ONLINE SUPPLEMENTAL MATERIAL

e-Table 1. Classification of exposure categories and regimens for secondary analyses exploring impact of concomitant ICS use

Exposure categories and regimens	Products included in regimen
LAMA and LABA *with* ICS	
LAMA+LABA/ICS	Concurrent use of LAMA single agent product and LABA/ICS combination product
LAMA+LABA+ICS	Concurrent use of three single agent products (LAMA, LABA, and ICS)
LAMA *with* ICS	
LAMA+ICS	Concurrent use of LAMA and ICS single agent products
LABA *with* ICS	
LABA+ICS	Concurrent use of LABA and ICS single agent products
LABA/ICS	Use of LABA/ICS combination product only
ICS mono-therapy	
ICS	Use of ICS single agent product only
LAMA and LABA *without* ICS	
LAMA+LABA	Concurrent use of LAMA and LABA single agent products
LAMA *without* ICS	
LAMA	Use of LAMA single agent product only
LABA *without* ICS	
LABA	Use of LABA single agent product only

Abbreviations ICS: Inhaled corticosteroid, LABA: Long-acting beta$_2$-agonist, LAMA: Long-acting muscarinic antagonist.

e-Table 2. Classification of severity of COPD

Severity of COPD	Criteria
Very severe	• 1 or more hospitalisations in 2 years before cohort entry in which COPD-related respiratory disease was the principal diagnosis; **or** • 4 or more exacerbations* in previous 2 years
Severe	• 1 hospitalisation in 2 years before cohort entry in which COPD-related respiratory disease was principal diagnosis; **or** • 2 or 3 exacerbations* in previous 2 years
Mild/moderate	• 0 – 1 exacerbations* in previous 2 years

Abbreviation COPD: chronic obstructive pulmonary disease.

* Cohort members were classified as having had a COPD exacerbation if they were dispensed antibiotics (amoxicillin, augmentin, doxycycline, or roxithromycin) and prednisone 20mg tablets on the same date, **or** were dispensed prednisone 20mg tablets at any time in the 7 days before or after one of the above antibiotics was dispensed.

e-Table 3. Full characteristics of cases and controls. Values are numbers (percentages) unless stated otherwise

Characteristic	Cases (n=5,399)	Controls (n=51,563)
Median age at cohort entry (years, IQR)	74.3 (65.8 – 80.8)	73.8 (65.6 – 80.2)
Median follow-up from cohort entry to index date (years, IQR)	1.6 (0.6 – 3.1)	1.6 (0.6 – 3.1)
Sex		
Female	2,388 (44.2)	22,709 (44.0)
Male	3,011 (55.8)	28,854 (56.0)
Ethnicity, prioritised*		
European	4,274 (79.2)	41,165 (79.8)
Māori	716 (13.3)	5,129 (10.0)
Pacific	158 (2.9)	1,758 (3.4)
Asian	129 (2.4)	1,420 (2.8)
Other	17 (0.3)	223 (0.4)
Missing	105 (1.9)	1,868 (3.6)
NZDep06 quintile		
1 (least disadvantaged)	600 (11.1)	6,969 (13.5)
2	732 (13.6)	8,057 (15.6)
3	1,119 (20.7)	10,922 (21.2)
4	1,472 (27.3)	13,344 (25.9)
5 (most disadvantaged)	1,465 (27.1)	12,159 (23.6)
Missing	11 (0.2)	112 (0.2)
Charlson comorbidity score at cohort entry†		
0	2,224 (41.2)	29,214 (56.7)
1	1,133 (21.0)	11,090 (21.5)
2	823 (15.2)	5,614 (10.9)
$\geq$ 3	1,219 (22.6)	5,645 (11.0)
COPD severity at cohort entry		
Mild/moderate	3,401 (63.0)	33,460 (64.9)
Severe	1,164 (21.6)	10,990 (21.3)
Very severe	834 (15.5)	7,113 (13.8)
Hospital discharge diagnoses at any time before cohort entry		
Acute coronary syndrome	1,883 (34.9)	7,539 (14.6)
Other ischaemic heart disease	2,081 (38.5)	9,297 (18.0)
Raised blood pressure	2,523 (46.7)	15,076 (29.2)
Dyslipidaemia	1,305 (24.2)	6,091 (11.8)
Heart failure	1,267 (23.5)	6,402 (12.4)

