Supplementary Materials

e-Appendix 1

Analyses were performed for each region separately. Exacerbation rates were analyzed using a generalized linear model assuming a negative binomial distribution with covariates of treatment group, sex, exacerbation history (≤1, ≥2 moderate/severe), smoking status (Screening), and post-bronchodilator percent predicted FEV_1 (Screening). Time-to-first moderate/severe exacerbation was analyzed using a Cox proportional hazards model with covariates of treatment group, sex, exacerbation history (≤1, ≥2 moderate/severe), smoking status (Screening) and post-bronchodilator percent predicted FEV_1 (Screening). Analyses of changes from baseline in trough FEV_1 and SGRQ total score were performed using repeated measures models with covariates of treatment group, smoking status (Screening), visit, baseline, baseline by visit, and treatment group by visit interactions. The SGRQ responder analysis was performed using a generalized linear mixed model with a logit link function and covariates of treatment group, smoking status (Screening), visit, baseline, baseline by visit, and treatment group by visit interactions.

Analysis of treatment by region interaction for exacerbations was performed using a generalized linear model assuming a negative binomial distribution and covariates of treatment group, sex, exacerbation history (≤1, ≥2 moderate/severe), smoking status (Screening), geographical region, post-bronchodilator percent predicted FEV_1 (Screening), and a treatment group by geographical region interaction. Analyses of treatment by region interaction for trough FEV_1 and SGRQ total score were performed using a repeated measures model with covariates of treatment group, smoking status (Screening), geographical region, visit, baseline, baseline by visit, and treatment group by visit by geographical region interactions.

Supplementary Table 1: Baseline characteristics by treatment (ITT populations)

	Western Europe			North America			ITT		
	FF/UMEC/VI (N = 1252)	FF/VI (N = 1274)	UMEC/VI (N = 638)	FF/UMEC/VI (N = 1071)	FF/VI (N = 1046)	UMEC/VI (N = 522)	FF/UMEC/VI (N = 4151)	FF/VI (N = 4134)	UMEC/VI (N = 2070)
Age, mean (SD), years	64.1 (8.1)	64.3 (7.9)	64.0 (7.9)	65.1 (8.2)	65.1 (8.6)	65.1 (8.7)	65.3 (8.2)	65.3 (8.3)	65.2 (8.3)
Male, n (%)	822 (66)	808 (63)	384 (60)	531 (50)	520 (50)	279 (53)	2766 (67)	2748 (66)	1356 (66)
Ethnicity, n (%)									
Not Hispanic/Latino	1232 (98)	1247 (98)	629 (99)	1038 (97)	1019 (97)	507 (97)	3490 (84)	3471 (84)	1732 (84)
Hispanic/Latino	20 (2)	26 (2)	9 (1)	33 (3)	27 (3)	15 (3)	661 (16)	662 (16)	338 (16)
BMI, mean (SD), kg/m^2	27.3 (5.8)	27.0 (5.7)	26.9 (5.6)	28.4 (7.0)	28.6 (6.9)	28.3 (6.3)	26.6 (6.2)	26.7 (6.1)	26.6 (5.9)
Smoking status, n (%)									
Former smoker	767 (61)	755 (59)	373 (58)	670 (63)	633 (61)	308 (59)	2715 (65)	2711 (66)	1342 (65)
Current smoker	485 (39)	519 (41)	265 (42)	401 (37)	413 (39)	214 (41)	1436 (35)	1423 (34)	728 (35)
Smoking history (pack-years), mean (SD)	42.9 (21.9)	43.5 (23.6)	43.2 (2.5)	51.6 (28.6)	51.7 (27.7)	53.3 (29.0)	46.7 (26.7)	46.4 (26.2)	47.0 (27.4)
Post-bronchodilator FEV$_1$, L, mean (SD)	1.362 (0.482)	1.345 (0.491)	1.315 (0.465)	1.215 (0.501)	1.219 (0.478)	1.259 (0.496)	1.275 (0.488)	1.272 (0.486)	1.268 (0.481)
Post-bronchodilator FEV$_1$ % predicted, mean (SD)	46.3 (14.3)	46.1 (14.0)	45.3 (13.5)	44.1 (15.2)	44.2 (14.6)	44.8 (14.8)	45.7 (15.0)	45.5 (14.8)	45.4 (14.7)
Post-bronchodilator FVC, L, mean (SD)	2.831 (0.822)	2.803 (0.857)	2.758 (0.813)	2.563 (0.836)	2.590 (0.826)	2.641 (0.836)	2.728 (0.819)	2.731 (0.827)	2.710 (0.802)
Post-bronchodilator FEV$_1$/FVC ratio, mean (SD)	0.485 (0.115)	0.484 (0.115)	0.482 (0.115)	0.475 (0.119)	0.475 (0.117)	0.480 (0.120)	0.470 (0.119)	0.469 (0.119)	0.472 (0.122)
SGRQ total score, mean (SD)	48.4 (16.0)	48.3 (16.1)	48.0 (14.9)	55.1 (15.2)	54.8 (15.1)	54.4 (15.6)	50.8 (16.8)	50.7 (17.0)	50.2 (16.7)
Exacerbation history in prior 12 months, n (%)									
<2 moderate and 0 severe	355 (28)	384 (30)	193 (30)	356 (33)	351 (34)	180 (34)	1198 (29)	1242 (30)	616 (30)
≥2 moderate or ≥1 severe	897 (72)	890 (70)	445 (70)	715 (67)	695 (66)	342 (66)	2953 (71)	2892 (70)	1454 (70)
Blood eosinophil count (cells/µL), median (IQR)	180 (110–280)	180 (110–280)	190 (120–290)	150 (90–240)	160 (90–250)	160 (90–250)	160 (90–270)	170 (100–270)	170 (100–280)
COPD medication at screening*, n (%)									
ICS+LAMA+LABA	631 (50)	643 (50)	338 (53)	489 (46)	494 (47)	234 (45)	1672 (40)	1647 (40)	864 (42)
LAMA+LABA	242 (19)	220 (17)	127 (20)	45 (4)	38 (4)	17 (3)	389 (9)	349 (8)	196 (9)
ICS+LABA	182 (15)	203 (16)	82 (13)	344 (32)	300 (29)	174 (33)	1354 (33)	1340 (32)	647 (31)

