

SPIRIVA[®] (TIOTROPIUM BROMIDE) MILESTONE TRIALS

MEDIA BACKGROUND

Introduction

Since Spiriva[®] (tiotropium bromide) was first introduced as 18 µg via HandiHaler[®] over ten years ago, it has become the most prescribed maintenance treatment for COPD worldwide.¹ Spiriva[®] is the first long-acting anticholinergic COPD maintenance treatment proven to provide significant and sustained improvements in lung function with the convenience of inhaled, once-daily dosing.^{2,3,4} In addition, it has proven clinical efficacy in reducing the risk of exacerbations, reducing shortness of breath and increasing the quality of life in patients with COPD.^{3,5,6,7} With extensive clinical study data, in more than 230 COPD tiotropium clinical trials⁸ and more than 40 million patient-years of real-life experience*, Spiriva[®] has a well-established efficacy, safety and tolerability profile, making it a foundation of maintenance treatment.^{9,10,11} Three major milestone trials completed with tiotropium significantly added to the current knowledge about COPD treatment as mirrored in guidelines around the world.

Milestone trials

1. **The UPLIFT[®] Study** (published in *The New England Journal of Medicine* in 2008)
2. **The POET-COPD[®] Study** (published in *The New England Journal of Medicine* in 2011)
3. **The TIOSPIR[™] Trial** (published in *The New England Journal of Medicine* in 2013)

1. The UPLIFT^{®†} Study: The long-term impact of Spiriva[®] on COPD

The **Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT[®])** study was a randomised, double-blind, placebo-controlled trial that compared four years of therapy with either tiotropium (18 µg delivered via HandiHaler[®]) or control in patients with COPD. The UPLIFT[®] study demonstrated that treatment with tiotropium was associated with improvements in lung function, quality of life and reduction in COPD exacerbations during a four year period but did not significantly reduce the rate of decline in forced expiratory volume in 1 second (FEV₁) versus control.⁴

* Combined figures for HandiHaler[®] and Respimat[®]

† While Spiriva[®] 18 µg via HandiHaler[®] did not alter the rate of decline in lung function, a coprimary study endpoint in the UPLIFT[®] trial, it sustained greater improvements in lung function vs. control (placebo)

Rationale

Spiriva® (tiotropium) is the most prescribed COPD maintenance treatment worldwide and is a once-daily, inhaled anticholinergic drug that provides at least 24-hour improvements in airflow and hyperinflation in patients with COPD.⁴ Historical studies lasting six weeks to 12 months had shown improvements in multiple endpoints in patients with COPD^{12,13,14,15,16,17} and a retrospective analysis of one year placebo-controlled trials indicated that tiotropium had the potential to slow the rate of decline in FEV₁.⁶ Given these favourable clinical outcomes, the UPLIFT® trial was designed to extend these observations to four years and evaluate the long-term effects of tiotropium therapy on the clinically important outcomes of reducing the risk of COPD exacerbations, related hospitalisations, health-related quality of life and mortality.

Study design

The UPLIFT® trial was a four year randomised, double-blind, placebo-controlled, parallel-group trial involving patients with moderate to very severe COPD (46% of patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II (moderate) disease, 44% with GOLD stage III (severe) disease and 9% with GOLD stage IV (very severe) disease[‡]).^{2,4} Patients were at least 40 years of age (mean age 65±8 years), had a smoking history of at least 10 pack-years, with a FEV₁ of 70% or less after bronchodilation and a ratio of FEV₁ to forced vital capacity (FVC) of 70% or less.⁴ Of a total of 5,993 patients 2,987 were randomly assigned to the tiotropium (18 µg delivered via HandiHaler®) group and 3,006 to the control group. All patients were permitted to use all respiratory medications except inhaled anticholinergic drugs.

Study endpoints

The two co-primary endpoints were the yearly rate of decline in the mean FEV₁ before and after bronchodilation from day 30 until completion. Secondary endpoints included measures of FVC, health-related quality of life, as measured by the St. George's Respiratory Questionnaire (SGRQ), COPD exacerbations and related hospitalisations and mortality.

