

Comparative Efficacy of Once-Daily Umeclidinium/Vilanterol and Tiotropium/Olodaterol in Symptomatic Chronic Obstructive Pulmonary Disease: A Randomized Study

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Abbreviations

- CAT COPD assessment test
- CFB change from baseline
- CI confidence interval
- COPD chronic obstructive pulmonary disease
- DPI dry powder inhaler
- E-RS_{COPD} evaluating respiratory symptoms - COPD
- FEV₁ forced expiratory volume in 1 second
- FVC forced vital capacity
- IC inspiratory capacity
- IRB institutional review board
- ITT intent-to-treat
- LABA long-acting β_2 -agonist
- LAMA long-acting muscarinic antagonist
- NI non-inferiority
- OLO olodaterol
- OR odds ratio
- LS least squares
- PP per protocol
- SE standard error
- TIO tiotropium
- UMEC umeclidinium
- VI vilanterol

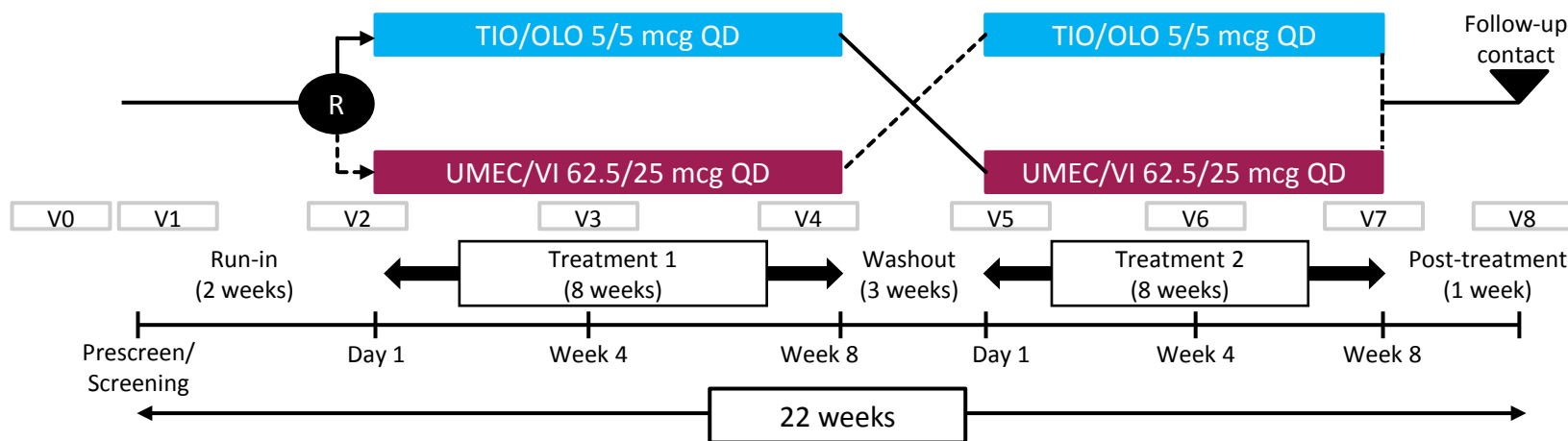
Introduction

- The cornerstone of pharmacological therapy for COPD is bronchodilation, with either a LAMA, a LABA, or a combination of the two.¹⁻³ In the LAMA class, UMEC was recently found to have superior efficacy to TIO, providing significantly greater increases in trough FEV₁ after 12 weeks⁴
- Clinical studies have demonstrated greater improvements in lung function and patient-reported outcomes with LAMA/LABA combinations vs LAMA or LABA monotherapies in patients with stable COPD⁵⁻¹¹
- Indirect evidence suggests that a potential effectiveness gradient exists between LAMA/LABA combination therapies, at least with regard to lung function,¹²⁻¹⁴ but direct head-to-head data are required to confirm this
- This 8-week, multicenter, randomized, open-label, two-period crossover study is the first direct comparison of the efficacy and safety of the once-daily LAMA/LABA combinations UMEC/VI 62.5/25 mcg, delivered via a multi-dose DPI (ELLIPTA), and TIO/OLO 5/5 mcg, delivered via a soft mist inhaler (Respimat)

