasone led to a mean improvement (95 % CI) vs. baseline in morning PEF of 41.5 l/min. Adding salmeterol/tiotropium produced similar improvements in PEF and RAW, but also improved FEV1 by 0.17 and reduced exhaled NO by 2.86. RV and TLC were not altered by either treatment; there were no significant changes in symptoms or quality of life compared with baseline. Addition of salmeterol/tiotropium to half the dose of fluticasone afforded small, but significant improvements in pulmonary function. These effects were not associated with commensurate changes in subjective symptoms or quality of life.

P07-13821

Brashier B; Dhembare P; Jantikar A; Mahadik P; Gokhale P; Gogtay JA; Salvi SS. **Tiotropium administered by a pressurized metered dose inhaler (pMDI) and spacer produces a similar bronchodilator response as that administered by a Rotahaler in adult subjects with stable moderate-to-severe COPD.** Respir Med 2007; 101 (12): 2464-2471.

This study aimed to compare the bronchodilator effects of a single dose of 18 mcg of tiotropium administered via a pressurized MDI and spacer with the currently available dry powder inhaler form through Rotahaler in patients with COPD. A randomized, double-blind, double-dummy, 3-period, placebo-controlled, crossover, single-center study was conducted in 19 patients with stable COPD. Single doses of tiotropium (18 mcg) or placebo were administered on 3 separate study days (4 - 7 days apart) through a Rotahaler and pressurized MDI with a non-static spacer (Zerostat). During each study visit FEV_1 and FVC were measured over a period of 24 h at 11 different time points (0, 15, 30 min, 1, 2, 3, 4, 6, 8, 12 and 24 h), using a bellows spirometer while static parameters like inspiratory capacity, residual volume, intrathoracic gas volume and TLC were measured by bodyplethysmography at 0 min, 3, 8 and 24 h. Tiotropium administered through both pressurized MDI (and spacer) and dry powder inhaler showed significantly better mean FEV1 and mean FVC differences from baseline, in terms of mean maximum change and AUC0-24h, as compared to placebo. The mean inspiratory capacity and trough FEV1 values also improved significantly with tiotropium administered through both the devices as compared to placebo. For all these parameters, there was no difference in the efficacy between pressurized MDI and dry powder inhaler. There was also no significant difference between the time to onset, time to maximum response and duration of response between tiotropium administered through both the study devices. On the other hand, there was no significant difference in residual volume, intrathoracic gas volume and TLC by a single dose of tiotropium delivered through either of the devices when compared with placebo over a period of 24 h. In conclusion, this is the first study to demonstrate that tiotropium

administered by pressurized MDI and spacer shows a superior time-dependent bronchodilator response when compared to placebo, and that this therapeutic efficacy is similar to tiotropium administered by dry powder inhaler. The authors recommend the use of tiotropium administered through a pressurized MDI and spacer to those COPD patients who prefer to use the pressurized MDI device, and especially in those who cannot generate sufficient inspiratory flows required for dry powder inhaler devices.

P08-14038

Incorvaia C; Riario-Sforza GG; Pravettoni C; Yacoub MR; Frati F. **Impairment of small airways in COPD patients with frequent exacerbations and effects of treatment with tiotropium.** Int J Chronic Obstruct Pulm Dis 2008; 3 (1): 123-126.

Disease exacerbations are an important aspect of COPD, because they affect its course and are associated with higher lung function decline. On the other hand, data obtained by biopsies have demonstrated that the progression of COPD is related to an increasing impairment of small airways. The authors sought to evaluate the small airway impairment (FEF25-75) in 2 groups of COPD patients (each group had 37 subjects) in relation to the frequency of exacerbations and the effectiveness of treatment with tiotropium bromide (18 mcg once daily) on the small airway impairment. The mean number of exacerbations was 3.6/year and 1.38/year in frequent and in infrequent exacerbators, respectively. The mean value of FEF25-75 at baseline was 624 mL and 865 mL in frequent and in infrequent exacerbators, respectively. The changes in respiratory parameters versus baseline showed increases in mean FEV1, FVC, and FEF25-75 in both groups but only the increase in FEF25-75 in frequent exacerbators was statistically significant. During the 3-month period of the study the mean number of exacerbations was 0.66 in frequent and 0.12 in infrequent exacerbators. These findings indicate that COPD patients with frequent exacerbations have a higher impairment of small airways. Treatment with tiotropium in COPD subjects with frequent exacerbations proved to be effective in improving small airway impairment.

P08-15229

Titova ON; Ignatiev VA; Didur MD; Kameneva MY; Sukhovskaya OA. [**Combination of thiotropium bromide with almitrine and pulmonary rehabilitation in the treatment of patients with chronic obstructive pulmonary disease.]** Ter Arkh 2008; 80 (3): 28-33.

The study objective was to elucidate efficacy of a combination almitrine + tiotropium bromide + pulmonary rehabilitation in chronic obstructive pulmonary disease of stage II - III complicated with chronic respiratory failure. Efficacy of therapy was compared in 2 groups of patients: group 1 (n = 22) received tiotropium bromide in a dose 18 mcg/day for 1 year, almitrine in a dose 10 mg/kg/day for 3 months, an 8 week course of pulmonary rehabilitation, group 2 (n = 17) received tiotropium bromide and pulmonary rehabilitation. The treatment efficacy was determined by spirometric parameters of external respiration function, blood gases, dyspnea indices, exercise tolerance assessed by 6-min walk test, quality of life (St. George Hospital Respiratory Questionnaire). Group 1 patients walked a longer distance after a course of pulmonary rehabilitation and 1 year later (by 90.5 +/- 25.4 and 44.5 +/- 10.2 m, respectively), had a reduced desaturation measured by pulsoxymetry at the end of 6-min walk

test, increased PaO2 in baseline under 70 mmHg (by 5.8 +/- 1.2 mmHg), a decreased exacerbation rate per 1 patient a year (by 25 %). In conclusion, combination treatment with tiotropium bromide, almitrine and pulmonary rehabilitation is indicated for COPD patients with moderate hypoxemia.

P08-16085

Drescher GS; Carnathan BJ; Imus S; Colice GL. **Incorporating tiotropium into a respiratory therapist-directed bronchodilator protocol for managing in-patients with COPD exacerbations decreases bronchodilator costs.** Respir Care 2008; 53 (12): 1678-1684.

