

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

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## Abbreviations

*CI* confidence interval

*COPD* chronic obstructive pulmonary disease

*FEV<sub>1</sub>* forced expiratory volume in 1 second

*FVC* forced vital capacity

*PK* pharmacokinetic

*TIOSPIR*® TIOtropium Safety and Performance In Respimat®

## Introduction

- The long-acting anticholinergic, or muscarinic antagonist, tiotropium bromide (SPIRIVA®) provides significant clinical benefits for maintenance treatment of COPD, including reduction of exacerbations [1-4]
- Tiotropium is available in two formulations:
  - Dry-powder formulation: HandiHaler® (18 µg once daily)
  - Aqueous solution: Respimat® Soft Mist™ Inhaler (5 µg once daily)
- Existing studies have compared the efficacy of HandiHaler® with different doses of Respimat®, but a comprehensive review is lacking
- This review summarizes the spirometric dose-response relationship for tiotropium administered via Respimat® (1.25, 2.5, 5, 10 or 20 µg) or via HandiHaler® 18 µg

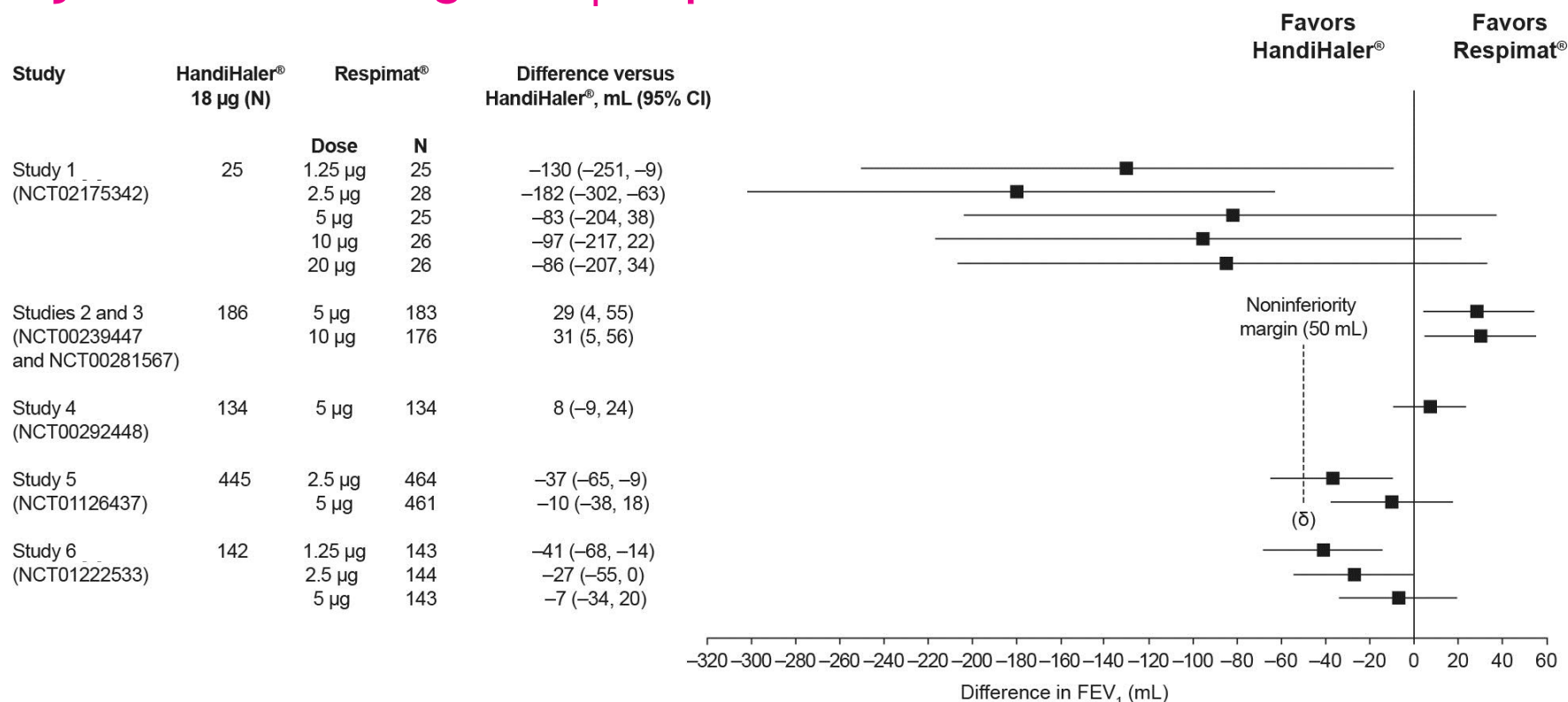
1. Bateman ED, Tashkin D, Siafakas N, et al. *Respir Med*. 2010;104(10):1460-72; 2. Cooper CB, Celli BR, Jardim JR, et al. *Chest*. 2013;144(2):490-7; 3. Tashkin DP, Celli B, Senn S, et al. *N Engl J Med*. 2008;359(15):1543-54; 4. Vogelmeier C, Hederer B, Glaab T, et al. *N Engl J Med*. 2011;364(12):1093-103.