Results

Mean absolute improvements in FEV₁ in the tiotropium group were maintained throughout the trial (ranging from 87 to 103 ml before bronchodilation and from 47 to 65 ml after bronchodilation, as compared with the control group (P<0.001)).⁴ After day 30 the differences between the two groups in the rate of decline in the mean FEV₁, before and after bronchodilation, were not significant. The mean absolute score on the SGRQ was improved (lower) in the tiotropium group, compared with the control group, at each time point throughout the four year period (ranging from 2.3 to 3.3 units, P<0.001). In addition, treatment with tiotropium over the four years was associated with a decrease in mortality risk (risk of on-treatment mortality was reduced by 16%

[‡] Data were missing in this category for 2% of patients

versus control).[§] Tiotropium was associated with a reduction in the risk of exacerbations, related hospitalisations and respiratory failure.^{4,18}

In a secondary analysis of the UPLIFT[®] study, focussing on the subgroup of patients not on other maintenance treatment at the time of randomisation, tiotropium was associated with:

- slower disease progression (as demonstrated by a reduced rate of decline in lung function (FEV₁) and in health status (SGRQ)),
- improvements in lung function¹⁹

In a further pre-specified subgroup analysis of patients with GOLD stage II disease (moderate disease),^{**} tiotropium produced a significant reduction in the rate of decline of postbronchodilator FEV₁, a reduction in the rate of exacerbations, improved health status and was associated with lower all-cause mortality compared with control.²⁰

In addition, a post-hoc analysis of the UPLIFT[®] study showed that tiotropium significantly reduced the number of COPD exacerbations, as well as significantly prolonging the time to the occurrence of the first exacerbation in patients both at high and low risk of exacerbations compared to control.²¹ Furthermore, based on this post-hoc analysis, one year of tiotropium treatment resulted in a favourable shift in the ratio for low risk / high risk for COPD exacerbations, suggesting Spiriva[®] has a stabilising effect on exacerbations.²¹

Safety and tolerability

The results of the study were consistent with the published pooled safety analysis and indicated a reduction in cardiac adverse events associated with tiotropium.^{4,11} The reduced risk of respiratory failure had also been observed in the previous pooled safety analysis of tiotropium, in which the relative risk of respiratory failure in the tiotropium group, as compared with the control group, was 0.59 (95% CI, 0.26 to 1.34).^{4,22} Tiotropium reduced respiratory morbidity (including a decreased risk of respiratory failure) and reduced cardiac morbidity.⁴

Conclusion

The results of the trial over four years did not result in changes in the rate of decline of lung function. However, there were important lung function benefits associated with tiotropium that were maintained during the four years, as well as positive effects on health-related quality of life,

§ In UPLIFT[®], a trial of nearly 6,000 COPD patients, Spiriva[®] 18 µg via HandiHaler[®] reduced risk of on-treatment mortality vs control (placebo). While Spiriva[®] 18 µg via HandiHaler[®] did not alter the rate of decline in lung function, a coprimary study endpoint in the UPLIFT[®] trial, it sustained greater improvements in lung function vs control (placebo). Mortality, a secondary safety endpoint, was evaluated in 3 analyses: 1) on treatment; 2) intention to treat at protocol-defined end of treatment period (Day 1,440); and 3) intention to treat after 30-day follow-up (Day 1,470). A significant reduced risk was seen on-treatment (pre-specified) and extended to the end of treatment period (Day 1,440, post-hoc). In the ITT analysis there was no significant difference in risk of mortality between the treatment arms within the pre-specified 30-day follow-up period (Day 1,470)

** GOLD stage II classification of severity of airflow limitation in COPD (based on postbronchodilator FEV₁); moderate, 50% ≤ FEV₁ < 80% predicted

a reduction in mortality and a reduced risk of exacerbations and exacerbation-related hospitalisation consistent with a relevant effect on the clinical course of COPD.^{4,18}

Results from two different UPLIFT[®] pre-specified analyses provide evidence that treatment with tiotropium as a first line maintenance respiratory treatment decreases disease progression in maintenance treatment naive patients with COPD¹⁹ and demonstrate benefits of treatment with tiotropium in the earlier stages of COPD.²⁰

2. The POET-COPD[®] Study: Assessing exacerbations in COPD

The **P**revention **O**f **E**xacerbations with **T**iotropium in COPD (POET-COPD[®]) study was a head-to-head (one year) study specifically designed to compare the effect of two different classes of long-acting bronchodilators – tiotropium (18 µg once daily via HandiHaler[®]) and salmeterol (50 µg twice daily via pressurised metered-dose inhaler [pMDI]^{††}) – on COPD exacerbations in patients with moderate to very severe COPD.⁷ The POET-COPD[®] study demonstrated that the long-acting anticholinergic Spiriva[®] (tiotropium) was more effective than the long-acting beta₂ agonist salmeterol in reducing the risk of moderate and severe COPD exacerbations.⁷

