SUPPLEMENTARY MATERIALS

Table S1. Excluded medications prior to Visit 1

Medication	Time interval
Depot corticosteroids	12 weeks
Systemic, oral or parenteral corticosteroids	6 weeks
Antibiotics (for lower respiratory tract infection)	6 weeks
LABA/ICS combination products if LABA/ICS therapy is discontinued completely	30 days
LABA/ICS combination products only If discontinuing ICS/LABA therapy and switching to ICS monotherapy[a]	48 h for the salmeterol or formoterol component 14 days for the vilanterol component
Use of ICS at a dose >1000 mcg/day of FP or equivalent[b]	30 days
Initiation or discontinuation of ICS use[b]	30 days
Phosphodiesterase 4 inhibitor (roflumilast)	14 days
Inhaled LABAs:	
-salmeterol, formoterol	48 h
-olodaterol, indacaterol, vilanterol	14 days
LAMAs: -tiotropium, aclidinium, glycopyrronium, umeclidinium	7 days
LAMA/LABA combination products if LAMA/LABA therapy is discontinued completely	Apply whichever mono component has the longest washout
Theophyllines	48 h
Oral beta$_2$-agonists	
Long-acting	48 h
Short-acting	12 h
Inhaled short-acting β_2-agonists[c]	4 h
Inhaled short-acting anticholinergics	4 h
Inhaled short-acting anticholinergic/short-acting β_2-agonist combination products	4 h
Any other investigational medication	30 days or within 5 drug half-lives (whichever is longer)

FP, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonists; LAMA, long-acting muscarinic antagonists; TIO, tiotropium; UMEC, umeclidinium.

[a]The dose of ICS must have been a dose of FP or equivalent but must not have exceeded 1000 mcg/day; [b]use of ICS was permitted provided the dose did not exceed FP 1000 mcg or equivalent; ICS use was not to be initiated or discontinued within 30 days prior to Visit 1, except for patients receiving LABA/ICS therapy who could have discontinued the ICS/LABA product as indicated in the table above and switched to ICS monotherapy; [c]use of study provided albuterol/salbutamol was permitted during the study, except in the 4-h period prior to spirometry testing.

Blinding procedure

The tiotropium (TIO) capsules had trade markings but the placebo (PBO) capsules, while closely matched in color, did not have trade markings. Both were packaged similarly. Blister packages for both TIO and PBO were covered with opaque over-labels in order to shield information appearing on the commercial blister packaging

of TIO. Furthermore, the identifying marks on the inhaler were masked by covering them with labels. As neither patients nor research staff were aware of how the labels related to the treatments, they were blinded to the allocation group. As this was a double-dummy study, each patient took one dose from the HandiHaler® dry powder inhaler (DPI) and one dose from the ELLIPTA™ DPI each morning. The study participants, investigator, and the coordinator involved with efficacy and safety assessments were blinded to treatment assignment to guard against the possibility that they would observe and draw inferences from the presence or absence of markings on capsules removed from the blisters.

Table S2. FVC (ITT population)

	UMEC 62.5 mcg (N=509)	**TIO 18 mcg (N=508)**	**Treatment Diff. vs TIO (95% CI)**
Trough FVC at Day 2	n=497	n=492	
LS mean change from baseline, mL (SE)	152 (14)	131 (14)	21 (-17, 60); p=0.274
Trough FVC at Day 28	n=491	n=489	
LS mean change from baseline, mL (SE)	194 (16)	138 (16)	56 (13, 99); p=0.011
Trough FVC at Day 56	n=473	n=480	
LS mean change from baseline, mL (SE)	174 (16)	118 (16)	56 (11, 102); p=0.016
Trough FVC at Day 84	n=469	n=474	
LS mean change from baseline, mL (SE)	187 (16)	108 (16)	79 (34, 125); p<0.001
Trough FVC at Day 85	n=459	n=466	
LS mean change from baseline, mL (SE)	192 (17)	112 (17)	80 (34, 127); p<0.001

CI, confidence interval; FVC, forced vital capacity; ITT, intent-to-treat; LS, least squares; SE, standard error; TIO, tiotropium; UMEC, umeclidinium.

Analyses were performed using a repeated measures model with covariates of treatment, baseline FVC (the mean of the two assessments made 30 min and 5 min pre-dose on Day 1), center group,
24 h subset flag, day, day-by-baseline and day-by-treatment interactions.

Table S3. Symptomatic and health-related quality of life endpoints at other time points

	UMEC 62.5 mcg (N=509)	**TIO 18 mcg (N=508)**	**Treatment Diff. vs TIO (95% CI)**
TDI focal score at Day 28	n=489	n=490	
LS mean, (SE)	1.50 (0.12)	1.52 (0.12)	-0.02 (-0.35, 0.32); p=0.924
TDI responder at Day 28, n (%)[a]	271 (54)	262 (52)	OR: 1.07 (0.84, 1.37); p=0.583
TDI focal score at Day 56	n=476	n=482	
LS mean, (SE)	1.75 (0.13)	1.70 (0.13)	0.04 (-0.31, 0.40); p=0.809
TDI responder at Day 56, n (%)[b]	275 (54)	271 (54)	OR: 1.02 (0.80, 1.31); p=0.850
SGRQ score at Day 28	n=473	n=477	
LS mean change from baseline, (SE)	-4.09 (0.50)	-3.99 (0.50)	-0.10 (-1.48, 1.29); p=0.891
SGRQ responder at Day 28[c]	226 (46)	229 (47)	OR: 0.98 (0.76, 1.27); p=0.892
CAT score, Day 28	n=493	n=492	
LS mean change from baseline, (SE)	-1.34 (0.24)	-1.03 (0.24)	-0.31 (-0.97, 0.34); p=0.349
CAT responder at Day 28	233 (46)	221 (44)	OR: 1.11 (0.86, 1.43); p=0.437

CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ITT, intent-to-treat; OR, odds ratio; SGRQ, St George's Respiratory Questionnaire; SE, standard error; TDI, transition dyspnea; TIO, tiotropium; UMEC, umeclidinium. [a]UMEC n=504, TIO n=504; [b]UMEC n=505, TIO n=504; [c]UMEC n=490, TIO n=492.