## Summary of Study Designs

- All dose-response studies of Respimat<sup>®</sup> conducted in comparison with HandiHaler<sup>®</sup> were included in this analysis

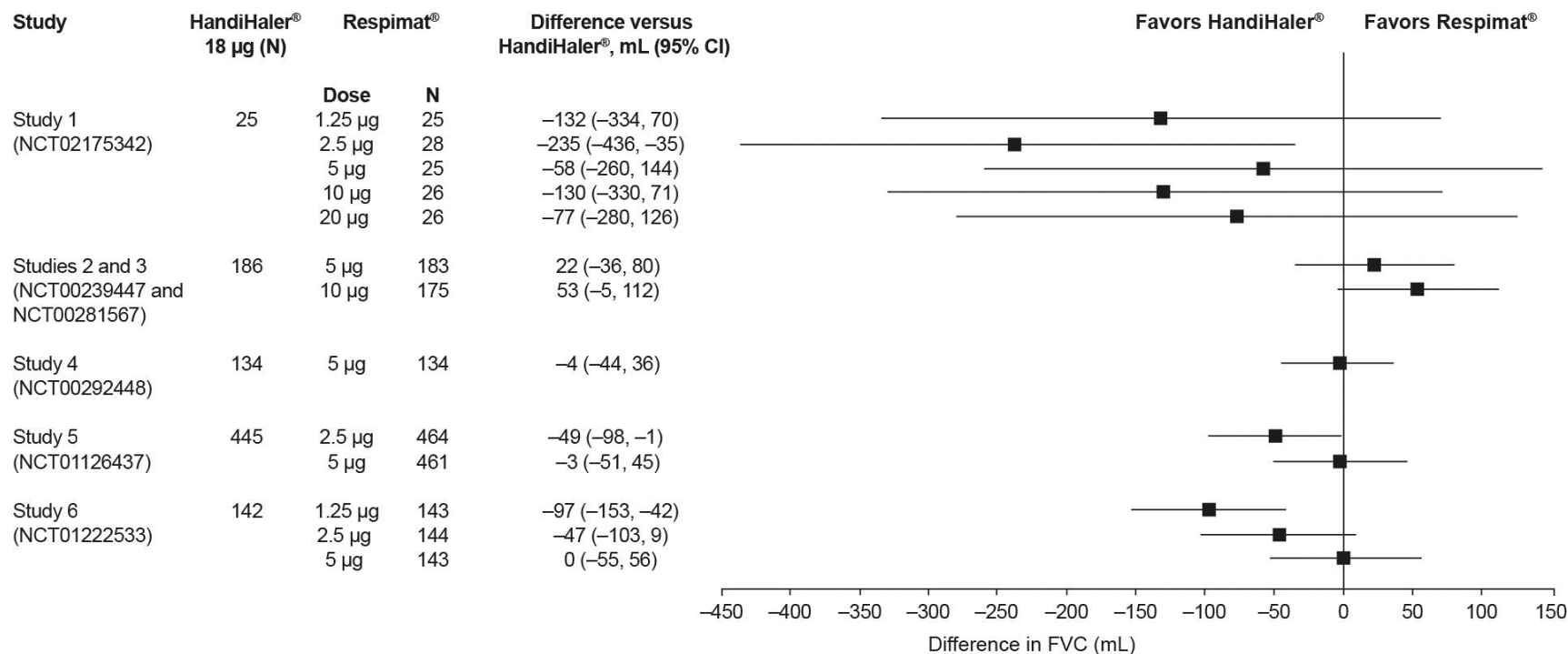
Study	Study design	Treatment groups and size	End points (1°: primary; 2°: secondary)
Study 1: NCT02175342	Multicenter, randomized, double-blind within device, parallel-group, placebo-controlled, 3-week dose-ranging study	Respimat 1.25, 2.5, 5, 10, or 20 µg; HandiHaler 18 µg; or placebo: N = 202	1°: Change from baseline in trough FEV <sub>1</sub> on day 21 2°: FVC, as above
Study 2 and 3: NCT00239447 & NCT00281567	Prespecified, pooled analysis of two identical, double-blind, double-dummy, 4-week crossover studies	Respimat 5 or 10 µg, HandiHaler 18 µg, or placebo: N = 207	1°: Trough FEV <sub>1</sub> response (change from baseline to the end of each 4-week treatment period [day 29]) 2°: Trough FVC, as above
Study 4: NCT00292448	Randomized, double-blind, double-dummy, two-way, 4-week crossover study	Respimat 5 µg and HandiHaler 18 µg: N = 157	1°: Trough FEV <sub>1</sub> response from baseline to day 29 2°: Trough FVC, as above
Study 5: NCT01126437	Substudy of a randomized, double-blind, double-dummy, parallel-group, event-driven trial of 2–3 years' duration in patients with COPD	Respimat 5 and 2.5 µg versus HandiHaler 18 µg: N = 1370	Trough FEV <sub>1</sub> and FVC from weeks 24–120
Study 6: NCT01222533	Multicenter, placebo-controlled, randomized, double-blind (within Respimat groups), five-way crossover trial with 4-week treatment periods	Respimat 1.25, 2.5, and 5 µg with HandiHaler 18 µg and placebo: N = 154	1°: PK assessments 2°: Trough FEV <sub>1</sub> and FVC.

