SUPPLEMENTAL MATERIAL

Table S1. Baseline Demographics and Clinical Characteristics of Unmatched Patients

	I/S Comparator n=554	Originator n=5638	*P*-value[a]
Year when patients received index prescription, mean±SD	2011±0.8	2006±0.6	<0.001
Age when patients received index prescription, mean±SD	58.9±12.1	58.3±11.6	0.391
Age, categories, n (%)			
35-60 y	322 (58.1)	3346 (59.3)	
60-80 y	193 (34.8)	2290 (40.6)	<0.001
>80 y	39 (7.0)	2 (0)	
Gender, n (%) Males	217 (39.2)	2020 (35.8)	0.118
Asthma diagnosis, n (%)	259 (46.8)	2348 (41.6)	0.020
Rhinitis diagnosis, n (%)	135 (24.4)	1017 (18.0)	<0.001
GERD[b], n (%)	216 (39.0)	1818 (32.2)	0.001
Ischemic heart disease diagnosis, n (%)	155 (28.0)	1247 (22.1)	0.002
Prescribed NSAIDs, n (%)	203 (36.6)	1955 (34.7)	0.354
Prescribed beta-blockers, n (%)	165 (29.8)	1375 (24.4)	0.005
Charlson Comorbidity Index score[c], n (%)			
0	70 (12.7)	1267 (22.5)	
1-4	228 (41.3)	2360 (41.9)	<0.001
≥5	254 (46.0)	2005 (35.6)	
Moderate and severe COPD exacerbations in the year before and including the index prescription date, n			

	I/S Comparator n=554	Originator n=5638	*P*-value[a]
(%)			
0	164 (29.6)	2505 (44.4)	
1	150 (27.1)	1648 (29.2)	<0.001
2	101 (18.2)	746 (13.2)	
≥3	139 (25.1)	739 (13.1)	
Severe COPD exacerbations in the year before and including the index prescription date, n (%)			
0	367 (66.2)	4102 (72.8)	
1	127 (22.9)	1085 (19.2)	0.010
2	39 (7.0)	287 (5.1)	
≥3	21 (3.8)	164 (2.9)	

AE=adverse event; COPD=chronic obstructive pulmonary disease; GERD=gastroesophageal reflux disease; I/S=ipratropium/salbutamol; NSAIDs=nonsteroidal anti-inflammatory drugs; SD=standard deviation.

[a] *P*-value was based on t-test, Mann-Whitney U test, or Chi-square test depending on the variable (see methods).

[b]Includes diagnosis and/or therapy.

[c]Charlson Comorbidity Index [17] is a method of predicting 1-year mortality for a patient who may have a range of comorbid conditions that are each assigned a "weight" corresponding to risk of death associated with the condition; scores are then summed to give a total score predicting mortality.

Items shaded in gray were among the final matching criteria.

Table S2. Baseline Use of Respiratory Therapies in Unmatched Patients

	I/S Comparator n=554	Originator n=5638	*P*-value[a]
≥1 prescription for respiratory therapies in the year before patients received the index prescription, n (%)			
ICS	253 (45.7)	2098 (37.2)	<0.001
LABA	216 (39.0)	1787 (31.7)	<0.001
LAMA	72 (13.0)	488 (8.7)	<0.001
SAMA nebulizer	36 (6.5)	293 (5.2)	0.193
SAMA inhaler	7 (1.3)	100 (1.8)	0.379
SABA nebulizer	81 (14.6)	602 (10.7)	0.005
SABA inhaler	246 (44.4)	1924 (34.1)	<0.001
Prescribed daily dose of SABA inhalers (µg)[b] in the year before patients received the index prescription, categorized, n (%)			
0	308 (55.6)	3714 (65.9)	
1-200	140 (25.3)	891 (15.8)	<0.001
>200	106 (19.1)	1033 (18.3)	
Prescriptions of acute oral corticosteroids[c] for lower respiratory events[d] in the year before patients received the index prescription, n (%)			
0	263 (47.5)	3399 (60.3)	
1	131 (23.6)	1313 (23.3)	<0.001
2	61 (11.0)	445 (7.9)	

	I/S Comparator n=554	Originator n=5638	*P*-value[a]
≥3	99 (17.9)	481 (8.5)	
Prescriptions for antibiotics for lower respiratory events[d] in the year before patients received the index prescription, n (%)			
0	234 (42.2)	3224 (57.2)	
1	143 (25.8)	1347 (23.9)	<0.001
2-3	118 (21.3)	860 (15.3)	
≥4	59 (10.6)	207 (3.7)	

ICS=inhaled corticosteroid; I/S=ipratropium/salbutamol; LABA=long-acting β_2 agonist; LAMA=long-acting muscarinic antagonist; SABA=short-acting β_2 agonist; SAMA=short-acting muscarinic antagonist.

