Appendix 1: Confounders and propensity matching, extended

To account for confounders, propensity score matching was undertaken prior to statistical analysis. Inclusion in the matching process required a covariate to have no more than 20% missing data. Where data were missing, a variable was encoded into a categorical variable with a category added for the observations with missing values. The propensity score was generated from logistic regression modelling using all available patient-level baseline characteristics that were expected on clinical grounds to be related to the outcome or to both the outcome and treatment allocation (age, gender, body mass index, smoking status, season of index date, comorbidities, recent exacerbation history, recent acute oral corticosteroid use, recent antibiotics for a lower-respiratory tract infection indication, ICS average daily dose in baseline year and pulmonary function measurements). The logit of the propensity score was used as the matching scale with a calliper width equal to 0.2 of the standard deviation of the logit of the propensity score, in line with the recommendations of Austin (2011).

Matching rate (>60% of smaller treatment group matched) and multivariable balance (<90% of baseline variables showing <10% standard mean difference) were used to establish criteria for accepting a matching set. Residual bias potential after propensity matching was assessed using the relative change in coefficient of the treatment when each baseline characteristic was added into the outcome model fitted to the propensity score matched samples. Where bias statistics were at least 2%, baseline variables were added to the outcome model in a forward selection approach, in descending order of highest bias potential.

Appendix 2: Table 1 extended: Further demographic and clinical features of unmatched and matched populations commencing formulations containing extrafine beclometasone/long-acting bronchodilators (ef-BDP/LABD) or long-acting bronchodilators (LABD).

Variable		Unmatched		Matched	
		Initiating ef-BDP/LABD n = 5561	Initiating LABD n = 18492	Initiating ef-BDP/LABD n = 5142	Initiating LABD n = 5142
Season of index date	Spring, n (%)	1625 (29.2)	5116 (27.7)	1481 (28.8)	1445 (28.1)
	Summer, n (%)	1257 (22.6)	4277 (23.1)	1152 (22.4)	1198 (23.3)
	Autumn, n (%)	1248 (22.4)	4076 (22.0)	1161 (22.6)	1125 (21.9)
	Winter, n (%)	1431 (25.7)	5023 (27.2)	1348 (26.2)	1374 (26.7)
Comorbidities					
Mental disorder	Yes, n (%)	103 (1.9)	374 (2.0)	96 (1.9)	88 (1.7)
Glaucoma	Yes, n (%)	168 (3.0)	563 (3.0)	156 (3.0)	155 (3.0)
Cataract	Yes, n (%)	712 (12.8)	2444 (13.2)	655 (12.7)	633 (12.3)
Atrial fibrillation	Yes, n (%)	380 (6.8)	1411 (7.6)	350 (6.8)	353 (6.9)
Moderate renal impairment	Yes, n (%)	548 (9.9)	1857 (10.0)	507 (9.9)	479 (9.3)
Pneumonia in baseline	Yes, n (%)	144 (2.6)	359 (1.9)	125 (2.4)	118 (2.3)
Bronchiectasis	Yes, n (%)	123 (2.2)	274 (1.5)	102 (2.0)	115 (2.2)
Hypertension	Yes, n (%)	3430 (37.2)	7249 (39.2)	1756 (34.2)	1739 (33.8)
Cardiovascular disease	Yes, n (%)	1535 (27.6)	5648 (30.5)	1409 (27.4)	1405 (27.3)
Coronary heart disease	Yes, n (%)	699 (12.6)	2733 (14.8)	652 (12.7)	633 (12.3)
Myocardial infarction	Yes, n (%)	388 (7.0)	1522 (8.2)	361 (7.0)	356 (6.9)
Cerebrovascular accident	Yes, n (%)	266 (4.8)	1039 (5.6)	250 (4.9)	256 (5.0)
Heat failure	Yes, n (%)	248 (4.5)	791 (4.3)	221 (4.3)	231 (4.5)
Ischaemic heart disease	Yes, n (%)	772 (13.9)	2951 (16.0)	718 (14.0)	686 (13.3)
Diabetes diagnosis or medication	Yes, n (%)	771 (13.9)	2658 (14.4)	714 (13.9)	732 (14.2)