Tiotropium is used in maintenance treatment of COPD, but there are no guidelines on when to start tiotropium following an exacerbation. The objective was to determine whether the addition of tiotropium to a respiratory-therapist-directed bronchodilator protocol affects bronchodilator costs for patients hospitalized for COPD exacerbation. The authors retrospectively analyzed data on the number and type of bronchodilator treatments administered to all patients admitted for COPD exacerbation during the 3-month period (January through March 2006) after tiotropium was added to their bronchodilator protocol, and compared that data to a historical control period (January through March 2004) before tiotropium was available in their hospital (and ipratropium bromide was a component of therapy). The costs of bronchodilator treatments, baseline patient characteristics, comorbidities, concomitant medications, length of stay, adverse events, and in-hospital deaths were compared. Baseline characteristics, comorbidities, and concomitant medications were similar in the 2004 control group (n = 181) and the 2006 intervention group (n = 174). The mean +/- SD number of bronchodilator treatments per admission was significantly higher in the control period (13.6 +/- 15.6) than in the intervention period (10.6 +/- 9.4). That difference correlated to a reduction in combination therapy (short-acting inhaled beta2 agonist plus ipratropium), which decreased from a per-admission average of 6.7 +/- 14.2 in the control period to 1.9 +/- 5.1 in the intervention period. Calculated bronchodilator costs were significantly lower in the intervention period than in the control period. Length of stay also significantly decreased, from 6.5 +/- 5.0 d to 5.5 +/- 4.0 d. There were no adverse events related to tiotropium. Pulmonary-related in-hospital deaths were not significantly different between the 2 periods. In conclusion, early addition of maintenance-treatment tiotropium to a respiratory-therapist-directed bronchodilator protocol for patients hospitalized for COPD exacerbation reduced costs and produced no safety concerns.

DATABASE PUBLICATIONS WITH MENTION OF ADVERSE EVENTS OR EXACERBATIONS

P08-12019

Singh S; Loke YK; Furberg CD. **Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis.** JAMA 2008; 300 (12): 1439-1450.

The objective of this study was to ascertain the cardiovascular risks of inhaled anticholinergics, including cardiovascular death, myocardial infarction, and stroke. Systematic searches were conducted on March 19, 2008, of relevant articles in MEDLINE, the Cochrane Database of systematic reviews, regulatory authority Web sites in the United States and the United Kingdom, and manufacturers' trial registries with no date restrictions. Randomized controlled trials of any inhaled anticholinergic for treatment of COPD that had at least30 days of treatment and reported on cardiovascular events were selected. The primary outcome was a composite of cardiovascular death, myocardial infarction, or stroke. The secondary outcome was all-cause mortality. Relative risks were estimated using fixed-effects models and statistical heterogeneity was estimated with the I2 statistic. After a detailed screening of 103 articles, 17 trials enrolling 14783 patients were analyzed. Follow-up duration ranged from 6 weeks to 5 years. Cardiovascular death, myocardial infarction, or stroke occurred in 135 of 7472 patients receiving inhaled anticholinergics and 86 of 7311 patients receiving control therapy. Among individual components of the primary end point, inhaled anticholinergics significantly increased the risk of myocardial infarction and cardiovascular death without a statistically significant increase in the risk of stroke. All-cause mortality was reported in 149 of the patients treated with inhaled anticholinergics and 115 of the control patients. A sensitivity analysis restricted to 5 long-term trials (> 6 months) confirmed the significantly increased risk of cardiovascular death, myocardial infarction, or stroke. In conclusion, inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, myocardial infarction, or stroke among patients with COPD.

P07-13582

Jara M; Lanes SF; Wentworth C; May C; Kesten S. **Comparative safety of long-acting inhaled bronchodilators: a cohort study using the UK THIN primary care database.** Drug Saf. 2007;30(12):1151-1160.

To compare the risk of total mortality and certain respiratory and cardiac adverse events among users of the 2 types of recommended long-acting bronchodilators, the authors conducted a cohort study. Specifically, the study compared the safety of the only approved long-acting anticholinergic, inhaled tiotropium bromide (Spiriva), with the single-ingredient long-acting beta-agonists salmeterol or formoterol in a broad population of users. Automated general practitioner data from the UK THIN (The Health Information Network) database were used as the data source for this study. The authors used Cox proportional hazard models to compute hazard ratio estimates and 95 % CI controlling for propensity scores comprising various baseline demographic variables, medical therapies and illnesses. The 1061 tiotropium users and 1801 long-acting beta-agonist users were similar with regard to risk of total

mortality and most cardiac events, including angina, atrial fibrillation or flutter, myocardial infarction and tachycardia. Though imprecise, there was evidence of a decreased risk of heart failure in tiotropium users. As regards respiratory endpoints, the risk of COPD exacerbation and pneumonia were similar among users of each type of drug, although there was a decreased risk of asthma exacerbation in tiotropium users compared with long-acting beta agonist users. In conclusion, users of tiotropium and single-ingredient long-acting beta agonists had similar risk of total mortality and cardiovascular endpoints. The decreased risk of asthma exacerbations with tiotropium may be due to residual confounding by indication. Confidence limits for most events include reduced risks for tiotropium and also small increases in risk. Nevertheless, the point estimates suggest that tiotropium was associated with a lower risk of each cardiac event except myocardial infarction.

P07-07347

Luise C de; Lanes SF; Jacobsen J; Pedersen L; Sorensen HT. **Cardiovascular and respiratory hospitalizations and mortality among users of tiotropium in Denmark**. Eur J Epidemiol. 2007;22(4):267-272.

Tiotropium (Spiriva) is an inhaled, once-daily anticholinergic medication for COPD. The authors conducted a population-based cohort study to examine the risk of cardiovascular and respiratory hospitalizations and mortality with tiotropium. Using the Danish healthcare registries, persons >/= 40 years old in 3 counties were identified who were hospitalized for COPD from 1/1/1977 to 12/31/2003. Respiratory and cardiovascular medications were assessed from dispensing records. Cox regression was used to compute incidence rate ratios and 95 % confidence intervals for hospitalization and death between 1/1/2002 and 12/31/2003, associated with periods of tiotropium use compared to non-use, controlling for age, gender, time since COPD, concomitant respiratory and cardiovascular medications, prior hospitalizations and Charlson comorbidity index. Among persons with COPD (10,603), 75 % were >/= 60 years old. Follow-up was >/= 18 months for 64 %. Among those exposed to tiotropium compared to periods of non-use, the rate ratios for total and cause-specific hospitalization endpoints were not elevated except for COPD hospitalization (rate ratio = 1.52). Mortality endpoints included total mortality (rate ratio = 0.77), respiratory mortality (rate ratio = 0.79), sudden death (rate ratio = 0.71), cardiac arrest (rate ratio = 0.74), heart failure (rate ratio = 0.84), and myocardial infarction (rate ratio = 1.25). Compared to periods of non-use, tiotropium was associated with reduced respiratory and overall mortality and was not associated with increased cardiac mortality. An increase in COPD hospitalization is inconsistent with clinical trial data and suggests preferential prescribing due to disease severity.

P08-10308

Gershon AS; Wang L; To T; Luo J; Upshur REG. **Survival with tiotropium compared to long-acting beta-2-agonists in chronic obstructive pulmonary disease.** COPD J Chronic Obstruct Pulm Dis 2008; 5 (4): 229-234.

COPD is the 4th-leading cause of chronic morbidity and mortality in North America and its burden continues to increase. Tiotropium has been shown to reduce exacerbations,

hospitalizations, symptoms, and improve health-related quality of life in patients with COPD. Its effect on mortality and its effects relative to long-acting beta-agonists, however, remain unknown. To examine the association between tiotropium use compared to long-acting beta-agonists use on all-cause mortality in older patients with COPD, a longitudinal, population-based cohort study was conducted in Ontario, Canada. Subjects were individuals 65 years and older discharged from hospital with a diagnosis of COPD. The hazard of receiving a prescription for tiotropium compared to a long-acting beta-agonist on all-cause mortality at 180 days post-hospital discharge, controlling for a number of potential confounders, was eliminated. Data from 7218 eligible patients were analyzed. Of these, 1046 died in the follow-up period. Patients who received tiotropium were 20 % less likely to die than those receiving a long-acting beta-agonist. In conclusion, in older patients recently discharged from hospital for COPD, receiving tiotropium was found to be associated with reduced mortality at 6 months compared to receiving a long-acting beta-agonist. This result suggests that tiotropium might also be associated with decreased mortality compared to no treatment at all. Randomized placebo-control trials are needed to confirm these findings.