Rationale

International treatment guidelines such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD), recommend inhaled long-acting bronchodilators as first line maintenance therapy in moderate to very severe COPD as they are proven to improve symptoms and reduce exacerbations. However, guidelines to date do not give a preference for either a long-acting anticholinergic or long-acting beta₂ agonists (LABA).²

The POET-COPD[®] study was the first long-term study specifically designed and powered to investigate whether Spiriva[®] (tiotropium), a once-daily long-acting anticholinergic, is superior to the long-acting beta₂ agonist, salmeterol (as pMDI), in reducing the risk of COPD exacerbations in patients with moderate to very severe COPD.⁷

According to GOLD, prevention of COPD exacerbations is a key goal of COPD treatment.² Exacerbations are associated with substantial personal, medical, societal and economic burden. Frequent COPD exacerbations, also sometimes referred to as COPD lung attacks, are an acute worsening of COPD symptoms and indicate deterioration and progression of the disease. They can occur even in the early stages of COPD (e.g. GOLD Stages I and II)^{‡‡} and may recur throughout the course of the disease.²³

^{††} EU formulation

^{‡‡} Since the start of the POET-COPD[®] study, GOLD has updated its guidelines on the categorisation of COPD patients, now referring to groups A-D, based on assessment of COPD using a combination of a patient's spirometry results, severity of symptoms and history of exacerbations

Study design

The POET-COPD[®] study was a one year, randomised, double-blind, double-dummy, parallel-group trial involving 7,376 patients in 25 countries in 725 centres.⁷ Designed as a head-to-head comparison, COPD patients received either tiotropium (18 µg via HandiHaler[®]) or salmeterol (50 µg twice daily via pMDI).

In this trial, a COPD exacerbation was defined as:⁷

- An increase in, or new onset of, more than one symptom of COPD: cough, sputum, wheezing, breathlessness or chest tightness. At least one symptom had to last at least three days or more and require treatment with systemic glucocorticoids or antibiotics
- If both glucocorticoids and antibiotics were required this defined a moderate exacerbation
- An exacerbation was considered to be severe if hospitalisation was required
- Key patient inclusion criteria were:⁷
 - Age ≥40 years
 - Smoking history ≥10 pack-years
 - Diagnosis of moderate to very severe COPD (GOLD Stages II to IV)
 - Documented history of at least one exacerbation within the previous year requiring treatment with either systemic steroids and/or antibiotics or hospitalisation

All patients in both treatment groups were allowed to continue their other COPD maintenance therapies (except LABAs and anticholinergics), including inhaled corticosteroids (ICS) and methylxanthines. All patients were offered salbutamol as rescue medication.⁷

Study endpoints

The primary endpoint was the time to first COPD exacerbation during the one year treatment period.⁷ Key secondary endpoints included: time to first severe (hospitalised) COPD exacerbation, time to first moderate COPD exacerbation and number of patients with at least one COPD exacerbation, hospitalised COPD exacerbation and time to premature discontinuation of trial medication.²⁴

Results

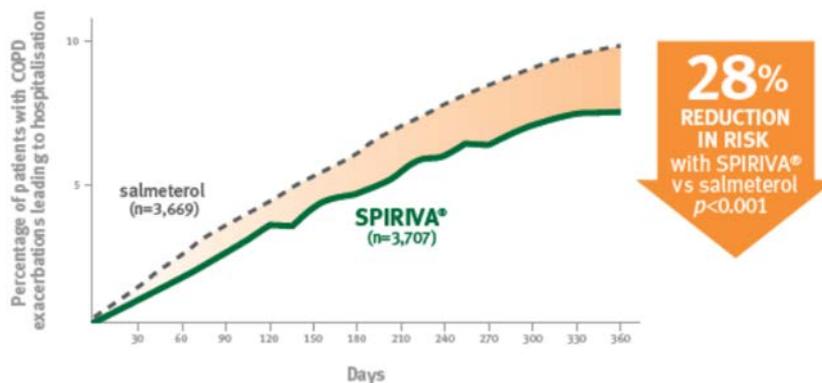
The POET-COPD[®] study results demonstrated that Spiriva[®] was superior to salmeterol in reducing the risk of COPD exacerbations over the course of one year.⁷