1. Cazzola M, et al. *Pharmacol Rev* 2012; 64: 450-504; 2. Tashkin DP, et al. *Chest* 2004; 125: 249-59; 3. Tashkin DP, et al. *Respir Res* 2013; 14: 49; 4. Feldman G, et al. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 719-30; 5. Bateman ED, et al. *Eur Respir J* 2013; 42: 1484-94; 6. Buhl R, et al. *Eur Respir J* 2015; 45: 969-79; 7. Decramer M, et al. *Lancet Respir Med* 2014; 2: 472-86; 8. Maleki-Yazdi MR, et al. *Respir Med* 2014; 108: 1752-60; 9. Singh D, et al. *Respir Med* 2015; 109: 1312-9; 10. Wedzicha JA, et al. *Lancet Respir Med* 2013; 1: 199-209; 11. ZuWallack R, et al. *Int J Chron Obstruct Pulmon Dis* 2014; 12: 1133-44; 10. Calzetta L, et al. *Chest* 2016; 149: 1181-96; 13. Schlueter M, et al. *Ther Adv Respir Dis* 2016; 10: 89-104; 14. Sion KYJ, et al. *Pulm Ther* 2017. DOI 10.1007/s41030-017-0048-0

Study design

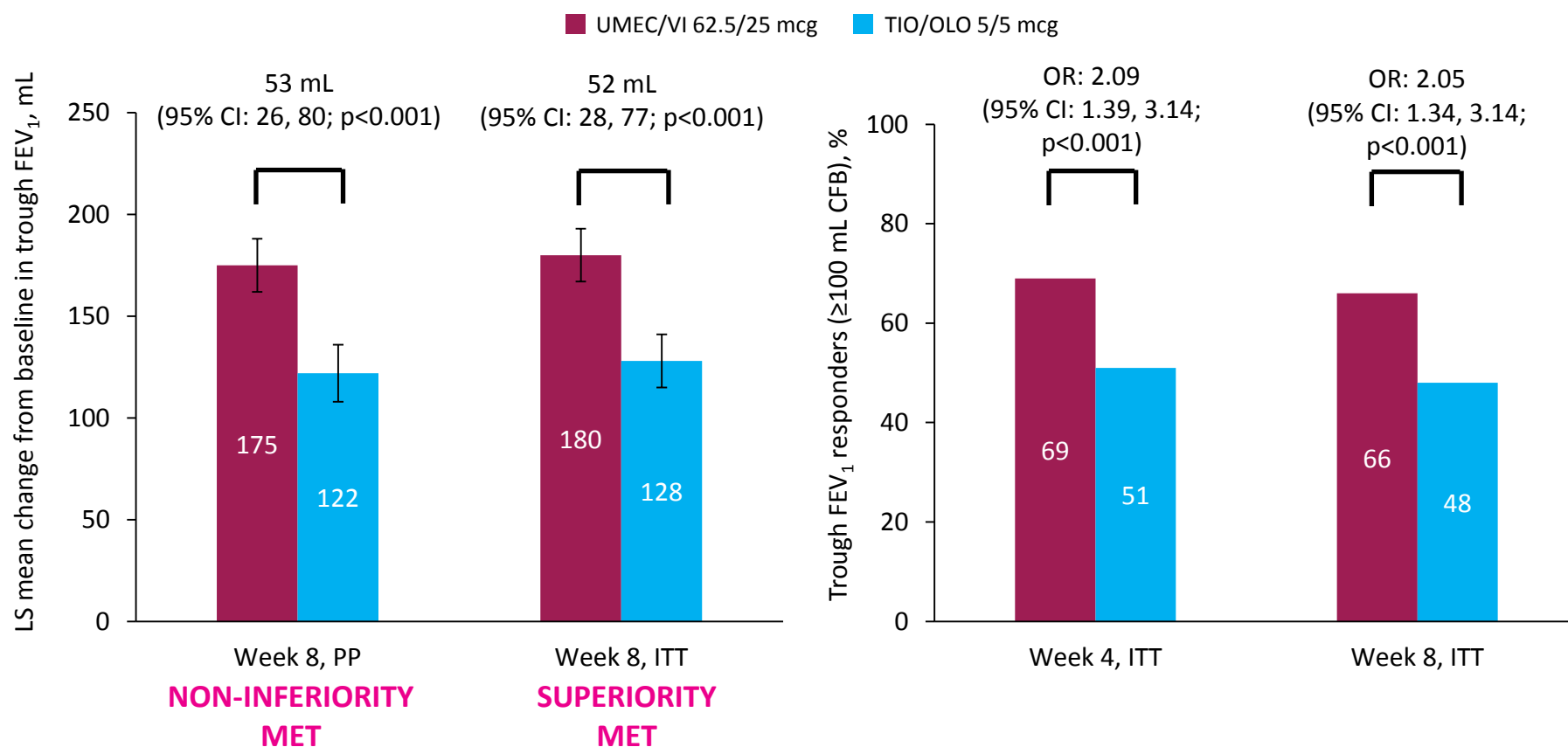
- Patients: age ≥ 40 years; post-bronchodilator FEV_1/FVC ratio < 0.70 ; post-bronchodilator $FEV_1 \leq 70\%$ to $\geq 50\%$ predicted; mMRC dyspnea score ≥ 2 ; ICS-naïve
 - Intent-to-treat, N=236; per-protocol, N=227
- Open-label treatment*
 - UMEC/VI 62.5/25 mcg (delivered dose 55/22 mcg) one inhalation once daily via the ELLIPTA inhaler
 - TIO/OLO 5/5 mcg (two inhalations of 2.5/2.5 mcg) once daily via the Respimat inhaler
 - Technicians performing spirometry were blinded to treatment allocation throughout the study
- Study conducted in Germany, Spain, the UK and the US



