Adv Ther (2016) 33:786–793
DOI 10.1007/s12325-016-0322-9

ORIGINAL RESEARCH

Tiotropium Respimat® Versus HandiHaler®: Comparison of Bronchodilator Efficacy of Various Doses in Clinical Trials

Peter M. A. Calverley · Michael Könen-Bergmann · Frank Richard · Susan Bell · Jens M. Hohlfeld

Received: January 25, 2016 / Published online: March 28, 2016
© The Author(s) 2016. This article is published with open access at Springerlink.com

ABSTRACT

Introduction: The long-acting muscarinic antagonist tiotropium bromide is approved in many countries as maintenance therapy for chronic obstructive pulmonary disease (COPD). Tiotropium is available as a dry-powder formulation delivered via HandiHaler® (18 μg once daily) and is now also approved as an aqueous solution delivered via the Respimat® Soft Mist™ Inhaler (5 μg once daily, 2 puffs of 2.5 μg). Several studies have compared the efficacy of tiotropium HandiHaler (18 μg once daily) with different doses of Respimat. We aimed to compare available bronchodilator efficacy data of once-daily Respimat 1.25, 2.5, 5, 10, 20 μg, and HandiHaler 18 μg to investigate which dose of tiotropium delivered by Respimat is the closest match to tiotropium HandiHaler.

Methods: Evaluation of six clinical trials (duration from 3 weeks to 2–3 years) that included lung function measures (trough forced expiratory volume in 1 s and trough forced vital capacity) as key outcomes.

Results: In the six trials, bronchodilator efficacy of Respimat 5 μg and HandiHaler 18 μg was similar; however, reduced bronchodilator efficacy was observed with lower doses of Respimat (1.25 and 2.5 μg).

Conclusion: These findings support the use of the marketed once-daily dose of Respimat 5 μg for the maintenance treatment of patients with COPD.

Funding: Boehringer Ingelheim.

Enhanced content To view enhanced content for this article go to http://www.medengine.com/Redeem/E984F060256965B2.

P. M. A. Calverley (✉)
Pulmonary and Rehabilitation Medicine, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK
e-mail: pmacal@liverpool.ac.uk

M. Könen-Bergmann
Clinical Development + Medical Affairs, Boehringer Ingelheim, Ingelheim, Germany

F. Richard
Medicine TA Respiratory Diseases, Boehringer Ingelheim, Ingelheim, Germany

S. Bell
Statistics, Boehringer Ingelheim, Bracknell, UK

J. M. Hohlfeld
Clinical Airway Research, Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM), Hannover, Germany

Keywords: Bronchodilator; Chronic obstructive pulmonary disease (COPD); Dose–response; Efficacy; Long-acting muscarinic antagonist; Lung function; Once-daily; Pulmonology; Respimat®; Spirometry; Tiotropium

INTRODUCTION

The long-acting anticholinergic, or muscarinic antagonist, tiotropium bromide (SPIRIVA®, Boehringer Ingelheim, Ingelheim am Rhein, Germany), improves lung function, quality of life, symptoms (dyspnea), and exercise endurance, as well as reducing exacerbations in chronic obstructive pulmonary disease (COPD) [1–4]. Tiotropium is approved as a dry-powder formulation delivered via HandiHaler® (Boehringer Ingelheim, Ingelheim, Germany; 18 μg once daily) [5] and as an aqueous solution delivered via the Respimat® Soft Mist™ Inhaler (Boehringer Ingelheim; 5 μg once daily, 2 puffs of 2.5 μg) [6] in many countries. Tiotropium Respimat 5 μg and HandiHaler 18 μg have similar exacerbation and bronchodilator efficacy, safety, and pharmacokinetic (PK) profiles [7–11]. Several studies have compared the efficacy of tiotropium HandiHaler (18 μg) with different doses of Respimat [7–13]; however, to date a comprehensive review of the published dataset has not yet been undertaken.

This report summarizes the spirometric dose–response relationships of once-daily tiotropium given by soft mist inhalation (1.25, 2.5, 5, 10, and 20 μg) and as dry powder (18 μg), across six studies; each of these assessed trough forced expiratory volume in 1 s (FEV_1; defined as the difference between pre-dose FEV_1 on day 1 [baseline] and the pre-dose FEV_1 at the end of the treatment period, i.e., before the last dose) and trough forced vital capacity (FVC) as efficacy end points [7–13]. The trial durations ranged from 3 weeks [10] to 2–3 years [7–13].

