Pulmonary Therapy

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Umeclidinium/vilanterol versus tiotropium/olodaterol in maintenance-naïve patients with moderate symptomatic chronic obstructive pulmonary disease: a post hoc analysis

Alcázar-Navarrete B, et al. Pulm Ther. 2018.

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Abbreviations

AE	adverse event
CAT	COPD Assessment Test
CFB	change from baseline
CI	confidence interval
COPD	chronic obstructive pulmonary disease
E-RS_{COPD}	Evaluating Respiratory Symptoms - COPD
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
IC	inspiratory capacity
ICS	inhaled corticosteroid
ITT	intent-to-treat
LABA	long-acting β_2-agonist
LAMA	long-acting muscarinic antagonist
LS	least squares
MCID	minimal clinically important difference
MN	maintenance naive
OLO	olodaterol
OR	odds ratio
QD	once daily
SAE	serious adverse event
SE	standard error
TIO	tiotropium
UMEC	umeclidinium
VI	vilanterol

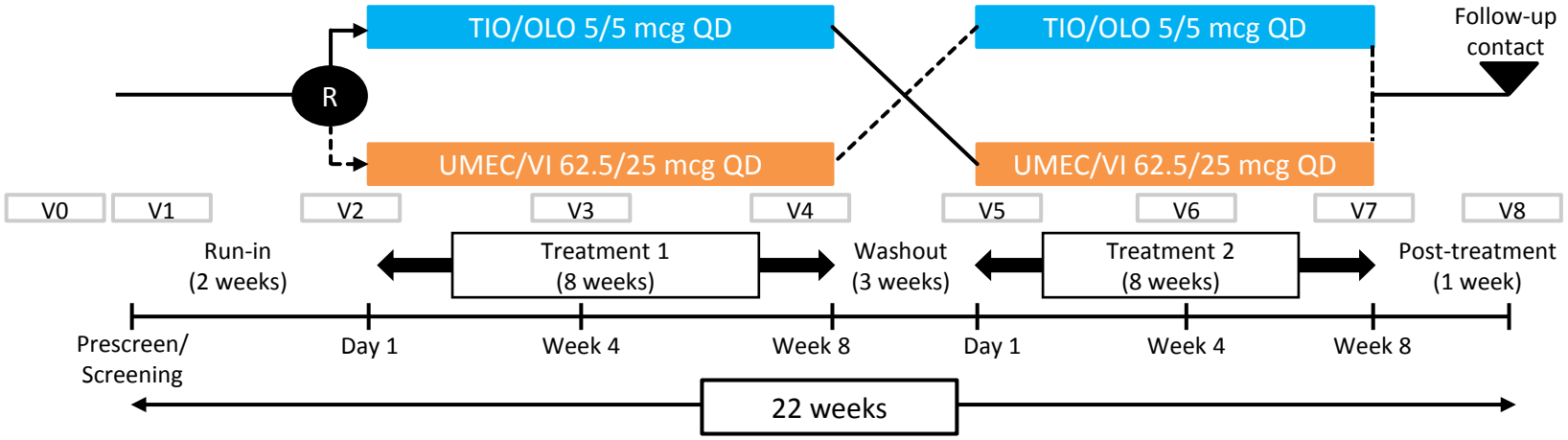
Introduction

- Long-acting bronchodilators form the foundation of COPD pharmacological therapy.[1-4]
- LAMA/LABA combinations have consistently demonstrated improved efficacy compared with either LAMA or LABA alone in patients with persistent symptomatic COPD.[4-11]
- Two once-daily LAMA/LABA combinations are currently approved in the USA and Europe: UMEC/VI 62.5/25 mcg and TIO/OLO 5/5 mcg.[12, 13]
- A previous 8-week, head-to-head study of UMEC/VI and TIO/OLO in patients with moderate symptomatic COPD found that UMEC/VI was superior to TIO/OLO for the primary endpoint of trough FEV_1.[14]
- This post hoc analysis investigated the efficacy and safety of UMEC/VI and TIO/OLO in a large subgroup of patients from this head-to-head study who were naïve to COPD maintenance therapy at randomization (MN subgroup).