- Tiotropium reduced the risk of first severe exacerbations, i.e. exacerbations resulting in hospitalisation, by 28% (p<0.001) versus the long-acting beta₂ agonist salmeterol
- Tiotropium reduced the risk of first moderate exacerbation by 14% (p=0.001) versus salmeterol

- Tiotropium significantly delayed the occurrence of the first exacerbation compared with salmeterol, with a risk reduction of 17% ($p < 0.001$) versus salmeterol
- There were 4,411 exacerbations among 2,691 patients in the study. 44% of the patients with an exacerbation were classified as having moderate COPD (i.e. GOLD Stages I to II) reinforcing the need to prevent or reduce the risk for exacerbations with adequate maintenance therapy early on during the course of the disease

A post-hoc analysis from the POET-COPD[®] study revealed a favourable shift towards a lower risk of exacerbations after one year of Spiriva[®] treatment.²⁵ In addition, data from this study reconfirmed the higher efficacy of Spiriva[®] compared with salmeterol, in reducing the number of COPD exacerbations, as well as prolonging the time to the occurrence of the first exacerbation in patients both at high and low risk of exacerbations.²⁵

Significant reduction in risk of COPD exacerbations leading to hospitalisation with tiotropium compared to a long-acting beta₂ agonist (salmeterol)⁷



In a further pre-specified analysis of the POET-COPD[®] study, focussing on two subgroups of patients with GOLD stage II disease (moderate disease) and those not on other maintenance treatment at the time of randomisation, treatment with tiotropium significantly increased the time to first exacerbation compared to salmeterol.²⁶ In addition, the annual rate of exacerbations was significantly lower with tiotropium in the maintenance naive subgroup compared with salmeterol.²⁶

The POET-COPD[®] study results reinforced that effective long-acting bronchodilator therapy reduces the impact and frequency of COPD exacerbations, and thus may improve outcomes of patients living with COPD.

Safety and tolerability

No unexpected (unanticipated) safety observations were made. The rates of serious adverse events, adverse events leading to treatment discontinuation and fatal adverse events, were similar between both treatments.⁷

Conclusion

Data suggest that, in patients with moderate-to-severe COPD and a history of exacerbations, Tiotropium should be considered first choice over salmeterol as maintenance treatment.⁷

3. The TIOSPIR™ Trial: Safety and performance in Respimat®

Tiotropium **S**afety and **P**erformance **I**n **R**espimat® (TIOSPIR™), a landmark global trial in more than 17,000 patients, was one of the largest COPD trials ever conducted. Participants were recruited between May 2010 and April 2011 and were randomised to treatment in more than 1,200 investigator sites in 50 countries. The trial compared the safety and efficacy of the two available Spiriva® formulations - Spiriva® Respimat® Soft Mist™ Inhaler 2.5 µg (2 puffs, once daily^{§§}) and Spiriva® HandiHaler® 18 µg, once daily. A Spiriva® Respimat® 1.25 µg dose (2 puffs, once daily^{***}) was also included for investigational purposes.

Over the 2 – 3-year duration of the trial, TIOSPIR™ demonstrated that Spiriva® Respimat® 2.5 µg or 1.25 µg has similar safety outcomes and exacerbation efficacy to the well-established profile of Spiriva® HandiHaler® 18 µg in COPD.²⁷

Rationale

Certain meta-analyses of earlier Spiriva® Respimat® data have shown a numerical imbalance (which was not statistically significant) in the number of deaths with Spiriva® Respimat® 2.5 µg (2 puffs, once daily) as compared to Respimat® placebo, particularly in patients with known cardiac disorders.^{28,29} To provide further evidence on the relative safety and efficacy of the two formulations of Spiriva®, Boehringer Ingelheim initiated the TIOSPIR™ trial. TIOSPIR™ was specifically designed to be of an adequate size and duration, to enable analysis of all-cause mortality and time to first COPD exacerbation in a large COPD patient population. The trial had broad inclusion criteria that closely reflect the real-world COPD patient population.³⁰ In addition, the trial results enabled further analysis of specific sub-populations of patients such as those with prior cardiac disorders.