METHODS

All dose–response studies of Respimat conducted in comparison with HandiHaler were chosen for inclusion in this analysis. Detailed methods for the six studies included in this report have been published previously [7–13].

Summary of Study Design and Statistical Analyses

Study 1 [7]

In this multicenter, randomized, double-blind within device, parallel-group, placebo-controlled, 3-week dose-ranging study, 202 patients with COPD were allocated to Respimat 1.25, 2.5, 5, 10, or 20 μg, HandiHaler 18 μg, or placebo (ClinicalTrials.gov identifier: NCT02175342) [7]. The primary end point was the change from baseline in trough FEV_1 on day 21. FEV_1 and FVC measurements were taken at baseline (day 0) and on days 7, 14, and 21.

The primary FEV_1 and secondary FVC end points were evaluated by an analysis of covariance (ANCOVA), with baseline data as a covariate and treatment effect as a factor. This trial was not designed and powered specifically to assess non-inferiority; it aimed to test whether each dose of Respimat was more effective than placebo and to detect a 150-mL difference in mean FEV_1 response between Respimat and placebo.

Studies 2 and 3 [10]

In a prespecified, pooled analysis of two identical, double-blind, double-dummy, 4-week crossover studies (ClinicalTrials.gov

identifiers: NCT00239447 and NCT00281567), 207 patients with COPD were randomized to Respimat 5 or 10 μg, HandiHaler 18 μg, or placebo [10]. The primary end point was trough FEV_1 response (change from baseline to the end of each 4-week treatment period [day 29]); secondary end points included trough FVC. Spirometry assessments were conducted at the beginning (until 3 h post dosing) and end of each treatment period.

An ANCOVA with terms for center, patients within center, period, period baseline, and treatment was performed for FEV_1 and FVC. A stepwise procedure first tested Respimat 5 and 10 μg for superiority over placebo, and then for non-inferiority compared with HandiHaler 18 μg (95% confidence interval [CI] compared with non-inferiority delta of 50 mL). Missing trough FEV_1 values at the end of a treatment period were imputed by the lowest recorded value on the first test day (even if baseline).

Study 4 [9]

This randomized, double-blind, double-dummy, two-way, 4-week crossover study (ClinicalTrials.gov identifier: NCT00292448) of Respimat 5 μg and HandiHaler 18 μg was conducted in Japanese patients with COPD ($n = 184$; $n = 157$ received at least one dose of study medication) [9]. The primary end point was trough FEV_1 response from baseline to day 29; trough FVC response after 4 weeks was also assessed. Spirometry testing took place at the start (day 1) and end (day 29) of each treatment period.

Using an ANCOVA with terms for period, treatment and patient as fixed effects, and baseline FEV_1 as a covariate, Respimat 5 μg was tested for non-inferiority to HandiHaler 18 μg (one-sided test, lower bound of 95% CI compared with non-inferiority delta of −50 mL). Trough FVC response was analyzed in the same way.

Study 5 [12]

The TIOtropium Safety and Performance In Respimat® [TIOSPIR®] study (ClinicalTrials.gov identifier: NCT01126437) was a randomized, double-blind, double-dummy, parallel-group, event-driven trial of 2–3 years' duration in patients with COPD, which included a substudy of 1370 patients from centers experienced in performing spirometry [12]. Trough FEV_1 was assessed by a predefined test of non-inferiority of Respimat 5 and 2.5 μg versus HandiHaler 18 μg (averaged over weeks 24–120; non-inferiority margin 50 mL). Trough FEV_1 and FVC were measured at week 24 and every 24 weeks thereafter. For the majority of patients, spirometry measurements were available for weeks 24–120 [11–13].

Spirometry data from weeks 24 to 120 were analyzed using a restricted maximum likelihood (REML)-based repeated measures approach, including the fixed categorical effects of treatment, investigative site, visit, and treatment by visit interaction; the continuous fixed covariates of baseline and baseline by visit interaction, and a random term for patient. Missing FEV_1 and FVC values due to worsening of COPD were imputed using worst observation carried forward.

Hierarchical testing of trough FEV_1 was used first to evaluate the treatment effect of Respimat 5 μg versus HandiHaler 18 μg, specifically the 95% CIs compared with the non-inferiority delta of 50 mL. If successful, the treatment effect of Respimat 2.5 μg versus HandiHaler 18 μg was tested in the same way.