1. Cazzola M, et al. Pharmacol Rev 2012; 64: 450-504; 2. Tashkin DP, et al. Chest 2004; 125: 249-59; 3. Global Initiative for Chronic Obstructive Lung Disease Report 2018 [Available from: http://goldcopd.org/]; 4. Tashkin DP, et al. Respir Res 2013; 14: 49; 5. Bateman ED, et al. Eur Respir J 2013; 42: 1484-94; 6. Decramer M, et al. Lancet Respir Med 2014; 2: 472-86; 7. Tashkin DP, et al. COPD 2009; 6: 17-25; 8. van der Molen T, et al. Prim Care Respir J 2012; 21: 101-8; 9. Oba Y, et al. Thorax 2016; 71: 15-25; 10. Calzetta L, et al. Chest 2016; 149: 1181-96; 11. Sion KYJ, et al. Pulm Ther 2017; 3: 297-316; 12. ANORO™ ELLIPTA® Highlights of Prescribing Information [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203975s000lbl.pdf]; 13. STIOLTO™ RESPIMAT® Highlights of Prescribing Information [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206756s001lbl.pdf]; 14. Feldman GJ, et al. Adv Ther 2017; 34: 2518-33

Study design

- Post hoc analysis of the MN population[a] contained data from the 8-week, multicenter, randomized, two-period crossover study (NCT02799784; GSK study 204990).[1]
- Open-label treatment:
  - UMEC/VI 62.5/25 mcg (delivered dose 55/22 mcg) 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.
- The MN population constituted 63% (148/236) of the total ITT population.

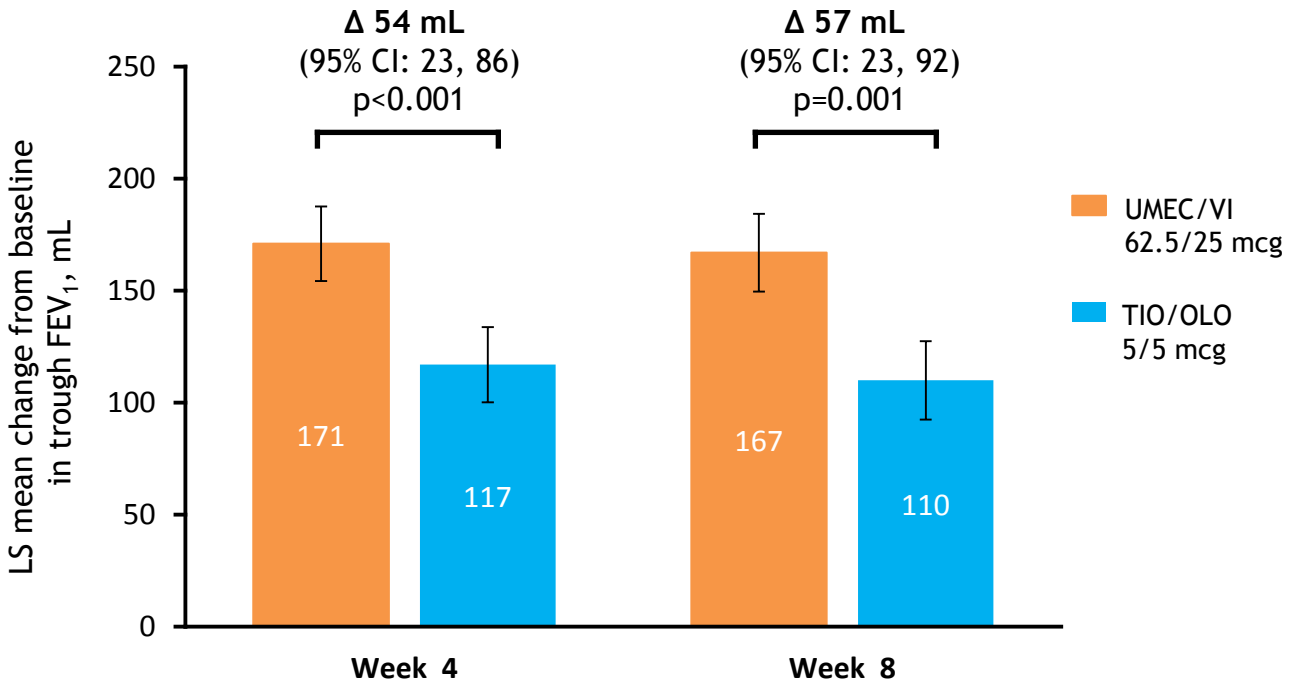


[a]MN patients had not received LAMA or LABA alone or in combination with ICS at least 6 weeks prior to randomization.