| LAMA | 97 (8) | 117 (9) | 57 (9) | 82 (8) | 96 (9) | 48 (9) | 304 (7) | 365 (9) | 162 (8) |

*Between day of screening -3 days and date of screening (inclusive). BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FF, fluticasone furoate; FVC = forced vital capacity; ICS = inhaled corticosteroid; IQR = interquartile range; ITT = intent-to-treat; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; SD = standard deviation; UMEC = umeclidinium; VI = vilanterol.

Supplementary Table 2: Mean (SD) baseline blood eosinophil counts (cells/µL) by country

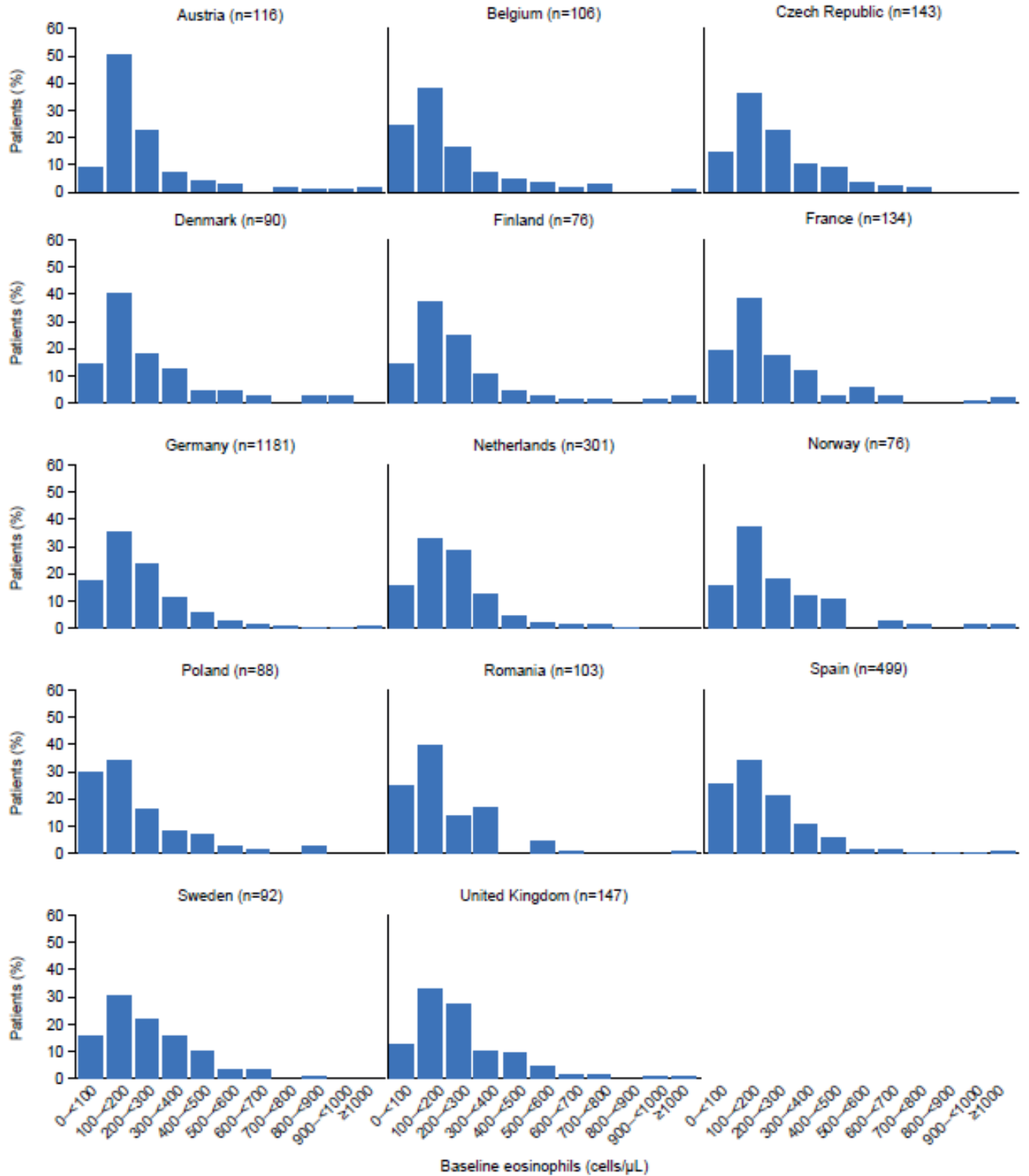|	FF/UMEC/VI n = 4151	FF/VI n = 4134	UMEC/VI n = 2070	Total n = 10355
Western Europe				
Austria	272 (306)	209 (163)	225 (109)	238 (226)
Belgium	200 (155)	230 (293)	237 (193)	219 (222)
Czech Republic	239 (157)	243 (155)	209 (129)	235 (150)
Denmark	246 (207)	258 (220)	233 (132)	248 (198)
Finland	214 (221)	273 (240)	286 (203)	251 (225)
France	216 (184)	222 (160)	268 (250)	230 (191)
Germany	233 (189)	219 (173)	239 (190)	229 (183)
Netherlands	225 (152)	214 (134)	232 (160)	222 (146)
Norway	277 (256)	239 (204)	200 (124)	247 (214)
Poland	169 (146)	223 (175)	223 (194)	201 (168)
Romania	207 (234)	196 (130)	216 (149)	204 (179)
Spain	198 (147)	222 (190)	190 (122)	206 (163)
Sweden	243 (175)	228 (122)	279 (176)	244 (155)
United Kingdom	221 (155)	291 (185)	231 (180)	251 (174)
North America				
Canada	261 (257)	186 (147)	236 (180)	226 (206)
Puerto Rico	356 (371)	227 (277)	133 (58)	257 (294)
United States	189 (165)	216 (277)	203 (199)	203 (222)

