SUPPLEMENTARY MATERIALS

Inclusion criteria

Patients were eligible for inclusion in the study provided they met all of the following inclusion criteria:

- Male or female outpatients ≥40 years of age with signed and dated written informed consent prior to study participation.
- Female subjects of non-reproductive potential or postmenopausal, or with a negative pregnancy test at screening and agreement to use contraception from 30 days prior to the first dose of study medication until follow-up contact.
- A diagnosis of chronic obstructive pulmonary disease (COPD) in accordance with the definition by the American Thoracic Society/European Respiratory Society[20].
- Current or former cigarette smokers with a history of ≥10 pack years (where number of pack years = [number of cigarettes per day/20] x number of years smoked; pipe and/or cigar smoking not included); former smokers were defined as those who had stopped smoking for at least 6 months prior to Visit 1.
- A pre- and post-albuterol/salbutamol forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio of <0.70.
- A post albuterol FEV_1 of ≤70% and ≥50% of predicted normal values at Visit 1.
- A score of ≥2 on the modified Medical Research Council Dyspnoea Scale (mMRC) at Visit 1.

Exclusion criteria

Patients were excluded from the study if they met any of the following criteria:

- Current diagnosis of asthma; patients with a prior history of asthma were eligible if they had a current diagnosis of COPD that was the primary cause of respiratory symptoms.
- The use of inhaled corticosteroid treatment in the 30 days prior to screening.
- The use of the long-acting β_2-agonist (LABA) olodaterol, indacaterol or vilanterol within 48 hours or screening or of the LABA salmeterol or formoterol in the 14 days prior to screening.
- The use of the long-acting muscarinic antagonist (LAMA) tiotropium, aclidinium, glycopyrronium or umeclidinium in the 7 days prior to screening.

- The use of LAMA/LABA combination in a time interval prior to screening determined by the monotherapy component with the longest washout.
- α1-antitrypsin deficiency as the underlying cause of COPD.
- Active tuberculosis or other respiratory disorder (e.g. clinically significant bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension or interstitial lung disease) that were the primary cause of respiratory symptoms.
- Considered unlikely to survive the duration of the study period or had any rapidly progressing disease or immediate life-threatening illness (e.g. cancer).
- Any other condition (e.g. a neurological condition) that was considered likely to affect respiratory function.
- Current active liver or biliary disease (with the exception of Gilbert's syndrome, asymptomatic gallstones or otherwise stable chronic liver disease [including table hepatitis B and C] according to investigator assessment).
- Unstable or life-threatening cardiac disease.
- Any history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, sympathomimetic, lactose/milk protein or magnesium stearate.
- Medical conditions such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy, or bladder neck obstruction where the risks of treatment, in the opinion of the investigator, outweighed the benefits.
- A hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1; patients with pneumonia and/or experiencing a moderate or a severe COPD exacerbation that had not resolved at least 14 days prior to screening and at least 30 days following the last dose of oral/systemic corticosteroids (if applicable); or patients with other respiratory tract infections that have not resolved at least 7 days prior to screening.
- Lung volume reduction surgery (including procedures such as endobronchial valves) within the 12 months prior to screening.
- Abnormal electrocardiogram findings.
- Unable to withhold albuterol for 4 hours prior to spirometry testing at each study visit.
- Regular use (prescribed for daily/regular use, not for as-needed use) of short-acting bronchodilators (e.g. albuterol).

- Use of long-term oxygen therapy, described as resting oxygen therapy >3 L/min at screening.
- Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to screening; patients in the maintenance phase of a pulmonary rehabilitation program were not excluded.
- A known or suspected history of alcohol or drug abuse within 2 years prior to screening that in the opinion of the investigator would prevent the subject from completing the study procedures.

Supplementary Table S1. Medications permitted during the study.

Permitted medication
Study-provided albuterol, for use as relief medication throughout the run-in and treatment periods
Short-acting inhaled muscarinic antagonists (during the washout period only, and provided they were washed out ≥4 hours prior to Visit 5)
Mucolytics (e.g. acetylcysteine)
Rhinitis medications (e.g. intranasal corticosteroids, antihistamines, cromolyn, nedocromil, nasal decongestants)
Influenza vaccine
Pneumonia vaccine
Antibiotics for short-term treatment (≤14 days) of acute infections including COPD exacerbations
Systemic corticosteroids for short term (≤14 consecutive days) treatment of COPD exacerbations
As-needed oxygen use (i.e. ≤12 hours per day)
Treatments from a pulmonary rehabilitation program in the maintenance phase
Smoking cessation therapies, including a stable regimen of nicotine replacement
Positive airway pressure for sleep apnea
Localised corticosteroid injections (e.g. intra-articular and epidural)
Oral muscarinic antagonists for the treatment of overactive bladder, though only with caution as they may exacerbate medical conditions that are contraindicated for anticholinergics (e.g. narrow angle glaucoma and bladder outflow obstruction)
Immunotherapy injections
Topical or ophthalmic corticosteroids

COPD, chronic obstructive pulmonary disease.