1. Feldman GJ, et al. Adv Ther 2017; 34: 2518-33

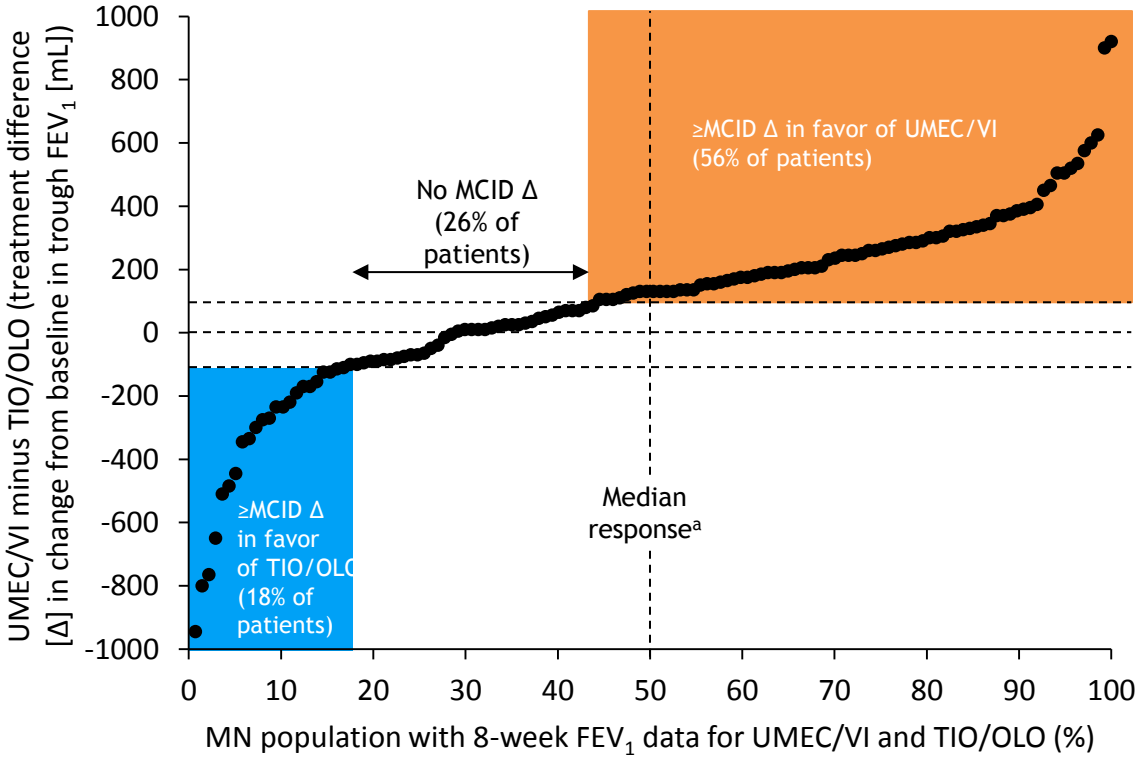
Trough FEV_1 results

- Trough FEV_1 CFB was significantly greater with UMEC/VI versus TIO/OLO at Week 4 and Week 8.
- The percent CFB in trough FEV_1 response equated to an 11% increase on UMEC/VI compared with 8% on TIO/OLO at Week 8 (CFB: 3% [95% CI: 1, 5]; p=0.004).



Within-patient differences in trough FEV_1 response (descriptive data)

- Overall, 56% of individuals achieved a MCID within-patient increase (≥100 mL) in trough FEV_1 response with UMEC/VI compared with TIO/OLO, 18% achieved a MCID increase favoring TIO/OLO versus UMEC/VI, and 26% showed no MCID difference.