P08-15645

Griffin J; Lee S; Caiado M; Kesten S; Price D. **Comparison of tiotropium bromide and combined ipratropium/salbutamol for the treatment of COPD: a UK General Practice Research Database 12-month follow-up study.** Prim Care Respir J 2008; 17 (2): 104-110.

The aim of this study was to compare the effectiveness of the long-acting anticholinergic, tiotropium with ipratropium/salbutamol in reducing the risk of exacerbations and COPD-related referrals in patients with COPD. Data were obtained from the General Practice Research Database. Propensity score matching was used to balance prognostic covariates between treatment groups. Incidence rate ratios and 95 % confidence intervals during a 12-month follow-up period were estimated. 4193 Patients (3385, tiotropium; 808, ipratropium/salbutamol) in the General Practice Research Database met the inclusion/exclusion criteria. Patients treated with tiotropium had more severe COPD than patients treated with ipratropium/salbutamol. Following propensity score matching, 1222 tiotropium-treated patients and 633 ipratropium/salbutamol-treated patients were included in the final analysis. Incidence rate ratios (95 % confidence intervals) were 0.74 (0.64 - 0.85) for exacerbations and 0.57 (0.46 - 0.70) for COPD-related referrals/hospitalizations. In conclusion, tiotropium is associated with a reduced risk of exacerbations and COPD-related referrals and hospitalization compared to combined ipratropium/salbutamol in patients with COPD.

17.6 APPENDIX: SPIRIVA® HANDIHALER® (TIOTROPIUM BROMIDE INHALATION POWDER) PRESCRIBING INFORMATION

ATTENTION PHARMACIST: Detach "Patient Information" and "Patient's Instructions for Use" from package insert and dispense with the product.

Spiriva® HandiHaler®

(tiotropium bromide inhalation powder)

Do Not Swallow Spiriva Capsules

For Use With HandiHaler Device Only

FOR ORAL INHALATION ONLY

Rx only

Prescribing Information

DESCRIPTION

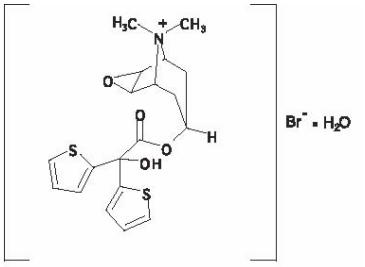
SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) consists of a capsule dosage form containing a dry powder formulation of tiotropium intended for oral inhalation only with the HandiHaler device.

Each light green, hard gelatin SPIRIVA capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate as the carrier.

The dry powder formulation within the SPIRIVA capsule is intended for oral inhalation only.

The active component of SPIRIVA HandiHaler is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1α, 2ß, 4ß, 5α, 7ß)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

The structural formula is: Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of $C_{19}H_{22}NO_4S_2Br \cdot H_2O$.



The HandiHaler device is an inhalation device used to inhale the dry powder contained in the SPIRIVA capsule. The dry powder is delivered from the HandiHaler device at flow rates as low as 20 L/min. Under standardized *in vitro* testing, the HandiHaler device delivers a mean of
10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2L total). In a study of 26 adult patients with chronic obstructive pulmonary disease (COPD) and severely compromised lung function [mean FEV_1 1.02 L (range 0.45 to 2.24 L); 37.6% of predicted (range 16%–65%)], the median peak inspiratory flow (PIF) through the HandiHaler device was
30.0 L/min (range 20.4 to 45.6 L/min). The amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow through the HandiHaler device, which may vary from patient to patient, and may vary with the exposure time of the SPIRIVA capsule outside the blister pack.

For administration of SPIRIVA HandiHaler, a SPIRIVA capsule is placed into the center chamber of the HandiHaler device. The SPIRIVA capsule is pierced by pressing and releasing the green piercing button on the side of the HandiHaler device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece (see **Patient's Instructions for Use**).

CLINICAL PHARMACOLOGY

Mechanism of Action

Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M_1 to M_5. In the airways, it exhibits pharmacological effects through inhibition of M_3-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine-induced bronchoconstriction effects were dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

Pharmacokinetics

Tiotropium is administered by dry powder inhalation. In common with other inhaled drugs, the majority of the delivered dose is deposited in the gastrointestinal tract and, to a lesser extent, in the lung, the intended organ. Many of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Absorption

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. It is expected from the chemical structure of the compound (quaternary ammonium compound) that tiotropium is poorly absorbed from the gastrointestinal tract. Food is not expected to influence the absorption of tiotropium for the same reason. Oral solutions of tiotropium have an absolute bioavailability of 2–3%. Maximum tiotropium plasma concentrations were observed five minutes after inhalation.

Distribution

Tiotropium shows a volume of distribution of 32 L/kg, indicating that the drug binds extensively to tissues. The drug is bound by 72% to plasma proteins. At steady state, peak tiotropium plasma levels in COPD patients were 17-19 pg/mL when measured 5 minutes after dry powder inhalation of an 18 mcg dose and decreased rapidly in a multi-compartmental manner. Steady-state trough plasma concentrations were 3–4 pg/mL. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not readily penetrate the blood-brain barrier.

Biotransformation

The extent of biotransformation appears to be small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol *N*-methylscopine and dithienylglycolic acid, neither of which bind to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Elimination

The terminal elimination half-life of tiotropium is between 5 and 6 days following inhalation. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers with an inter-individual variability of 22%. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). After dry powder inhalation, urinary excretion is 14% of the dose, the remainder being mainly non-absorbed drug in the gut which is eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating active secretion into the urine. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2–3 weeks with no accumulation thereafter.

Drug Interactions

An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once daily was

conducted.
Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the $AUC_{0–4h}$, a 28% decrease in the renal clearance of tiotropium and no significant change in the C_{max} and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium. Therefore, no clinically significant interaction occurred between tiotropium and cimetidine or ranitidine.

Electrophysiology

In a multicenter, randomized, double-blind trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30–60 msec was higher in the SPIRIVA HandiHaler group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical studies with SPIRIVA HandiHaler did not detect an effect of the drug on QTc intervals. The effect of Spiriva HandiHaler on QT interval was also evaluated in a randomized, placebo and positive controlled crossover study in 53 healthy volunteers. Subjects received Spiriva HandiHaler 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for SPIRIVA HandiHaler 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥60 msec.

Special Populations

Elderly Patients

As expected for drugs predominantly excreted renally, advanced age was associated with a decrease of tiotropium renal clearance (326 mL/min in COPD patients <58 years to 163 mL/min in COPD patients >70 years), which may be explained by decreased renal function. Tiotropium excretion in urine after inhalation decreased from 14% (young healthy volunteers) to about 7% (COPD patients). Plasma concentrations were numerically increased with advancing age within COPD patients (43% increase in $AUC_{0–4}$ after dry powder inhalation), which was not significant when considered in relation to inter- and intra-individual variability (see **DOSAGE AND ADMINISTRATION**).