Study 6 [8]

This multicenter, placebo-controlled, randomized, double-blind (within Respimat

groups), five-way crossover trial (ClinicalTrials.gov identifier: NCT01222533) with 4-week treatment periods compared tiotropium Respimat 1.25, 2.5, and 5 μg with open-label tiotropium HandiHaler 18 μg and placebo ($n = 154$) [8]. The primary end points were PK assessments; secondary end points included trough FEV_1 and FVC.

The trough FEV_1 or FVC value was assigned to zero time and defined as the measurement before administration of the last once-daily dose of study drug at the end of each 4-week treatment period. The data were analyzed using an REML-based repeated-measures approach adjusted for the fixed, categorical effects of sequence, period, and treatment, and the random effect of patient within sequence.

For each trial, forest plots of the 95% CIs for mean trough FEV_1 and FVC responses were produced to summarize and compare the bronchodilator efficacy of tiotropium Respimat doses with HandiHaler 18 μg.

Compliance with Ethics Guidelines

The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Study 1 [7]

Compared with HandiHaler 18 μg, mean adjusted trough FEV_1 response on day 21 was lower for Respimat 1.25 μg (difference −130 mL; 95% CI −251 to −9 mL; $P = 0.035$) and Respimat 2.5 μg (difference −182 mL; 95% CI −302 to −63 mL; $P = 0.003$). Mean trough FEV_1 was numerically lower than HandiHaler 18 μg for Respimat 5 μg (difference −83 mL; 95% CI −204 to 38 mL), Respimat 10 μg (difference −97 mL; 95% CI −217 to 22 mL), and Respimat 20 μg (difference −86 mL; 95% CI −207 to 34 mL; Fig. 1). Mean adjusted trough FVC on day 21 was lower than HandiHaler 18 μg for Respimat 2.5 μg (difference −235 mL; 95% CI −436 to –35 mL; $P = 0.02$), and numerically lower for Respimat 1.25 μg (difference −132 mL; 95% CI −334 to 70 mL), Respimat 5 μg (difference −58 mL; 95% CI −260 to 144 mL), Respimat 10 μg (difference −130 mL; 95% CI −330 to 71 mL), and Respimat 20 μg (difference −77 mL; 95% CI −280 to 126 mL; Fig. 2).

Studies 2 and 3 [10]

Both Respimat 5 and 10 μg were superior to placebo ($P < 0.0001$) and non-inferior to HandiHaler 18 μg (Respimat 5 μg: $P \leq 0.0001$; Respimat 10 μg: $P < 0.0001$) for the primary end point of trough FEV_1 response at day 29. Compared with HandiHaler 18 μg, the adjusted mean trough FEV_1 response on day 29 was higher for Respimat 5 μg (difference 29 mL; 95% CI 4 to 55 mL; $P < 0.03$) and Respimat 10 μg (difference 31 mL; 95% CI 5 to 56 mL; $P = 0.02$; Fig. 1). Mean adjusted trough FVC response on day 29 was numerically higher for Respimat 5 μg compared with HandiHaler 18 μg (difference 22 mL; 95% CI −36 to 80 mL) and Respimat 10 μg compared with HandiHaler 18 μg (difference 53 mL; 95% CI −5 to 112 mL; Fig. 2), but these differences did not reach statistical significance.

Study 4 [9]

Mean adjusted trough FEV_1 response on day 29 was similar for Respimat 5 μg and HandiHaler