Osteoporosis	Yes, n (%)	286 (5.1)	996 (5.4)	256 (5.0)	254 (4.9)
Parkinson disease	Yes, n (%)	15 (0.3)	62 (0.3)	14 (0.3)	18 (0.4)
Sleep disorder	Yes, n (%)	674 (12.1)	2291 (12.4)	633 (12.3)	613 (11.9)
LAMA before index date	No LAMA, n (%)	3209 (57.7)	-	3106 (60.4)	-
	Glycopyrronium, n (%)	318 (5.7)	-	262 (5.1)	-
	Tiotropium, n (%)	1506 (27.1)	-	1315 (25.6)	-
	Aclidinium, n (%)	277 (5.0)	-	237 (4.6)	-
	Umeclidinium, n (%)	251 (4.5)	-	222 (4.3)	-
LABA (mono or FDC) prescriptions	0, n (%)	4516 (81.2)	-	4279 (83.2)	5142 (100.0)
	1-2, n (%)	280 (5.0)	-	261 (5.1)	0 (0.0)
	3-5, n (%)	233 (4.2)	-	199 (3.9)	0 (0.0)
	6-9, n (%)	261 (4.7)	-	199 (3.9)	0 (0.0)
	≥10, n (%)	271 (4.9)	-	204 (4.0)	0 (0.0)
LAMA prescriptions	0, n (%)	3209 (57.7)	-	3106 (60.4)	5142 (100.0)
	1-2, n (%)	565 (10.2)	-	535 (10.4)	0 (0.0)
	3-5, n (%)	568 (10.2)	-	499 (9.7)	0 (0.0)
	6-9, n (%)	537 (9.7)	-	453 (8.8)	0 (0.0)
	≥10, n (%)	682 (12.3)	-	549 (10.7)	0 (0.0)
SABA prescriptions	0, n (%)	1794 (32.3)	7963 (43.1)	1771 (34.4)	1827 (35.5)
	1-2, n (%)	1440 (25.9)	6283 (34.0)	1420 (27.6)	1370 (26.6)
	3-5, n (%)	900 (16.2)	2162 (11.7)	828 (16.1)	799 (15.5)
	6-9, n (%)	700 (12.6)	1193 (6.5)	584 (11.4)	582 (11.3)
	≥10, n (%)	727 (13.1)	891 (4.8)	539 (10.5)	564 (11.0)
SAMA prescriptions	≥1, n (%)	192 (3.5)	667 (3.6)	181 (3.5)	189 (3.7)
Theophylline prescriptions	≥1, n (%)	29 (0.5)	16 (0.1)	10 (0.2)	14 (0.3)
Leukotriene Receptor Antagonists prescriptions	≥1, n (%)	23 (0.4)	30 (0.2)	15 (0.3)	18 (0.4)
Macrolides prescriptions	0, n (%)	4762 (85.6)	16295 (88.1)	4436 (86.3)	4417 (85.9)
	1, n (%)	510 (9.2)	1599 (8.6)	461 (9.0)	478 (9.3)
	2, n (%)	176 (3.2)	401 (2.2)	152 (3.0)	153 (3.0)
	3, n (%)	57 (1.0)	117 (0.6)	51 (1.0)	54 (1.1)
	4, n (%)	28 (0.5)	40 (0.2)	21 (0.4)	19 (0.4)