Hepatically-impaired Patients

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. However, hepatic insufficiency is not expected to have relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors (see **DOSAGE AND ADMINISTRATION**).

Renally-impaired Patients

Since tiotropium is predominantly renally excreted, renal impairment was associated with increased plasma drug concentrations and reduced drug clearance after both intravenous infusion and dry powder inhalation. Mild renal impairment (CrCl 50–80 mL/min), which is

often seen in elderly patients, increased tiotropium plasma concentrations (39% increase in AUC_{0-4} after intravenous infusion). In COPD patients with moderate to severe renal impairment (CrCl <50 mL/min), the intravenous administration of tiotropium resulted in doubling of the plasma concentrations (82% increase in AUC_{0-4}), which was confirmed by plasma concentrations after dry powder inhalation (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**).

CLINICAL STUDIES

The SPIRIVA HandiHaler (tiotropium bromide inhalation powder) clinical development program consisted of six Phase 3 studies in 2,663 patients with COPD (1,308 receiving SPIRIVA HandiHaler): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had an FEV_1 less than or equal to 60% or 65% of predicted, and a ratio of FEV_1/FVC of less than or equal to 0.7.

In these studies, SPIRIVA HandiHaler, administered once-daily in the morning, provided improvement in lung function (forced expiratory volume in one second, FEV_1), with peak effect occurring within 3 hours following the first dose.

In the 1-year, placebo-controlled trials, the mean improvement in FEV_1 at 30 minutes was 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to baseline after the first dose (Day 1). Further improvements in FEV_1 and FVC were observed with pharmacodynamic steady state reached by Day 8 with once-daily treatment. The mean peak improvement in FEV_1, relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week (Day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance.

In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial FEV_1 values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the improvement in pulmonary function (FEV_1) with SPIRIVA HandiHaler, which persisted over the spirometric observational period. Effectiveness was maintained for 24 hours after administration over the 6-month treatment period.

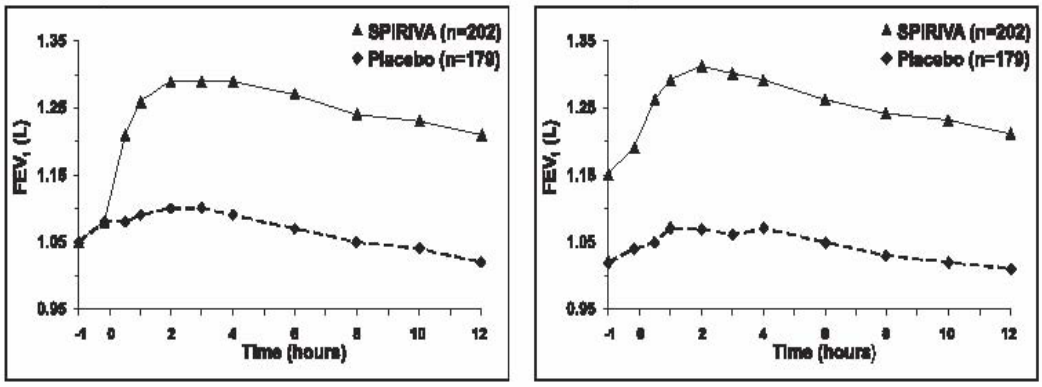


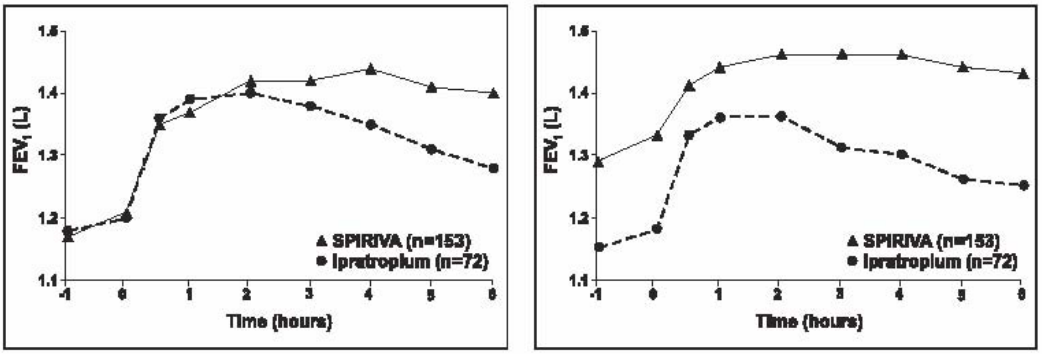
Figure 1 Mean FEV_1 Over Time (prior to and after administration of study drug)on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)

* * Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the SPIRIVA HandiHaler and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using last observation or least favorable observation carried forward.

Results of each of the one-year ipratropium-controlled trials were similar to the results of the one-year placebo-controlled trials. The results of one of these trials are shown in Figure 2.

Figure 2 Mean FEV_1 Over Time (0 to 6 hours post-dose) on Days 1 and 92, respectively for one of the two Ipratropium-Controlled Studies*

Day 1 Day 92



* Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the SPIRIVA HandiHaler and ipratropium groups, respectively, completed through three months of observation. The data for the remaining patients were imputed using last observation or least favorable observation carried forward.

A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo, regardless of whether SPIRIVA HandiHaler was administered in the morning or in the evening.

Throughout each week of the one-year treatment period in the two placebo-controlled trials, patients taking SPIRIVA HandiHaler had a reduced requirement for the use of rescue short-acting beta2-agonists. Reduction in the use of rescue short-acting beta2-agonists, as compared to placebo, was demonstrated in one of the two 6-month studies.

INDICATIONS AND USAGE

SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

CONTRAINDICATIONS

SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, including ipratropium, or to any component of this product.

WARNINGS

SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm, i.e., rescue therapy.

Immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue or throat), itching, and rash may occur after administration of SPIRIVA HandiHaler. If such a reaction occurs, therapy with SPIRIVA HandiHaler should be stopped at once and alternative treatments should be considered.

Inhaled medicines, including SPIRIVA HandiHaler, may cause paradoxical bronchospasm. If this occurs, treatment with SPIRIVA HandiHaler should be stopped and other treatments considered.

PRECAUTIONS

General

As an anticholinergic drug, SPIRIVA HandiHaler (tiotropium bromide inhalation powder) may potentially worsen symptoms and signs associated with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction and should be used with caution in patients with any of these conditions.

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**, **Special Populations**, *Renally-impaired Patients*).

Information for Patients

It is important for patients to understand how to correctly administer SPIRIVA capsules using the HandiHaler device (see **Patient's Instructions for Use**). SPIRIVA capsules should only be administered via the HandiHaler device and the HandiHaler device should not be used for administering other medications. **The contents of SPIRIVA capsules are for oral inhalation only and must not be swallowed**.

SPIRIVA capsules should always be stored in sealed blisters. Remove only one

SPIRIVA capsule immediately before use, or its effectiveness may be reduced. Additional SPIRIVA capsules that are exposed to air (i.e., not intended for immediate use) should be discarded.

Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. Should any of these signs and symptoms develop, consult a physician immediately. Miotic eye drops alone are not considered to be effective treatment.

Care must be taken not to allow the powder to enter into the eyes as this may cause blurring of vision and pupil dilation.

SPIRIVA HandiHaler is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems, i.e., as a rescue medication.

Drug Interactions

SPIRIVA HandiHaler has been used concomitantly with other drugs commonly used in COPD without increases in adverse drug reactions. These include short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids. However, the co-administration of SPIRIVA HandiHaler with other anticholinergic-containing drugs (e.g., ipratropium) has not been studied and is therefore not recommended.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to
0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to 25, 35, and 0.5 times the Recommended Human Daily Dose (RHDD) on a mg/m2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDD on a mg/m2 basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times than the RHDD on a mg/m2 basis). The fertility index, however, was not affected at inhalation doses up to 1.689 mg/kg/day (approximately 760 times the RHDD on a mg/m2 basis). These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

Pregnancy

Pregnancy Category C.

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the recommended human daily dose (RHDD) on a mg/m2 basis. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation were observed at inhalation tiotropium doses of ≥0.078 mg/kg (approximately 35 times the RHDD on a mg/m2 basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDD on a mg/m2 basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to approximately 4 and 80 times the RHDD on a mg/m2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

There are no adequate and well-controlled studies in pregnant women. SPIRIVA HandiHaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery

The safety and effectiveness of SPIRIVA HandiHaler has not been studied during labor and delivery.

Nursing Mothers

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA HandiHaler is administered to a nursing woman.

Pediatric Use

SPIRIVA HandiHaler is approved for use in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not normally occur in children. The safety and effectiveness of SPIRIVA HandiHaler in pediatric patients have not been established.

Geriatric Use

Of the total number of patients who received SPIRIVA HandiHaler in the 1-year clinical trials, 426 were <65 years, 375 were 65–74 years and 105 were ≥75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the SPIRIVA HandiHaler and the comparator groups for most events. Dry mouth increased with age in the SPIRIVA HandiHaler group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA HandiHaler group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary

tract infections were – 0.6%, 4.6% and 4.5%. No overall differences in effectiveness were observed among these groups. Based on available data, no adjustment of SPIRIVA HandiHaler dosage in geriatric patients is warranted.

ADVERSE REACTIONS

Of the 2,663 patients in the four 1-year and two 6-month controlled clinical trials, 1,308 were treated with SPIRIVA HandiHaler (tiotropium bromide inhalation powder) at the recommended dose of 18 mcg once a day. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, increased heart rate, blurred vision, glaucoma (new onset or worsening), urinary difficulty, and urinary retention.

Four multicenter, 1-year, controlled studies evaluated SPIRIVA HandiHaler in patients with COPD. Table 1 shows all adverse events that occurred with a frequency of ≥3% in the SPIRIVA HandiHaler group in the 1-year placebo-controlled trials where the rates in the SPIRIVA HandiHaler group exceeded placebo by ≥1%. The frequency of corresponding events in the ipratropium-controlled trials is included for comparison.

Table 1 Adverse Experience Incidence (% Patients) in One-Year-COPD Clinical Trials

Body System (Event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA	Placebo	SPIRIVA	Ipratropium
	[n = 550]	[n = 371]	[n = 356]	[n = 179]
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
Musculoskeletal 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

Arthritis, coughing, and influenza-like symptoms occurred at a rate of ≥3% in the SPIRIVA HandiHaler treatment group, but were <1% in excess of the placebo group.

Other events that occurred in the SPIRIVA HandiHaler group at a frequency of 1–3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole:* allergic reaction, leg pain; *Central and Peripheral Nervous System:* dysphonia, paresthesia; *Gastrointestinal System Disorders:* gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders:* hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders:* skeletal pain; *Cardiac Events:* angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder:* depression; *Infections:* herpes zoster; *Respiratory System Disorder (Upper):* laryngitis; *Vision Disorder:* cataract. In addition, among the adverse events observed in the clinical trials with an incidence of <1% were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age (see **PRECAUTIONS, Geriatric Use**).
Two multicenter, 6-month, controlled studies evaluated SPIRIVA HandiHaler in patients with COPD. The adverse events and the incidence rates were similar to those seen in the 1-year controlled trials.

The following adverse reactions have been identified during worldwide post-approval use of SPIRIVA HandiHaler: application site irritation (glossitis, mouth ulceration, and pharyngolaryngeal pain), dizziness, dysphagia, epistaxis, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

OVERDOSAGE

High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium.

Accidental Ingestion

Acute intoxication by inadvertent oral ingestion of SPIRIVA capsules is unlikely since it is not well-absorbed systemically.

A case of overdose has been reported from post-marketing experience. A female patient was reported to have inhaled 30 capsules over a 2.5 day period, and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, SPIRIVA HandiHaler (tiotropium bromide inhalation powder) was discontinued, and the constipation was treated with an enema. The patient recovered and was discharged on the same day.

No mortality was observed at inhalation tiotropium doses up to 32.4 mg/kg in mice, 267.7 mg/kg in rats, and 0.6 mg/kg in dogs. These doses correspond to 7,300, 120,000, and 850 times the recommended human daily dose on a mg/m2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

DOSAGE AND ADMINISTRATION

SPIRIVA capsules must not be swallowed as the intended effects on the lungs will not be obtained. The contents of the SPIRIVA capsules are only for oral inhalation and should only be used with the HandiHaler device (see OVERDOSAGE section).

The recommended dosage of SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is the inhalation of the contents of one SPIRIVA capsule, once-daily, with the HandiHaler device (see "**Patient Information**" and "**Patient's Instructions for Use**").

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given SPIRIVA HandiHaler should be monitored closely (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**, **Special Populations** and

PRECAUTIONS).

HOW SUPPLIED

SPIRIVA HandiHaler consists of SPIRIVA capsules and the HandiHaler device. SPIRIVA capsules contain 18 mcg of tiotropium and are light green, with the Boehringer Ingelheim company logo on the SPIRIVA capsule cap and TI 01 on the SPIRIVA capsule body, or vice versa.

The HandiHaler device is gray colored with a green piercing button. It is imprinted with SPIRIVA HandiHaler (tiotropium bromide inhalation powder), the Boehringer Ingelheim company logo, and the Pfizer company logo. It is also imprinted to indicate that SPIRIVA capsules should not be stored in the HandiHaler device and that the HandiHaler device is only to be used with SPIRIVA capsules.

SPIRIVA capsules are packaged in an aluminum/aluminum blister card and joined along a perforated-cut line. SPIRIVA capsules should always be stored in the blister and only removed immediately before use. The drug should be used immediately after the packaging over an individual SPIRIVA capsule is opened.

The following packages are available:

carton containing 5 SPIRIVA capsules (1 unit-dose blister card) and 1 HandiHaler device (NDC 0597-0075-75)
carton containing 30 SPIRIVA capsules (3 unit-dose blister cards) and 1 HandiHaler device (NDC 0597-0075-41)
carton containing 90 SPIRIVA capsules (9 unit-dose blister cards) and 1 HandiHaler device (NDC 0597-0075-47)

Storage

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].