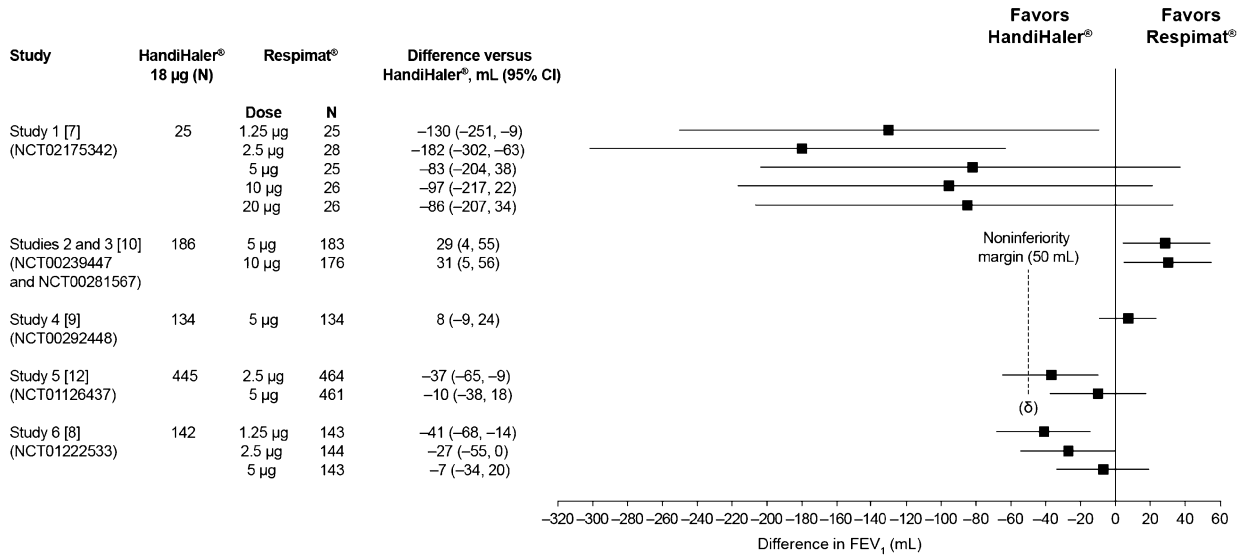

Fig. 1 Differences in adjusted mean trough FEV_1 response for tiotropium Respimat® 5 µg compared with tiotropium HandiHaler® 18 µg. *CI* confidence interval, *FEV_1* forced expiratory volume in 1 s

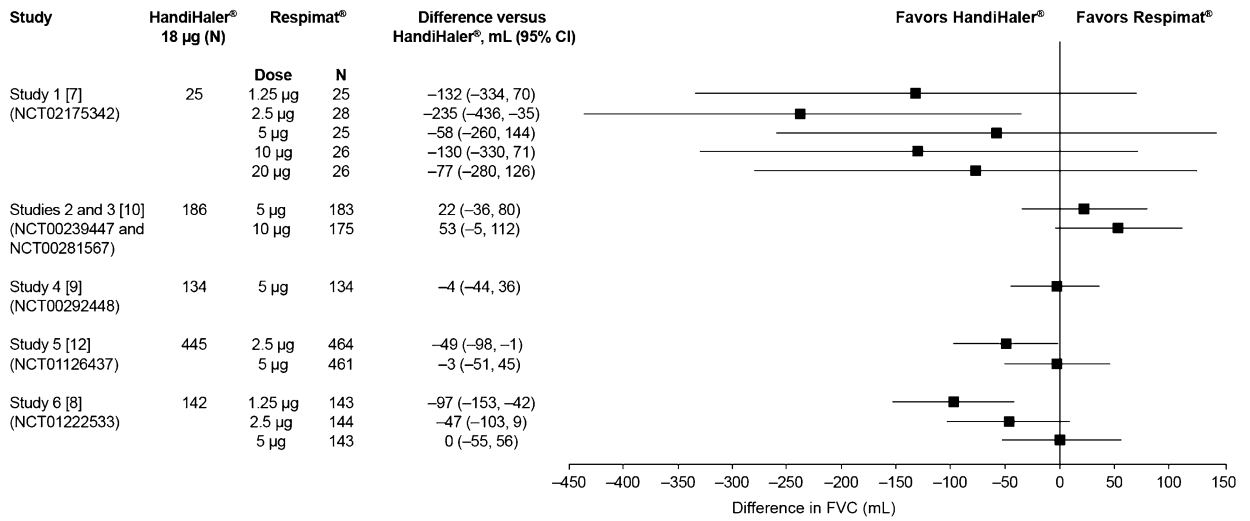

Fig. 2 Differences in adjusted mean trough FVC response for tiotropium Respimat® 5 µg compared with tiotropium HandiHaler® 18 µg. *CI* confidence interval, *FVC* forced vital capacity

18 µg (difference versus HandiHaler: 8 mL; 95% CI −9 to 24 mL; Fig. 1). Non-inferiority was demonstrated with a lower confidence limit >50 mL ($P < 0.001$). The adjusted mean trough FVC value on day 29 was also similar for Respimat 5 µg and HandiHaler 18 µg (difference −4 mL; 95% CI −44 to 36 mL; $P = 0.84$; Fig. 2).