FF = fluticasone furoate; SD = standard deviation; UMEC = umeclidinium; VI = vilanterol.

Supplementary Table 3: Interactions of treatment with geographical region (North America vs Western Europe)

	Treatment comparison	Estimate (95% CI)	*P*-value
Moderate/severe exacerbation annual rate	FF/UMEC/VI vs FF/VI	1.05 (0.89–1.24)	.537
	FF/UMEC/VI vs UMEC/VI	0.90 (0.73–1.09)	.271
	UMEC/VI vs FF/VI	1.18 (0.96–1.43)	.109
	Overall		**.276**
SGRQ total score at week 52	FF/UMEC/VI vs FF/VI	2.2 (0.4–4.0)	.018
	FF/UMEC/VI vs UMEC/VI	1.5 (-0.8–3.8)	.192
	UMEC/VI vs FF/VI	0.7 (-1.6–3.0)	.560
	Overall		**.054**
Trough FEV$_1$ at week 52, mL	FF/UMEC/VI vs FF/VI	-20 (-53–13)	.236
	FF/UMEC/VI vs UMEC/VI	-29 (-70–12)	.159
	UMEC/VI vs FF/VI	10 (-32–51)	.653
	Overall		**.291**

CI = confidence interval; FEV$_1$ = forced expiratory volume in 1 second; FF = fluticasone furoate; SGRQ = St George's Respiratory Questionnaire; UMEC = umeclidinium; VI = vilanterol.

Supplementary Figure 1: Histogram of blood eosinophils at baseline (linear scale) in Western Europe

Histogram of blood eosinophils at baseline (linear scale) in Western Europe. Individual panels shown for Austria (n=116), Belgium (n=106), Czech Republic (n=143), Denmark (n=90), Finland (n=76), France (n=134), Germany (n=1181), Netherlands (n=301), Norway (n=76), Poland (n=88), Romania (n=103), Spain (n=499), Sweden (n=92), and United Kingdom (n=147). Y-axis: Patients (%). X-axis: Baseline eosinophils (cells/µL), categories 0–<100, 100–<200, 200–<300, 300–<400, 400–<500, 500–<600, 600–<700, 700–<800, 800–<900, 900–<1000, ≥1000.

Supplementary Figure 2: Histogram of blood eosinophils at baseline (linear scale) In North America