The SPIRIVA capsules should not be exposed to extreme temperature or moisture. Do not store
SPIRIVA capsules in the HandiHaler device.

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

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Address medical inquiries to: www.Spiriva.com, (800) 542-6257 or (800) 459-9906 TTY.

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Rev: March 2009
Patient Information

SPIRIVA® (speh REE vah)
HandiHaler® (tiotropium bromide inhalation powder)

Important Information: Do not swallow SPIRIVA capsules. SPIRIVA capsules should only be used with the HandiHaler device. SPIRIVA HandiHaler should only be inhaled by mouth (oral inhalation).

Read the information that comes with your SPIRIVA HandiHaler before you start using it and each time you refill your prescription. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is SPIRIVA HandiHaler?

SPIRIVA HandiHaler is a prescription medicine that you use one time every day (a maintenance medicine) to control symptoms of chronic obstructive pulmonary disease (COPD). SPIRIVA HandiHaler helps make your lungs work better for 24

hours. SPIRIVA HandiHaler relaxes your airways and helps keep them open. You may start to feel like it is easier to breathe on the first day, but it may take longer for you to feel the full effects of the medicine. SPIRIVA HandiHaler works best and may help make it easier to breathe when you use it every day.

SPIRIVA HandiHaler is **not** a rescue medicine and should not be used for treating sudden breathing problems. Your doctor may give you other medicine to use for sudden breathing problems.

SPIRIVA HandiHaler has not been studied in children.

Who should not take SPIRIVA HandiHaler?

Do not use SPIRIVA HandiHaler if you:

are allergic to any of the ingredients in SPIRIVA capsules.

have had an allergic reaction to atropine or any medicines like it, such as ipratropium (Atrovent®).

What should I tell my doctor before using SPIRIVA HandiHaler?

Before taking SPIRIVA HandiHaler, tell your doctor about all your medical conditions, including if you:

have kidney problems.

have glaucoma. SPIRIVA HandiHaler may make your glaucoma worse.

- have an enlarged prostate, problems passing urine, or a blockage in your bladder.

SPIRIVA HandiHaler may make these problems worse.

are pregnant or plan to become pregnant. It is not known if SPIRIVA HandiHaler could harm your unborn baby.

are breast-feeding or plan to breast feed. It is not known if SPIRIVA HandiHaler passes into breast milk. You and your doctor will decide if SPIRIVA HandiHaler is right for you while you breast-feed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines and eye drops, vitamins, and herbal supplements. Some of your other medicines or supplements may affect the way SPIRIVA HandiHaler works. SPIRIVA HandiHaler is an anticholinergic medicine. You should not take other anticholinergic medicines while using SPIRIVA HandiHaler, including ipratropium. Ask your doctor or pharmacist if you are not sure if one of your medicines is an anticholinergic.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I take SPIRIVA HandiHaler?

Use SPIRIVA HandiHaler exactly as prescribed. Use SPIRIVA HandiHaler one time every day.

Read the “Patient’s Instructions for Use” at the end of this leaflet before you

use SPIRIVA HandiHaler. Talk with your doctor if you do not understand the instructions.

Do not swallow SPIRIVA capsules.

Only use SPIRIVA capsules with the HandiHaler device.

Do not use the HandiHaler device to take any other medicine.

SPIRIVA HandiHaler comes as a powder in a SPIRIVA capsule that fits the HandiHaler device. Each SPIRIVA capsule, containing only a small amount of SPIRIVA powder, is one full dose of medicine.

Separate one blister from the blister card. Then take out one of the SPIRIVA capsules from the blister package right before you use it.

After the capsule is pierced, take a complete dose of SPIRIVA HandiHaler by breathing in the powder by mouth two times, using the HandiHaler device (take 2 inhalations from one SPIRIVA capsule). See the "Patient's Instructions for Use" at the end of this leaflet.

Throw away any SPIRIVA capsule that is not used right away after it is taken out of the blister package. Do not leave the SPIRIVA capsules open to air; they may not work as well.

If you miss a dose, take it as soon as you remember. Do not use SPIRIVA HandiHaler more than one time every 24 hours.

If you use more than your prescribed dose of SPIRIVA HandiHaler, call your doctor or a poison control center.

What should I avoid while using SPIRIVA HandiHaler?

Do not let the powder from the SPIRIVA capsule get into your eyes. Your vision may get blurry and the pupil in your eye may get larger (dilate). If this happens, call your doctor.

What are the possible side effects of SPIRIVA HandiHaler?

SPIRIVA HandiHaler can cause serious side effects. If you get any of the following side effects, stop taking SPIRIVA HandiHaler and get medical help right away.

Allergic reaction. Symptoms may include**:** itching, rash, swelling of the lips, tongue, or throat (trouble swallowing).

Sudden narrowing and blockage of the airways into the lungs (bronchospasm).

Your breathing suddenly gets worse.

- **New or worsened increased pressure in the eyes (glaucoma).**

Symptoms of acute narrow-angle glaucoma may include: eye pain, blurred vision, seeing halos (visual halos) or colored images along with red eyes.

Common side effects with SPIRIVA HandiHaler include:

dry mouth
constipation
upper respiratory infection
increased heart rate

blurry vision
glaucoma (new onset or worsening)
trouble passing urine

These are not all the possible side effects with SPIRIVA HandiHaler. Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store SPIRIVA HandiHaler?

Do not store SPIRIVA capsules in the HandiHaler device.
Store SPIRIVA capsules in the sealed blister package at room temperature [68°–77°F (20°–25°C)].
Keep SPIRIVA capsules away from heat and cold (do not freeze).
Store SPIRIVA capsules in a dry place. Throw away any unused SPIRIVA capsules that have been open to air.

Ask your doctor or pharmacist if you have any questions about storing your SPIRIVA capsules.

Keep SPIRIVA HandiHaler, SPIRIVA capsules, and all medicines out of the reach of children.
General information about SPIRIVA HandiHaler

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use SPIRIVA HandiHaler for a purpose for which it has not been prescribed. Do not give SPIRIVA HandiHaler to other people even if they have the same symptoms that you have. It may harm them.

For more information about SPIRIVA HandiHaler, talk with your doctor. You can ask your doctor or pharmacist for information about SPIRIVA HandiHaler that is written for health professionals.

For more information about SPIRIVA HandiHaler, you may also call 1-800-542-6257 or (TTY) 1-800-459-9906.

What are the ingredients in SPIRIVA HandiHaler?

Active ingredient: tiotropium Inactive ingredient: lactose monohydrate

What is COPD (Chronic Obstructive Pulmonary Disease)?

COPD is a serious lung disease that includes chronic bronchitis, emphysema, or both.
Most COPD is caused by smoking. When you have COPD, your airways become narrow. So, air moves out of your lungs more slowly. This makes it hard to breathe.

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Patient's Instructions for Use

Spiriva® HandiHaler®

(tiotropium bromide inhalation powder)

<u>Important Information:</u> Do not swallow SPIRIVA capsules. SPIRIVA capsules should only be used with the HandiHaler device. SPIRIVA HandiHaler should only be inhaled by mouth (oral inhalation).

First read the Patient Information that comes with SPIRIVA HandiHaler for important information about using SPIRIVA HandiHaler.