* Treatments had to be administered open-label as placebo Respimat inhalers were not available from Boehringer Ingelheim. ELLIPTA is a registered trademark of the GSK group of companies; Respimat is a registered trademark of Boehringer Ingelheim

Trough FEV₁ results

- UMEC/VI was superior to TIO/OLO on CFB in trough FEV₁ at Week 8
- A greater proportion of patients achieved a clinically meaningful improvement in trough FEV₁ (≥ 100 mL from baseline) with UMEC/VI versus TIO/OLO at Week 4 and Week 8

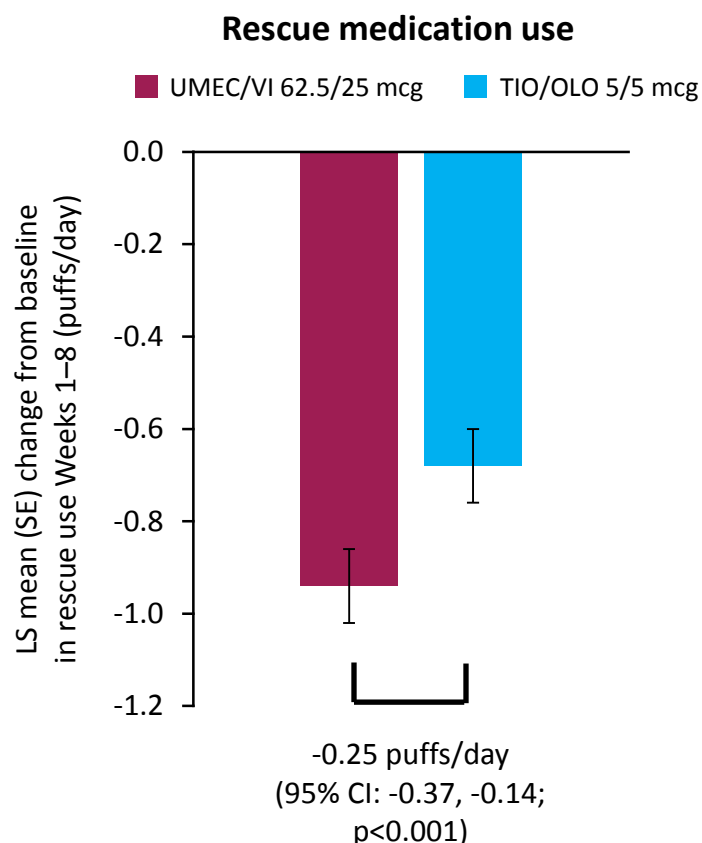


Other lung function endpoints

| | N | UMEC/VI | N | TIO/OLO | Difference/OR (95% CI) UMEC/VI vs TIO/OLO |
|-----------------------|-----|----------|-----|----------|--|
| CFB in FVC, mL | | | | | |
| Week 4 | 231 | 214 (18) | 224 | 174 (18) | 40 (5, 75) ^c |
| Week 8 | 225 | 202 (18) | 224 | 135 (18) | 67 (34, 100) ^a |
| CFB in IC, mL | | | | | |
| Week 4 | 223 | 164 (17) | 215 | 112 (18) | 52 (16, 88) ^b |
| Week 8 | 212 | 169 (17) | 212 | 122 (17) | 47 (14, 81) ^b |

All data are presented as LS mean (SE) CFB, unless otherwise stated; ^ap<0.001; ^bp<0.01; ^cp<0.05

Patient-reported outcomes



- There were no between-group differences in the percentage of rescue-medication-free days ($p=0.152$)
- A significant decrease in CAT score was observed with UMEC/VI versus TIO/OLO at week 4 ($p=0.042$), but not at week 8 ($p=0.695$)
- No statistically significant differences were observed between treatment groups in the percentage of CAT responders at either week 4 or week 8
- CFB in weekly E-RS_{COPD} total scores ranged from -1.79 to -1.61 in the UMEC/VI group and -1.72 to -1.31 in the TIO/OLO group over 8 weeks, with a statistically significant difference in favor of UMEC/VI observed at Week 5 ($p=0.031$)
- There were no statistically significant between-group differences in the proportion of E-RS_{COPD} responders
- Inhaler ease of use data were in favor of UMEC/VI for each of the criteria analysed ($p \leq 0.001$)

CAT and E-RS_{COPD} responders defined as patients with ≥ 2 units improvement from baseline