Study design

TIOSPIR™ was an event-driven trial that ran for three years. This large-scale, randomised, double-blind, double-dummy, parallel-group, trial was designed to continue until a pre-defined number of deaths was reached based on all-cause mortality rates observed in previous trials. The three treatment arms were:

^{§§} This is the marketed dose referred to in the *NEJM* TIOSPIR™ publication as tiotropium Respimat® 5 µg

^{***} This is an investigational dose that is referred to in the *NEJM* TIOSPIR™ publication as tiotropium Respimat® 2.5 µg

- Spiriva[®] Respimat[®] 2.5 µg (2 puffs, once daily)
- Spiriva[®] Respimat[®] 1.25 µg (2 puffs, once daily)
- Spiriva[®] HandiHaler[®] 18 µg (once daily)

The Respimat[®] 1.25 µg (2 puffs, once daily) arm was included because it is being investigated in clinical trials in a fixed-dose combination with a long-acting beta₂-agonist.³⁰ A placebo arm was not included because it would be impractical to maintain high levels of adherence and follow up without effective symptom-controlling therapy in such a large population.²⁷

In order to closely reflect the real-world COPD patient population, a broad spectrum of COPD patients – all COPD disease assessment categories (GOLD^{†††} groups A to D) – were included in TIOSPIR[™]. The trial enrolled participants aged ≥40 years with a clinical diagnosis of COPD, ≥10 pack-years smoking history, post-bronchodilator forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio ≤0.70, and FEV₁ ≤70% predicted. Participants with concomitant cardiac disease were included unless they had myocardial infarction within six months, were hospitalised for Class III/IV heart failure, or had unstable or life-threatening arrhythmia requiring new treatment within 12 months. All COPD medications except other inhaled anticholinergics were allowed.³⁰

Study endpoints

There were two primary endpoints: safety measured by non-inferior in terms of all-cause mortality and efficacy as measured by time to first COPD exacerbation. COPD exacerbations were defined as ≥2 worsening respiratory symptoms (dyspnoea, cough, sputum, chest tightness, or wheezing) of ≥3 days' duration requiring specified treatment changes. Mild exacerbations required new prescription of a maintenance bronchodilator only; moderate exacerbations, antibiotics, or systemic corticosteroids or both; and severe exacerbations required hospitalisation.²⁷

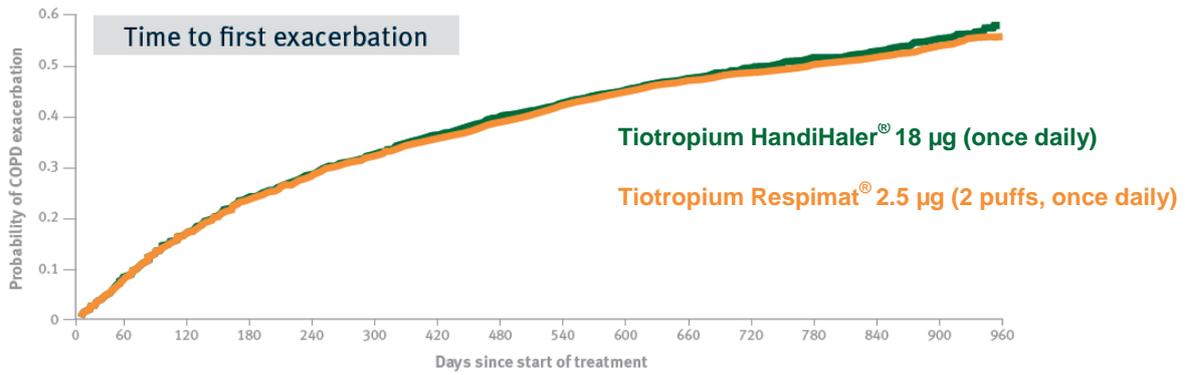
Secondary outcome measures included:²⁷

- Number of COPD exacerbations
- Time to first moderate or severe exacerbation
- Time to and number of severe exacerbations
- Time to first major adverse cardiovascular (CV) event

^{†††} The GOLD report (international guidelines developed by the Global Initiative for Obstructive Lung Disease) classifies COPD patients into groups A-D, based on a combination of spirometry results, severity of symptoms, and risk of exacerbations

Efficacy results

Spiriva® Respimat® 2.5 µg (2 puffs, once daily) and Spiriva® HandiHaler® 18 µg (once daily) demonstrated comparable COPD exacerbation efficacy.²⁷



