Supplementary material

Methods

SUPPLEMENTARY TABLE S1 Patient subgroups included in these subanalyses

Subgroups
COPD medication at screening
ICS+LABA
BUD+FOR
ICS+LABA+LAMA
LAMA alone
TIO alone
LAMA+LABA
Disease severity at screening
1. FEV_1 <50%, no moderate/severe exacerbations
2. FEV_1 <50%, ≥1 moderate/severe exacerbation
3. FEV_1 ≥50–<80%, ≥2 moderate/≥1 severe exacerbation
Exacerbation history in previous 12 months
0/1 exacerbation
≥2 moderate exacerbations (no severe exacerbations)
≥1 severe exacerbation

COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting β_2 agonist; BUD: budesonide; FOR: formoterol; LAMA: long-acting muscarinic antagonist; TIO, tiotropium; FEV_1: forced expiratory volume in 1 s.

Results

SUPPLEMENTARY TABLE S2 Mean change from baseline in trough FEV_1 and SGRQ Total score, in the COPD medication class, disease severity and exacerbation history subgroups at week 52 (EXT population)

Subgroup	Mean change from baseline in trough FEV_1, mL (95% CI)			Mean change from baseline in SGRQ Total score (95% CI)		
	FF/UMEC/VI	BUD/FOR	Difference, (95% CI), p-value	FF/UMEC/VI	BUD/FOR	Difference, (95% CI), p-value
COPD medication class at screening						
ICS+LABA	184 (128, 240)	5 (-53, 64)	178 (97, 260) <0.001	-6.2 (-9.2, -3.2)	-6.9 (-10.1, -3.6)	0.7 (-3.8, 5.1) 0.768
BUD+FOR	201 (100, 303)	-45 (-155, 64)	247 (91, 403) 0.003	-5.2 (-10.2, -0.2)	-1.3 (-6.9, 4.3)	-3.9 (-11.5, 3.7) 0.311
ICS+LABA+LAMA	52 (-11, 115)	-110 (-179, -41)	162 (68, 256) <0.001	-0.5 (-4.5, 3.5)	4.3 (0.0, 8.7)	-4.8 (-10.8, 1.1) 0.111
LAMA alone	229 (101, 358)	0 (-127, 126)	230 (45, 414) 0.016	-7.1 (-14.7, 0.4)	-0.8 (-8.2, 6.6)	-6.3 (-17.1, 4.4) 0.241
TIO alone	290 (139, 440)	25 (-118, 168)	264 (54, 475) 0.016	-5.8 (-14.5, 2.8)	-6.1 (-14.3, 2.1)	0.3 (-12.1, 12.6) 0.967
LAMA+LABA	114 (18, 209)	-157 (-273, -41)	270 (120, 421) <0.001	-4.6 (-10.7, 1.5)	-2.0 (-8.9, 4.8)	-2.5 (-11.7, 6.7) 0.580
Disease severity						
FEV_1 <50% predicted, no moderate/severe exacerbations	107 (43, 170)	-118 (-184, -51)	224 (135, 313) <0.001	-0.5 (-4.2, 3.1)	1.2 (-2.7, 5.0)	-1.7 (-7.0, 3.6) 0.531

FEV_1 <50% predicted, ≥1 moderate/ severe exacerbations	101 (41, 160)	-39 (-98, 20)	140 (59, 221) <0.001	-4.4 (-7.9, -0.9)	-2.3 (-5.7, 1.1)	-2.1 (-6.9, 2.7) 0.398
FEV_1 ≥50–<80% predicted, ≥2 moderate/ ≥1 severe exacerbations	162 (100, 224)	-17 (-78, 45)	179 (100, 258), <0.001	-7.9 (-11.2, -4.6)	-4.1 (-7.4, -0.7)	-3.8 (-8.5, 0.8) 0.106

Exacerbation history

0/1 moderate	124 (84, 164)	-46 (-87, -6)	170 (113, 227), <0.001	-4.3 (-6.6, -2.0)	-3.3 (-5.6, -0.9)	-1.0 (-4.3, 2.3) 0.543
≥2 moderate	126 (65, 188)	-73 (-135, -10)	199 (111, 287) <0.001	-5.2 (-9.0, -1.4)	1.0 (-2.9, 4.9)	-6.2 (-11.6, -0.7) 0.026
≥1 severe	166 (99, 234)	38 (-33, 108)	129 (30, 227) 0.011	-9.2 (-12.9, -5.6)	-8.4 (-12.2, -4.6)	-0.8 (-6.1, 4.5) 0.758

FEV_1: forced expiratory volume in 1 s; SGRQ: St George's Respiratory Questionnaire; COPD: chronic obstructive pulmonary disease; EXT: extension; CI: confidence interval; FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol; BUD/FOR: budesonide/formoterol; ICS: inhaled corticosteroid; LABA: long-acting β_2 agonists; LAMA: long-acting muscarinic antagonists; TIO, tiotropium.