	≥5, n (%)	28 (0.5)	40 (0.2)	21 (0.4)	21 (0.4)
Mucolytics prescriptions	0, n (%)	5161 (92.8)	17993 (97.3)	4864 (94.6)	4875 (94.8)
	1, n (%)	167 (3.0)	255 (1.4)	129 (2.5)	121 (2.4)
	2, n (%)	50 (0.9)	62 (0.3)	35 (0.7)	30 (0.6)
	≥3, n (%)	183 (3.3)	182 (1.0)	114 (2.2)	116 (2.3)
Maintenance OCS prescriptions	≥1, n (%)	136 (2.4)	264 (1.4)	113 (2.2)	115 (2.2)
Oral corticosteroids, average daily dose (mg)	0, n (%)	3059 (55.0)	13723 (74.2)	3033 (59.0)	3031 (58.9)
	>0 <2.5, n (%)	2146 (38.6)	4353 (23.5)	1890 (36.8)	1878 (36.5)
	≥2.5 <7.5, n (%)	302 (5.4)	305 (1.6)	171 (3.3)	180 (3.5)
	≥7.5, n (%)	54 (1.0)	111 (0.6)	48 (0.9)	53 (1.0)
Influenza vaccination	Yes, n (%)	2464 (44.3)	8167 (44.2)	2232 (43.4)	2256 (43.9)
Pneumococcal vaccination	Yes, n (%)	651 (11.7)	2206 (11.9)	595 (11.6)	584 (11.4)
Exacerbations	0, n (%)	2290 (41.2)	9978 (54.0)	2268 (44.1)	2304 (44.8)
	1, n (%)	1453 (26.1)	5194 (28.1)	1407 (27.4)	1373 (26.7)
	2, n (%)	895 (16.1)	2090 (11.3)	812 (15.8)	803 (15.6)
	3, n (%)	455 (8.2)	774 (4.2)	363 (7.1)	374 (7.3)
	4, n (%)	233 (4.2)	282 (1.5)	167 (3.2)	159 (3.1)
	≥5, n (%)	235 (4.2)	174 (0.9)	125 (2.4)	129 (2.5)
Acute OCS courses	0, n (%)	3293 (59.2)	14296 (77.3)	3253 (63.3)	3244 (63.1)
	1, n (%)	1230 (22.1)	2997 (16.2)	1158 (22.5)	1154 (22.4)
	2, n (%)	548 (9.9)	777 (4.2)	446 (8.7)	440 (8.6)
	3, n (%)	245 (4.8)	264 (1.4)	169 (3.3)	175 (3.4)
	4, n (%)	121 (2.2)	101 (0.5)	71 (1.4)	76 (1.5)
	≥5, n (%)	124 (2.2)	57 (0.3)	45 (0.9)	53 (1.0)
Antibiotics courses	0, n (%)	3265 (58.7)	12250 (65.2)	3119 (60.7)	3188 (62.0)
	1, n (%)	1246 (22.4)	3928 (21.2)	1143 (22.2)	1087 (21.1)
	2, n (%)	565 (10.2)	1469 (7.9)	502 (9.8)	492 (9.6)
	3, n (%)	269 (4.8)	523 (2.8)	217 (4.2)	223 (4.3)
	4, n (%)	118 (2.1)	193 (1.0)	91 (1.8)	77 (1.5)
	≥5, n (%)	98 (1.8)	129 (0.7)	70 (1.4)	75 (1.5)
Primary care service contact	<5, n (%)	1068 (19.2)	2657 (14.4)	1020 (19.8)	1040 (20.2)
	5 <10, n (%)	1539 (27.7)	6074 (32.8)	1465 (28.5)	1461 (28.4)
	10 <15, n (%)	1339 (24.1)	4770 (25.8)	1237 (24.1)	1214 (23.6)
	15 <20, n (%)	766 (13.8)	2451 (13.3)	673 (13.1)	696 (13.5)

20 <30, n (%)	616 (11.1)	1870 (10.1)	541 (10.5)	544 (10.6)
≧30, n (%)	233 (4.2)	670 (3.6)	206 (4.0)	187 (3.6)
	0, n (%)	333 (6.0)	519 (2.8)	646 (12.6)	638 (12.4)
GP consultations	1, n (%)	177 (3.2)	309 (1.7)	918 (17.9)	955 (18.6)
with respiratory	2, n (%)	150 (2.7)	400 (2.2)	1028 (20.0)	1013 (19.7)
indication	3, n (%)	188 (3.4)	607 (3.3)	845 (16.4)	870 (16.9)
	4-5, n (%)	506 (9.1)	1861 (10.1)	996 (19.4)	958 (18.6)
	≧6, n (%)	4207 (75.7)	14796 (80.0)	709 (13.8)	708 (13.8)