Study 5 [12]

The adjusted mean trough (pre-dose) FEV_1 (averaged over weeks 24–120) for Respimat 5 µg was comparable to HandiHaler 18 µg (difference versus HandiHaler: −10 mL; 95% CI −38 to 18 mL), but was lower than

HandiHaler 18 μg for Respimat 2.5 μg (difference versus HandiHaler: −37 mL; 95% CI −65 to −9 mL; Fig. 1) [13]. Hierarchical testing showed that Respimat 5 μg but not Respimat 2.5 μg was non-inferior to HandiHaler 18 μg for trough FEV_1. With regard to the adjusted mean trough FVC (averaged over weeks 24–120), Respimat 5 μg was comparable to HandiHaler 18 μg (difference versus HandiHaler: −3 mL; 95% CI −51 to 45 mL), but was lower than HandiHaler 18 μg for Respimat 2.5 μg (difference versus HandiHaler: −49 mL; 95% CI −98 to −1 mL; Fig. 2) [13].

Study 6 [8]

Trough FEV_1 on day 28 was comparable to HandiHaler 18 μg for Respimat 5 μg (difference versus HandiHaler 18 μg: −7 mL; 95% CI −34 to 20 mL), but was lower than HandiHaler 18 μg for Respimat 2.5 μg (difference −27 mL; 95% CI −55 to 0 mL) and Respimat 1.25 μg (difference −41 mL; 95% CI −68 to −14 mL; Fig. 1). Trough FVC on day 28 was comparable to HandiHaler 18 μg for Respimat 5 μg (difference 0 mL; 95% CI −55 to 56 mL) and numerically lower for Respimat 2.5 μg (difference −47 mL; 95% CI −103 to 9 mL) and was significantly lower than HandiHaler 18 μg for Respimat 1.25 μg (difference −97 mL; 95% CI −153 to −42 mL; Fig. 2).

DISCUSSION

Tiotropium dry powder (HandiHaler) and tiotropium solution (Respimat) are different formulations of tiotropium bromide. This report compares the bronchodilator efficacy of once-daily Respimat 1.25, 2.5, 5, 10, 20 μg, and HandiHaler 18 μg from six clinical trials that assessed lung function measures as key outcomes supporting Respimat 5 μg as the closest match for HandiHaler 18 μg.

In TIOSPIR, Respimat 5 μg was non-inferior to HandiHaler 18 μg for FEV_1- and FVC-based end points, while the bronchodilator efficacy of Respimat 2.5 μg was consistently inferior to HandiHaler 18 μg [13]. The non-inferiority of Respimat 5 μg and HandiHaler 18 μg for the primary end point of trough FEV_1 response was demonstrated on day 29 in the studies reported by van Noord et al. [10] and Ichinose et al. [9], and was supported by day 28 results from the Hohlfeld et al. study [8]. In another Respimat dose-ranging study (Caillaud et al. [7]), Respimat 5 μg was the most comparable dose to HandiHaler 18 μg in terms of trough FEV_1 and adjusted trough FVC outcomes at day 21. The effects of the Respimat 1.25 and 2.5 μg doses on the adjusted trough FEV_1 were lower than observed with HandiHaler 18 μg. Of note, the mean responses to Respimat in this study [7] were lower than observed in the other studies included in this analysis. Possible explanations for these results are the differences in study design characteristics in this study [7], as compared to other trials reviewed in this article, including a smaller sample size, a lack of a double-dummy design and shorter treatment duration.

A limitation of the current analysis is that it compared data from studies that had some differences in their design and patient demographics. The TIOSPIR sub-study was powered to demonstrate non-inferiority testing for Respimat 2.5 and 5 μg versus HandiHaler 18 μg for trough (pre-dose) FEV_1 but not for trough FVC [13]. The studies reported by van Noord et al. [10], Ichinose et al. [9], and Caillaud et al. [7] used an ANCOVA (with varying adjustments) for the assessment of lung function end points, whereas the Hohlfeld et al. [8] study used an REML-based

repeated-measures approach. Furthermore, the TIOSPIR [11–13] and the Ichinose et al. [9] studies did not have a placebo arm; instead, treatment differences were investigated between patients who were randomized to HandiHaler 18 μg, Respimat 2.5 and/or 5 μg. The study by Caillaud et al. [7] only enrolled a small sample of 25–28 patients per dose and, like the study by Hohlfeld et al. [8], was not blinded with double dummy; this needs to be taken into account when interpreting these results. The lung function response to HandiHaler 18 μg in the study by Caillaud et al. [7] was relatively high compared with the other trials. The timing of the pulmonary function tests also differed between studies: Caillaud et al. [7] assessed FEV_1 and FVC responses earlier at 3 weeks (in contrast to 4 weeks for the studies reported by van Noord et al. [10], Ichinose et al. [9], and Hohlfeld et al. [8]; in TIOSPIR [11–13]), pulmonary function was evaluated pre-dose (24 h after dosing the previous day), at baseline, and every 24 weeks (for the trial duration). Regarding the study populations, patients in the studies by van Noord et al. [10] had pre-bronchodilator FEV_1 <60% of predicted (compared with post-bronchodilator FEV_1 <80% predicted in the study by Hohlfeld et al. [8], FEV_1 <70% or <80% of predicted in TIOSPIR [11–13], FEV_1 ≤70% predicted in the study by Ichinose et al. [9], and FEV_1 <65% of predicted in the study by Caillaud et al. [7]). However, the post-bronchodilator FEV_1/FVC ratio was <70% in all six studies [7–13].