Trough FEV_1 responders and other lung function endpoints

- A greater percentage of patients achieved a MCID in trough FEV_1 (CFB ≥ 100mL) with UMEC/VI versus TIO/OLO at Week 4 and at Week 8.
- Both FVC and IC were greater with UMEC/VI versus TIO/OLO at Week 8.

	UMEC/VI	TIO/OLO	OR (95% CI)	Treatment difference (95% CI)	p-value
Trough FEV_1 responders, %					
Week 4	62	46	1.79 (1.10, 2.92)	-	0.020
Week 8	60	42	1.90 (1.123.22)	-	0.018
FVC, LS mean CFB (SE), mL					
Week 4	199 (24)	157 (24)	-	42 (-4, 89)	0.072
Week 8	193 (24)	122 (24)	-	71 (27, 116)	0.002
IC, LS mean CFB (SE), mL					
Week 4	161 (21)	95 (22)	-	66 (19, 113)	0.006
Week 8	151 (21)	96 (21)	-	55 (9, 102)	0.02

Patient-reported outcomes

- The LS mean (SE) CFB in rescue medication use in Weeks 1–8 in MN patients receiving UMEC/VI versus TIO/OLO was 0.80 [0.10] and 0.59 [0.10] puffs/day, respectively (difference: 0.20 [95% CI: 0.07, 0.34]; p=0.003).

- No significant differences between UMEC/VI and TIO/OLO in LS mean CFB in CAT score or in the proportion of CAT responders (≥ -2 units CFB in CAT score) were reported at Weeks 4 or 8.

- LS mean CFB in weekly E-RS_{COPD} total score ranged from -1.42 to -1.75 for UMEC/VI and from -1.15 to -1.66 for TIO/OLO over Weeks 1– 8.
  - Between-treatment differences were statistically significant at Week 5 only; difference in favor of UMEC/VI (-0.58 [95% CI: -1.13, -0.03]; p=0.039).

Safety

- The AE profiles in the MN population were similar to those in the ITT population.
  - 35 (24%) patients on UMEC/VI and 42 (29%) patients on TIO/OLO experienced at least one AE.

	UMEC/VI	TIO/OLO
Patients experiencing an AE, n (%)	35 (24)	42 (29)
Most frequently reported AEs[a], n (%)		
Upper respiratory tract infection	6 (4)	6 (4)
Viral upper respiratory tract infection	5 (3)	3 (2)
Sinusitis	1 (<1)	4 (3)
Exacerbation incidence, n (%)		
1 exacerbation	10 (7)	12 (8)
2 exacerbations	2 (1)	1 (<1)

[a]≥3% patients on either treatment

Conclusions

- In MN patients, UMEC/VI provided significantly greater improvements in trough FEV_1, FVC, IC and rescue medication use compared with TIO/OLO therapy.
- MN patients also had nearly two-fold increased odds of achieving a clinically important lung function benefit on trough FEV_1 (≥100 mL CFB) with UMEC/VI versus TIO/OLO.
- The magnitude of the treatment difference observed with UMEC/VI versus TIO/OLO was broadly consistent in the MN population and in the ITT population in the parent study.[1]
- As with the parent study,[1] the benefits observed with UMEC/VI versus TIO/OLO were not accompanied by any increased potential for AEs and SAEs.
- This post hoc analysis further highlights that an efficacy gradient exists within the LAMA/LABA class favoring once-daily UMEC/VI over TIO/OLO.
- Further long-term, prospective studies into the effect of first-line initiation of dual bronchodilator versus monotherapy are now needed.

1. Feldman GJ, et al. Adv Ther 2017; 34: 2518-33

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Disclosures

ARS, CC, DAL, IB and IN 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. Ellipta is owned by or licensed to the GlaxoSmithKline group of companies. Respimat is a registered trademark of Boehringer Ingelheim.

Ethics approval and consent to participate

The 204990 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-Komission [Germany], Comite Etico de Investigacion [Spain], Chesapeake IRB [US] and United Kingdom Ethics Committee). Informed consent was obtained from all patients prior to inclusion in the study.

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