## Respimat® 5 µg was noninferior to HandiHaler® 18 µg for differences in adjusted mean trough FEV<sub>1</sub> response



Note: the mean responses to Respimat® in Study 1 were lower than observed in the other studies included in this analysis. Possible explanations for these results are differences in study design, including a smaller sample size, the lack of a double-dummy design, and the timing of the pulmonary function test (assessed earlier at 3 weeks vs. 4 weeks in other studies). In Studies 2-5, noninferiority of Respimat® vs HandiHaler® was evaluated using 95% CI compared with a noninferiority delta of 50 mL.

## Respimat® 5 µg was noninferior to HandiHaler® 18 µg for differences in adjusted mean trough FVC response



Note: the mean responses to Respimat® in Study 1 were lower than observed in the other studies included in this analysis. Possible explanations for these results are differences in study design, including a smaller sample size, the lack of a double-dummy design, and the timing of the pulmonary function test (assessed earlier at 3 weeks vs. 4 weeks in other studies).

## Conclusions

- The results from the six tiotropium trials demonstrated a similar bronchodilator efficacy for Respimat® 5 µg and HandiHaler® 18 µg
- Reduced bronchodilator efficacy was observed with lower doses of Respimat® (1.25 and 2.5 µg)
- These findings support the use of the marketed once-daily dose of Respimat® 5 µg (2 puffs of 2.5 µg) for the maintenance treatment of patients with COPD

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### 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.

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