Conclusion

- In this first, direct comparison of the once-daily fixed-dose LAMA/LABA combinations UMEC/VI and TIO/OLO, superiority was observed with UMEC/VI on the primary endpoint of trough FEV₁ at Week 8 in patients with moderate/severe symptomatic COPD
- UMEC/VI was also associated with statistically significant improvements in trough FVC and IC, the proportion of trough FEV₁ responders and rescue medication use compared with TIO/OLO
- Inhaler ease of use questionnaire data showed significant patient preference for the ELLIPTA over the Respimat inhaler
- Both LAMA/LABA combinations were well tolerated and the incidence of exacerbations was low
- These findings confirm the results of previous indirect LAMA/LABA comparisons and show that an efficacy gradient exists within this medication class

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Disclosures

ARS, CC, DL, IN, JHR, NB, and SP are employees of GSK and hold stocks and shares in GSK. LT is a contingent worker on assignment at GSK. BAN reports personal fees and non-financial support from GSK, grants, personal fees and non-financial support from Novartis AG, personal fees and non-financial support from Boehringer Ingelheim, personal fees and non-financial support from Chiesi, grants, personal fees and non-financial support from Laboratorios Menarini, personal fees from Gebro, personal fees from AstraZeneca, outside the submitted work. In addition, BAN has a patent (P201730724) pending. GF does not have any conflicts of interest to declare.

Ethics approval and consent to participate

The study was conducted in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The protocol was reviewed and approved by all appropriate IRBs or independent ethics committees (Ethik-Kommission [Germany], Comité Etico de Investigación [Spain], Chesapeake IRB [US] and United Kingdom Ethics Committee). All patients provided written informed consent prior to study participation.

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