Read these Patient's Instructions for Use before you start to use SPIRIVA HandiHaler and each time you refill your prescription. There may be new information.

For more information, ask your healthcare provider or pharmacist.

SPIRIVA HandiHaler comes with SPIRIVA capsules and a HandiHaler device. The HandiHaler device is an inhalation device that is for use only with SPIRIVA capsules. Do not use the HandiHaler device to take any other medicine.

Becoming familiar with SPIRIVA HandiHaler:

Remove the HandiHaler device from the pouch and become familiar with its components. (Figure A)

1 dust cap
2 mouthpiece
3 mouthpiece ridge
4 base
5 green piercing button
6 center chamber
7 air intake vents

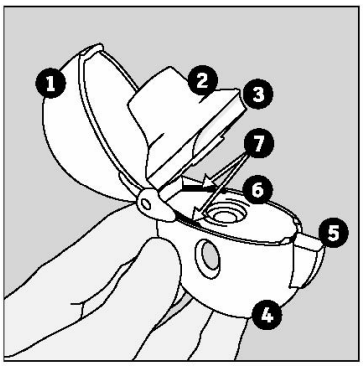
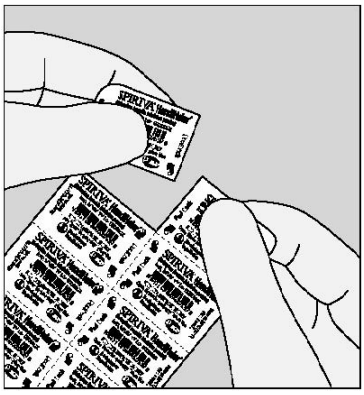


Figure A



Each SPIRIVA capsule is packaged in a blister. Each blister can be separated from the blister card by tearing along the perforation. (Figure B)

Figure B

How do I take my SPIRIVA HandiHaler using the HandiHaler device?

Taking your dose of medicine using the HandiHaler device has four main steps:

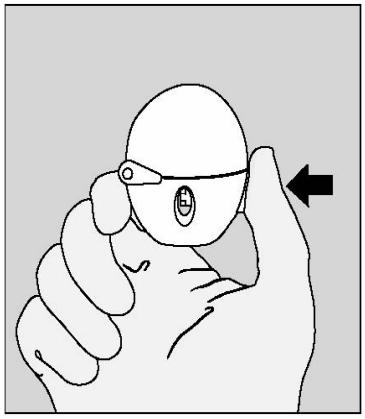
1 **Open** the HandiHaler device and the blister
2 **Insert** the SPIRIVA capsule
3 **Press** the green piercing button

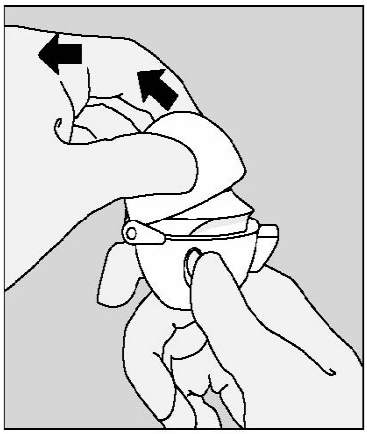
4 **Breathe in (inhale)** your medicine

(See below for details)

Opening the HandiHaler device:

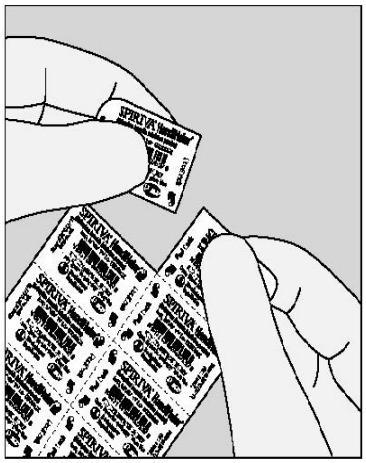
1. Open the dust cap by pressing the green piercing button. (Figure 1)





Pull the dust cap upwards to expose the mouthpiece. (Figure 2)

Removing a SPIRIVA capsule:

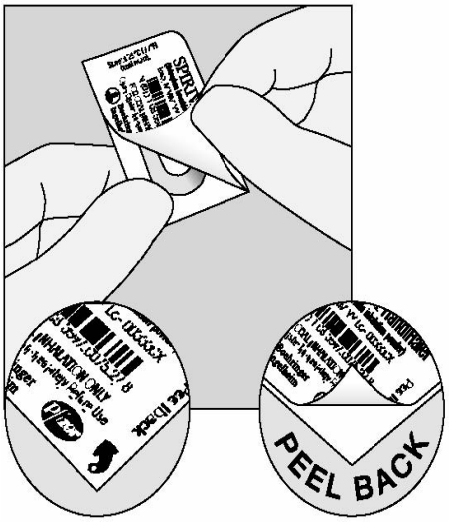


Open the mouthpiece by pulling the mouthpiece ridge upwards away from the base. (Figure 3)

Before removing a SPIRIVA capsule from the blister, separate one of the blisters from the blister card by tearing along the perforation. (Figure 4)

Do not swallow Spiriva capsules.

Always store SPIRIVA capsules in the sealed blisters. Remove only one SPIRIVA capsule from the blister right before use. Do not store SPIRIVA capsules in the HandiHaler device. Inhale the contents of the SPIRIVA capsule using the HandiHaler device right away after the blister packaging of an individual SPIRIVA capsule is opened, or else it may not work as well.



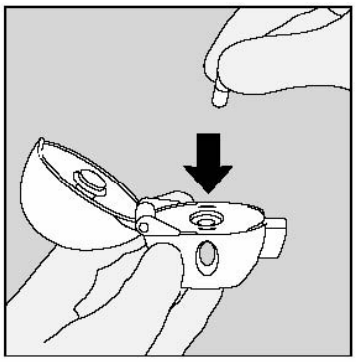
Right before you are ready to use your SPIRIVA HandiHaler:

Bend back and forth one of the corners of the blister that has an arrow and then with your finger separate the aluminum foil layers. Carefully peel back the printed foil until you can see the whole SPIRIVA capsule. (Figure 5)

Turn the blister upside down and tip the SPIRIVA capsule out, tapping the back of the blister, if needed.

Do not cut the foil or use sharp instruments to take out the SPIRIVA capsule from the blister.

If more SPIRIVA capsules are opened to air, they should not be used and should be thrown away.
Inserting the SPIRIVA capsule into the HandiHaler device:



2. Insert (put) the SPIRIVA capsule in the center chamber of the HandiHaler device. It does not matter which end of the SPIRIVA capsule you put in the chamber. (Figure 6)

Figure 6

Close the mouthpiece **until you hear a click**, but leave the dust cap open. (Figure 7)

Be sure that you have the mouthpiece sitting firmly against the gray base.