SUPPLEMENTARY TABLE S3 LS mean change from baseline in trough FEV_1 and SGRQ Total score, in the additional prior medication and disease severity subgroups at week 24 (ITT population)

Subgroup	**Mean change from baseline in trough FEV_1, mL (95% CI)**			**Mean change from baseline in SGRQ Total score (95% CI)**		
	FF/UMEC/VI	**BUD/FOR**	**Difference, (95% CI) p-value**	**FF/UMEC/VI**	**BUD/FOR**	**Difference, (95% CI) p-value**
Prior medication						
LABA	206 (145, 268)	-28 (-88, 32)	234 (147, 320) <0.001	-6.0 (-9.5, -2.6)	0.5 (-2.8, 3.8)	-6.5 (-11.3, -1.7) 0.009
Not on ICS+LABA+LAMA	160 (140, 180)	-11 (-31, 9)	171 (142, 199) <0.001	-7.7 (-8.8, -6.6)	-4.9 (-6.0, -3.8)	-2.8 (-4.3, -1.3) <0.001
Disease severity						
FEV_1 <50%, ≥2 moderate/ ≥1 severe exacerbation	205 (174, 235)	-12 (-43, 19)	216 (177, 256) <0.001	-8.4 (-10.0, -6.9)	-6.2 (-7.8, -4.6)	-2.2 (-4.4, -0.1) 0.044
FEV_1 <50%, 1 moderate exacerbation	114 (73, 155)	-22 (-63, 20)	136 (77, 195) <0.001	-5.1 (-7.5, -2.8)	-0.7 (-3.2, 1.7)	-4.4 (-7.8, -1.0) 0.011
FEV_1 ≥50%	210 (180, 241)	-6 (-37, 25)	216 (176, 256) <0.001	-8.5 (-10.1, -7.0)	-6.3 (-7.8, -4.7)	-2.3 (-4.4, -0.1) 0.039
FEV_1 ≥30%–<50%	122 (100, 144)	-34 (-57, -12)	156 (125, 188) <0.001	-6.1 (-7.3, -4.9)	-4.4 (-5.7, -3.2)	-1.7 (-3.4, 0.0) 0.054
FEV_1 <30%	43 (-8, 94)	-66 (-116, -16)	109 (42, 175) 0.001	-2.8 (-5.5, -0.2)	1.1 (-1.5, 3.6)	-3.9 (-7.5, -0.3) 0.035

LS: least squares; FEV_1: forced expiratory volume in 1 s; SGRQ: St George's Respiratory Questionnaire; ITT: intent-to-treat; CI: confidence interval; FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol; BUD/FOR: budesonide/formoterol; LABA: long-acting β_2 agonists; ICS: inhaled corticosteroid; LAMA: long-acting muscarinic antagonists.

SUPPLEMENTARY TABLE S4 On-treatment adverse events occurring in ≥2% of patients in either subgroup by exacerbation history in the previous 12 months, up to week 24 (ITT population)

Adverse events, n (%)	**<2 moderate exacerbations**		**≥2 moderate/ ≥1 severe exacerbation**	
	FF/UMEC/VI 100/62.5/25 µg (n=418)	**BUD/FOR 400/12 µg (n=421)**	**FF/UMEC/VI 100/62.5/25 µg (n=493)**	**BUD/FOR 400/12 µg (n=478)**
Nasopharyngitis	33 (8)	21 (5)	31 (6)	22 (5)
Headache	21 (5)	20 (5)	23 (5)	33 (7)
Back pain	8 (2)	12 (3)	11 (2)	6 (1)
COPD	7 (2)	12 (3)	8 (2)	11 (2)
URTI	9 (2)	7 (2)	11 (2)	12 (3)
Upper abdominal pain	6 (1)	8 (2)	–	–
Arthralgia	6 (1)	8 (2)	11 (2)	5 (1)
Hypertension	4 (<1)	9 (2)	–	–
Rhinitis	5 (1)	7 (2)	–	–
Pneumonia	8 (2)	2 (<1)	11 (2)	5 (1)
Pharyngitis	5 (1)	3 (<1)	10 (2)	6 (1)
Oropharyngeal pain	–	–	7 (1)	8 (2)
Rhinorrhoea	1 (<1)	4 (<1)	2 (<1)	8 (2)
Blood pressure increased	–	–	1 (<1)	8 (2)

ITT: intent-to-treat; FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol; BUD/FOR: budesonide/formoterol; COPD: chronic obstructive pulmonary disease; URTI: upper respiratory tract infection.