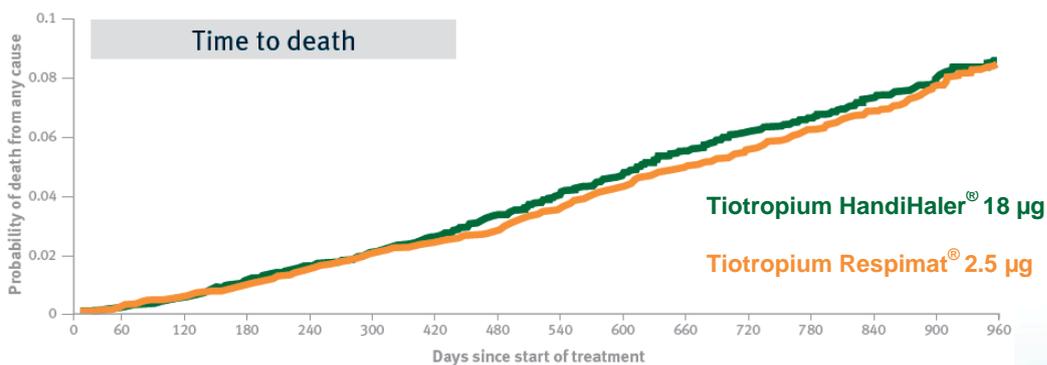
- Spiriva® Respimat® 2.5 µg (2 puffs, once daily) and Spiriva® HandiHaler® 18 µg (once daily) showed comparable results for median time to COPD exacerbation (the difference between the two treatment groups was not statistically significant).²⁷



- Spiriva® Respimat® 2.5 µg (2 puffs, once daily) and Spiriva® HandiHaler® 18 µg (once daily) showed comparable results for rate of COPD exacerbations and rate of COPD exacerbations associated with hospitalisation²⁷

Safety results

Spiriva® Respimat® and Spiriva® HandiHaler® 18 µg showed similar impact on survival as measured by all-cause mortality²⁷



- In patients with a history of cardiac arrhythmia, Spiriva® Respimat® 2.5 µg (2 puffs, once daily) and Spiriva® HandiHaler® 18 µg (once daily) showed similar impact on survival as measured by all-cause mortality²⁷

Adverse events

In the TIOSPIR™ trial, the incidence of adverse events was similar between treatment groups²⁷

- Serious adverse events were reported in 33% of participants. As expected, the highest rates of serious adverse events were lung disorders for all three treatment groups (17.8%, 16.8%, and 17.0%, for Respimat® 1.25 µg, 2.5 µg, and HandiHaler®, respectively)²⁷
- Overall incidence of major adverse CV events was 3.9%, 3.9%, and 3.6% in the Respimat® 1.25 µg, 2.5 µg, and HandiHaler® 18 µg treatment groups, respectively²⁷

Conclusion

- In TIOSPIR™, time to first COPD exacerbation was comparable for both Spiriva® available formulations Respimat® 2.5 µg (2 puffs, once daily) and HandiHaler® 18 µg (once daily)²⁷
- Building on the survival benefit of Spiriva® HandiHaler® 18 µg versus control in the milestone trial UPLIFT®^{###}, the TIOSPIR™ trial showed a similar impact on survival between Spiriva® Respimat® 2.5 µg (2 puffs, once daily) and Spiriva® HandiHaler® 18 µg^{4,27}
- TIOSPIR™ reinforces the safety and efficacy of Spiriva® in COPD patients, with or without a history of cardiac arrhythmias^{4,27,31}

^{###} In UPLIFT®, a trial of nearly 6,000 COPD patients, Spiriva® 18 µg via HandiHaler® reduced risk of on-treatment mortality vs control (placebo). While Spiriva® 18 µg via HandiHaler® did not alter the rate of decline in lung function, a coprimary study endpoint in the UPLIFT® trial, it sustained greater improvements in lung function vs control (placebo). Mortality, a secondary safety endpoint, was evaluated in 3 analyses: 1) on treatment; 2) intention to treat at protocol-defined end of treatment period (Day 1,440); and 3) intention to treat after 30-day follow-up (Day 1,470). A significant reduced risk was seen on-treatment (pre-specified) and extended to the end of treatment period (Day 1,440, post-hoc). In the ITT analysis there was no significant difference in risk of mortality between the treatment arms within the pre-specified 30-day follow-up period (Day 1,470)

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