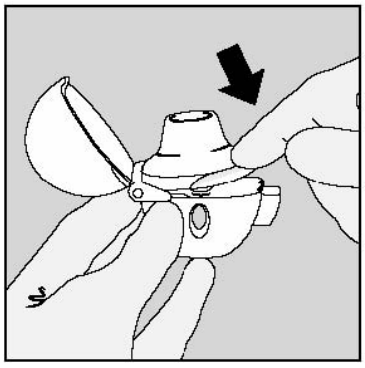
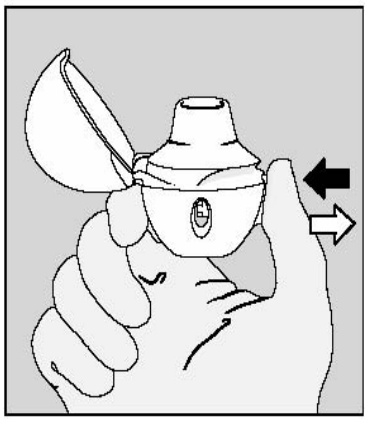
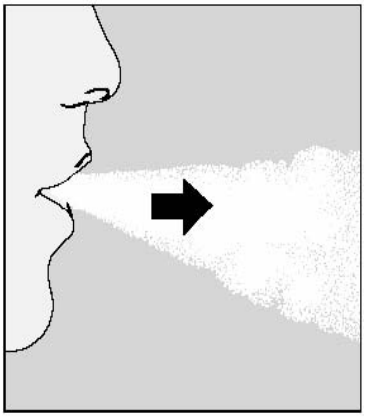


Figure 7

Taking your dose using the HandiHaler device:





Hold the HandiHaler device with the mouthpiece upright. It is important that you hold the HandiHaler device in an upright position (Figure 8) when pressing the green piercing button.

3. Press the green piercing button until it is flat (flush) against the base, and release. This is how you make holes in the SPIRIVA capsule so that you get the medicine when you breathe in.

Do not press the green button more than one time.

Breathe out completely. (Figure 9)

Important: Do not breathe (exhale) into the mouthpiece of the HandiHaler device at any time.

4. Breathe in (inhale)

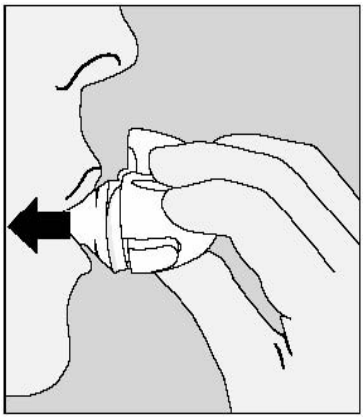
- Hold the HandiHaler device by the gray base. Do not block the air intake vents.
- Raise the HandiHaler device to your mouth and close your lips tightly around the mouthpiece.
- **Keep your head in an upright position. The HandiHaler device should be in a horizontal position.** (Figure 10)
- Breathe in **slowly and deeply** so that you **hear or feel the SPIRIVA capsule vibrate**.
- Breathe in until your lungs are full.
- Hold your breath as long as is comfortable and at the same time take the HandiHaler device out of your mouth. Breathe normally again.

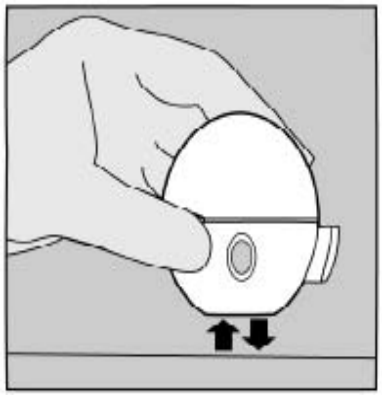
To make sure you get the full dose, you must breathe out completely, and inhale again as in step 4 above (Figure 10). *Do not press the green piercing button again.*

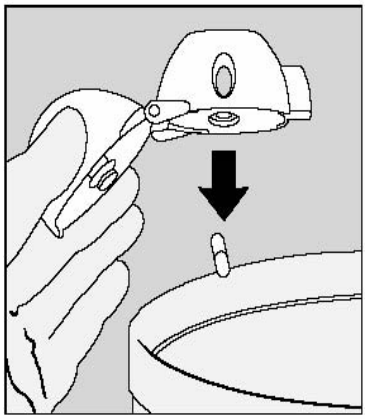
If you do not hear or feel the SPIRIVA capsule vibrate, **do not press the green piercing button again.** Instead, hold the HandiHaler device in an upright position and tap the HandiHaler device gently on a table. (Figure 11)

Check to see that the mouthpiece is completely closed. Then, breathe in again – slowly and deeply.

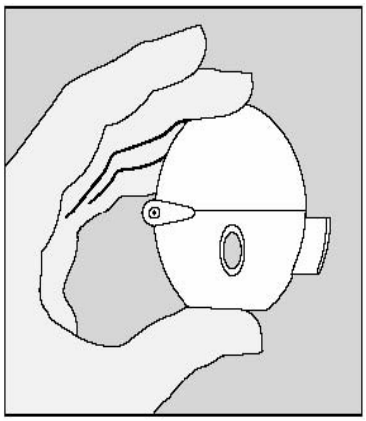
If you still do not hear or feel the SPIRIVA capsule vibrate after repeating the above steps, throw away the SPIRIVA capsule. Open the base by lifting the green piercing button and check the center chamber for pieces of the SPIRIVA capsule (SPIRIVA capsule fragments). SPIRIVA capsule fragments in the center chamber can cause a SPIRIVA capsule not to vibrate. Turn the HandiHaler device upside down and gently tap to remove the SPIRIVA capsule fragments. Call your doctor for instructions.







After you finished taking your daily dose of
SPIRIVA HandiHaler, open the mouthpiece again.
Tip out the used SPIRIVA capsule and throw it away.
(Figure 12)



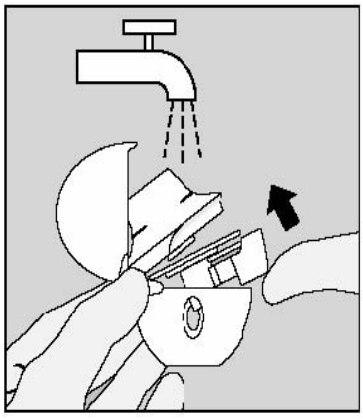
Close the mouthpiece and dust cap for storage of your HandiHaler device. (Figure 13)

Do not store used or unused SPIRIVA capsules in the HandiHaler device.

When and how should I clean my HandiHaler Device?

Clean the HandiHaler device one time each month or as needed. (Figure 14)

- Open the dust cap and mouthpiece.
- Open the base by lifting the green piercing button.
- Look at the center chamber for SPIRIVA capsule fragments or powder residue.
- Rinse the HandiHaler device with warm water. Check that any powder buildup or SPIRIVA capsule fragments are removed.
- Do not use cleaning agents or detergents.
- Do not place the HandiHaler device in the dishwasher for cleaning.
- Dry the HandiHaler device well by tipping the excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open.
- Do not use a hair dryer to dry the HandiHaler device.
- **It takes 24 hours to air dry, so clean the HandiHaler device right after you use it so that it will be ready for your next dose.**
- Do not use the HandiHaler device when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.



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SPIRIVA® (tiotropium bromide inhalation powder) is covered by U.S. Patent Nos. RE38,912, RE39,820, 5,478,578, 6,777,423, 6,908,928, 7,070,800 and 7,309,707 with
other patents pending. The HandiHaler® device is covered by U.S. Design Patent No.
D355,029 with other patents pending.

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