Supplementary Table S2. Change from baseline in trough FEV_1 in the per-protocol population at week 4 and 8

	N	UMEC/VI	N	TIO/OLO	Difference / OR (95% CI) UMEC/VI vs TIO/OLO
Trough FEV_1, mL					
Week 4	213	181 (13)	192	141 (13)	40 (14, 66)[a]
Week 8	202	175 (13)	192	122 (14)	53 (26, 80)[b]

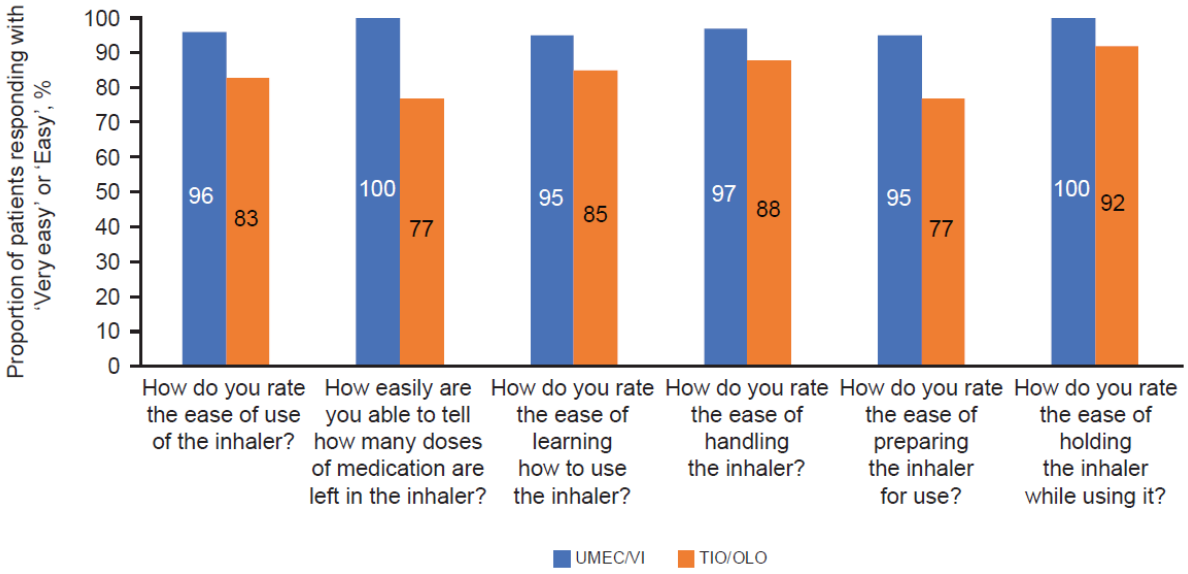
All data are presented as LS mean (SE) change from baseline, unless otherwise stated; [a]p=0.002; [b]p<0.001

CI, confidence interval; FEV_1, forced expiratory volume in 1 second; LS, least squares; SE, standard error; OR, odds ratio; TIO/OLO, tiotropium/olodaterol 5/5 mcg; UMEC/VI, umeclidinium/vilanterol 62.5/25 mcg

Inhaler ease of use

In the IN population, 96% of patients rated ELLIPTA as 'very easy' or 'easy' to use compared with 83% of patients using Respimat, with a greater proportion of patients rating ELLIPTA 'very easy' to use in all six questionnaire items (Supplementary Figure S1). Significantly more patients rated ELLIPTA higher than Respimat on overall ease of use (40% vs 11%; p=0.001), ease of telling the number of doses remaining (53% vs 1%; p<0.001); ease of learning to use (43% vs 4%; p<0.001); ease of handling (40% vs 4%; p<0.001); ease of preparation (49% vs 3%; p<0.001); and ease of holding while using (32% vs 4%; p<0.001).

Supplementary Figure S1. Summary of inhaler ease of use questionnaire responses (IN population; N=75)



IN, inhaler-naïve; TIO/OLO, tiotropium/olodaterol 5/5 mcg; UMEC/VI, umeclidinium/vilanterol 62.5/25 mcg.