Table S4. Post hoc analyses of trough FEV_1 at Day 85

	UMEC 62.5 mcg (N=509)	TIO 18 mcg (N=508)	Treatment Diff. vs TIO (95% CI)
GOLD Grade 2	n=281	n=281	
LS mean change from baseline, mL (SE)[a]	177 (14)	114 (14)	63 (25, 100); p=0.001
GOLD Grade 3	n=226	n=223	
LS mean change from baseline, mL (SE)[a]	108 (16)	69 (16)	39 (-4, 82); p=0.074
GOLD Group B	n=244	n=227	
LS mean change from baseline, mL (SE)[a]	171 (15)	114 (16)	57 (16, 98); p=0.006
GOLD Group D	n=263	n=277	
LS mean change from baseline, mL (SE)[a]	124 (15)	78 (14)	46 (7, 85); p=0.020
ICS users at screening	n=246	n=229	
LS mean change from baseline, mL (SE)[a]	147 (15)	81 (15)	66 (25, 107); p=0.002
ICS non-users at screening	n=262	n=275	
LS mean change from baseline, mL (SE)[a]	146 (14)	104 (14)	42 (3, 81); p=0.035
GOLD Grade 2 and ICS users at screening	n=122	n=114	
LS mean change from baseline, mL (SE)[a]	172 (21)	108 (21)	64 (6, 122); p=0.030
GOLD Grade 2 and ICS non-users at screening	n=159	n=167	
LS mean change from baseline, mL (SE)[a]	181 (19)	119 (18)	62 (13, 111); p=0.013
GOLD Grade 3 and ICS users at screening	n=124	n=115	
LS mean change from baseline, mL (SE)[a]	118 (22)	53 (22)	65 (7, 123); p=0.028
GOLD Grade 3 and ICS non-users at screening	n=102	n=108	
LS mean change from baseline, mL (SE)[a]	97 (24)	88 (23)	9 (-55, 72); p=0.784
Proportion of patients with trough FEV_1 ≥100 mL above baseline, n (%)	268 (53)	228 (45)	OR: 1.35 (1.06, 1.74); p=0.017

CI, confidence interval; GOLD, Global initiative for chronic Obstructive Lung Disease; OR, odds ratio; LS, least squares; SE, standard error; TIO, tiotropium; UMEC, umeclidinium. n values represent the number of patients with analyzable data for ≥1 time points. [a]Analysis performed using a repeated measures model with covariates of treatment, baseline FEV_1 (mean of the two assessments made 30 min and 5 min pre-dose on Day 1), center group, 24 h subset flag, GOLD grade/GOLD group/ICS use, day, day-by-baseline and day-by-GOLD grade/GOLD group/ICS use and Day by GOLD grade/GOLD group/ICS use by treatment interactions.

Table S5. Summary of change from baseline in vital signs at Day 85 (ITT population)

	UMEC 62.5 mcg (N=509)	TIO 18 mcg (N=508)
	n=463	n=470
Systolic blood pressure, mmHg	-0.5 (12.7)	-0.1 (11.5)
Diastolic blood pressure, mmHg	-0.9 (8.9)	-0.2 (8.2)
Heart rate, bpm	-0.5 (9.6)	0.9 (8.5)

bpm, beats per minute; ITT, intent-to-treat; SD, standard deviation; TIO, tiotropium; UMEC, umeclidinium. Values are presented as mean (SD); baseline was the most recent recorded value before dosing on Day 1.

Table S6. Summary of on-treatment adverse events of special interest (ITT population)

	UMEC 62.5 mcg (N=509)	TIO 18 mcg (N=508)
Cardiovascular Effects		
Any event	9 (2)	10 (2)
Cardiac arrhythmia (SMQ)		
Any term	7 (1)	3 (<1)
Atrial fibrillation	1 (<1)	0
Heart rate decreased	0	1 (<1)
Heart rate increased	1 (<1)	1 (<1)
Palpitations	1 (<1)	0
Syncope	0	1 (<1)
Tachycardia	4 (<1)	0
Cardiac failure (SMQ)		
Any term	0	3 (<1)
Cardiac failure congestive	0	1 (<1)
Edema	0	1 (<1)
Peripheral swelling	0	1 (<1)
Ischemic heart disease (SMQ)		
Any term	2 (<1)	2 (<1)
Angina pectoris	1 (<1)	2 (<1)
Angina unstable	1 (<1)	0
Central nervous system hemorrhages and cerebrovascular conditions (SMQ)		
Any term	0	2 (<1)
Cerebrovascular disorder	0	2 (<1)
Vascular encephalopathy	0	2 (<1)
Pneumonia		
Any event	2 (<1)	2 (<1)
Any term	2 (<1)	2 (<1)
Lobar pneumonia	1 (<1)	0
Pneumonia	1 (<1)	2 (<1)
LRTI (excluding pneumonia)		
Any event	5 (<1)	3 (<1)
Bronchitis	4 (<1)	1 (<1)
LRTI	0	1 (<1)
Infective exacerbation of chronic obstructive airways disease	1 (<1)	1 (<1)

ITT, intent-to-treat; LRTI, lower respiratory tract infection; MedDRA, Medical Dictionary of Regulatory Activities; SMQ, Standardized MedDRA Queries; TIO, tiotropium; UMEC, umeclidinium.