CONCLUSIONS

In conclusion, the results from six tiotropium trials in COPD demonstrated a similar bronchodilator efficacy of once-daily Respimat 5 μg compared with HandiHaler 18 μg, but reduced bronchodilator efficacy with lower doses (Respimat 1.25 and 2.5 μg). This informs the medical community of the dose–response studies conducted with Respimat, and supports the use of the marketed once-daily dose of Respimat 5 μg for the maintenance treatment of patients with COPD.

ACKNOWLEDGMENTS

All studies reported here were funded by Boehringer Ingelheim. The article processing charges and open access fee for this publication were funded by Boehringer Ingelheim. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. Scientific writing and editorial support was provided by Godfrey Lisk at PAREXEL and funded by Boehringer Ingelheim.

Disclosures. Peter M.A. Calverley received honoraria for advising Boehringer Ingelheim on clinical trials and has served on the Boehringer Ingelheim Advisory Board for TIOSPIR®. Michael Könen-Bergmann is an employee of Boehringer Ingelheim. Frank Richard was an employee of Boehringer Ingelheim at the time of writing this manuscript, but he is currently an employee of Sandoz/Hexal AG. Susan Bell is an employee of Boehringer Ingelheim. Jens M. Hohlfeld received honoraria for advising Boehringer Ingelheim on clinical trials and has served on the Boehringer Ingelheim Advisory Board for Early Clinical Development.

Compliance with Ethics Guidelines. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

Open Access. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

REFERENCES

1. Bateman ED, Tashkin D, Siafakas N, et al. A one-year trial of tiotropium Respimat plus usual therapy in COPD patients. Respir Med. 2010;104(10):1460–72.

2. Cooper CB, Celli BR, Jardim JR, et al. Treadmill endurance during 2-year treatment with tiotropium in patients with COPD: a randomized trial. Chest. 2013;144(2):490–7.

3. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359(15):1543–54.

4. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011;364(12):1093–103.

5. Boehringer Ingelheim. Summary of product characteristics (SPC): Spiriva 18 microgram inhalation powder, hard capsule. EMC. Available from: http://www.medicines.org.uk/emc/medicine/10039/SPC/Spiriva+18+microgram+inhalation+powder%2c+hard+capsule/. Last accessed April 16, 2015.

6. Boehringer Ingelheim. Summary of product characteristics (SPC): Spiriva Respimat 2.5 microgram, inhalation solution. EMC. Available from: http://www.medicines.org.uk/emc/medicine/20134/SPC. Last accessed April 16, 2015.

7. Caillaud D, Le Merre C, Martinat Y, Aguilaniu B, Pavia D. A dose-ranging study of tiotropium delivered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients. Int J Chron Obstruct Pulmon Dis. 2007;2(4):559–65.

8. Hohlfeld JM, Sharma A, van Noord JA, et al. Pharmacokinetics and pharmacodynamics of tiotropium solution and tiotropium powder in chronic obstructive pulmonary disease. J Clin Pharmacol. 2014;54(4):405–14.

9. Ichinose M, Fujimoto T, Fukuchi Y. Tiotropium 5 μg via Respimat and 18 μg via HandiHaler; efficacy and safety in Japanese COPD patients. Respir Med. 2010;104(2):228–36.

10. van Noord JA, Cornelissen PJ, Aumann JL, Platz J, Mueller A, Fogarty C. The efficacy of tiotropium administered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients. Respir Med. 2009;103(1):22–9.

11. Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med. 2013;369(16):1491–501.

12. Wise RA, Anzueto A, Calverley P, et al. The Tiotropium Safety and Performance in Respimat Trial (TIOSPIR), a large scale, randomized, controlled, parallel-group trial-design and rationale. Respir Res. 2013;14:40.

13. Anzueto A, Wise R, Calverley P, et al. The Tiotropium Safety and Performance in Respimat® (TIOSPIR®) Trial: spirometry outcomes. Respir Res. 2015;16:107.