[a] *P*-value was based on t-test, Mann-Whitney U test, or Chi-square test depending on the variable (see methods).

[b]Daily dose was calculated as [(count of inhalers x doses in pack) / 365] x µg strength.

[c]Defined as all courses where dosing instructions suggest exacerbation treatment and/or unlikely to be maintenance treatment.

[d]Defined as a COPD-related Emergency Department visit/hospital admission/ambulatory visit or a respiratory investigation recorded within a ±5-day window from the prescription.

Items shaded in gray were among the final matching criteria.

Table S3. Baseline Prevalence of AEs in Unmatched Patients

	I/S Comparator n=554	Originator n=5638	*P*-value[a]
Any AE, n (%)			<0.001
0	116 (20.9)	2152 (38.2)	
1	74 (13.4)	905 (16.1)	
≥2	364 (65.7)	2581 (45.8)	
Immune system disorders, n (%) (hypersensitivity reactions with angioedema, anaphylactic reactions)			0.015
0	550 (99.3)	5621 (99.7)	
1	2 (0.4)	15 (0.3)	
≥2	2 (0.4)	2 (0)	
Metabolic and nutritional disorders, n (%) (hypokalemia, urinary retention)			0.008
0	521 (94.0)	5445 (96.6)	
1	14 (2.5)	93 (1.6)	
≥2	19 (3.4)	100 (1.8)	
Psychiatric disorders, n (%) (restlessness, memory disorders, anxiety)			<0.001
0	436 (78.7)	4917 (87.2)	
1	42 (7.6)	250 (4.4)	
≥2	76 (13.7)	471 (8.4)	
Nervous system disorders, n (%) (headache, tremor, dizziness)			0.130

	I/S Comparator n=554	Originator n=5638	*P*-value[a]
0	514 (92.8)	5336 (94.6)	
1	28 (5.1)	193 (3.4)	
≥2	12 (2.2)	109 (1.9)	
Eye disorders, n (%) (cataract, glaucoma, accommodation disorders, mydriasis)			0.091
0	514 (92.8)	5353 (94.9)	
1	20 (3.6)	147 (2.6)	
≥2	20 (3.6)	138 (2.4)	
Skin and subcutaneous tissue disorders, n (%) (rash, urticaria, pruritus, hyperhidrosis)			0.992
0	547 (98.7)	5566 (98.7)	
1	5 (0.9)	53 (0.9)	
≥2	2 (0.4)	19 (0.3)	
Cardiovascular disorders, n (%) (palpitations, tachycardia, cardiac arrhythmias, atrial fibrillation, myocardial ischemia, peripheral vasodilation, coronary ischemic disease)			0.010
0	383 (69.1)	4209 (74.7)	
1	41 (7.4)	393 (7.0)	
≥2	130 (23.5)	1036 (18.4)	
Respiratory, thoracic, and mediastinal disorders, n (%) (laryngospasm, pharyngeal edema, throat irritation,			<0.001

	I/S Comparator n=554	Originator n=5638	*P*-value[a]
hoarseness/dysphonia, sinusitis, dyspnea, bronchospasm/paradoxical bronchospasm)			
0	285 (51.4)	3857 (68.4)	
1	121 (21.8)	960 (17.0)	
≥2	148 (26.7)	821 (14.6)	
Musculoskeletal and connective tissue disorders, n (%) (muscle cramps, myalgia)			0.003
0	498 (89.9)	5280 (93.7)	
1	26 (4.7)	177 (3.1)	
≥2	30 (5.4)	181 (3.2)	
Gastrointestinal disorders, n (%) (dry mouth, nausea, motility disorders [diarrhea, constipation, vomiting], mouth edema, stomatitis)			<0.001
0	417 (75.3)	4709 (83.5)	
1	49 (8.8)	338 (6.0)	
≥2	88 (15.9)	591 (10.5)	

I/S=ipratropium/salbutamol.

[a]*P*-value was based on t-test, Mann-Whitney U test, or Chi-square test depending on the variable (see methods).