Characteristic (continued)	**Cases (n=5,399)**	**Controls (n=51,563)**
Life-threatening arrhythmia	630 (11.7)	3,302 (6.4)
Ischaemic stroke	223 (4.1)	1,430 (2.8)
Transient ischaemic attack	265 (4.9)	1,526 (3.0)
Diabetes	956 (17.7)	5,174 (10.0)
Hyperthyroidism	51 (0.9)	300 (0.6)
Benign prostatic hypertrophy/bladder outflow obstruction	374 (6.9)	3,031 (5.9)
Closed-angle glaucoma	10 (0.2)	101 (0.2)
Osteoporotic fracture	50 (0.9)	293 (0.6)
Medication use in 6 months before cohort entry		
Statin	2,552 (47.3)	17,438 (33.8)
Antiplatelet	2,669 (49.4)	18,077 (35.1)
Blood pressure lowering	3,970 (73.5)	31,189 (60.5)
Non-steroidal anti-inflammatory	813 (15.1)	7,757 (15.0)
Oral theophylline	54 (1.0)	445 (0.9)

Abbreviations COPD: chronic obstructive pulmonary disease, IQR: interquartile range.

* Self-identified ethnicity categorised according to the Ministry of Health Ethnicity Data Protocols and prioritised in the following order: Māori, Pacific Peoples, Asian, Other, European.

† Based on hospital discharge diagnoses in the 5 years before cohort entry.

e-Table 4. Characteristics of cases and controls before index date. Values are numbers (percentages).

Characteristic	Cases (n=5,399)	Controls (n=51,563)
Hospital discharge diagnoses at any time before index date		
Acute coronary syndrome	1,883 (34.9)	7,539 (14.6)
Other ischaemic heart disease	2,292 (42.5)	9,971 (19.3)
Raised blood pressure	2,818 (52.2)	16,962 (32.9)
Dyslipidaemia	1,399 (25.9)	6,612 (12.8)
Heart failure	1,661 (30.8)	8,007 (15.5)
Life-threatening arrhythmia	744 (13.8)	3,926 (7.6)
Ischaemic stroke	305 (5.7)	1,893 (3.7)
Transient ischaemic attack	319 (5.9)	1,894 (3.7)
Diabetes	1,078 (20.0)	5,985 (11.6)
Hyperthyroidism	60 (1.1)	377 (0.7)
Benign prostatic hypertrophy/bladder outflow obstruction	427 (7.9)	3,495 (6.8)
Closed-angle glaucoma	11 (0.2)	132 (0.3)
Osteoporotic fracture	80 (1.5)	452 (0.9)
Medication use in 6 months before index date		
Statin	2,746 (50.9)	19,557 (37.9)
Antiplatelet	3,143 (58.2)	20,796 (40.3)
Blood pressure lowering	4,269 (79.1)	33,757 (65.5)
Non-steroidal anti-inflammatory	806 (14.9)	7,836 (15.2)
Oral theophylline	77 (1.4)	534 (1.0)

e-Table 5. Risk of acute coronary syndrome as a principal diagnosis in relation to long-acting bronchodilator exposure status in 30 days before index date

Exposure status	Cases (No. [%])	Controls (No. [%])	Matched unadjusted odds ratio (95% CI)	Matched adjusted odds ratio* (95% CI)
LAMA and LABA dual therapy	404 (10.3)	3,315 (8.8)	1.20 (1.04 – 1.38)	1.22 (1.05 – 1.41)
LAMA therapy	440 (11.2)	4,296 (11.4)	1.0	1.0
LABA therapy	1,501 (38.4)	13,595 (36.2)	1.09 (0.98 – 1.23)	1.12 (0.99 – 1.26)
Unexposed†	1,569 (40.1)	16,388 (43.6)	0.95 (0.84 – 1.06)	0.95 (0.85 –1.07)

Abbreviations CI: confidence interval, LABA: Long-acting beta$_2$-agonist, LAMA: Long-acting muscarinic antagonist, No: Number.

* Adjusted for ethnicity; NZDep06; Charlson comorbidity score; hospital discharge diagnosis before cohort entry of asthma, ACS; hospital discharge diagnosis before cohort entry and (separately) between cohort entry and index date of any ischaemic heart disease, raised blood pressure, dyslipidaemia, heart failure, life-threatening arrhythmia, ischaemic stroke, transient ischaemic attack, diabetes, benign prostatic hypertrophy/bladder outflow obstruction; hospital discharge diagnosis at any time before index date of hyperthyroidism, closed-angle glaucoma, osteoporotic fracture; use in 6 months before cohort entry and (separately) in 6 months before the index date of statin, antiplatelet, blood pressure lowering, non-steroidal anti-inflammatory, and theophylline therapy.

† No long-acting bronchodilator use in 30 days before index date.

e-Table 6. Risk of fatal acute coronary syndrome in relation to long-acting bronchodilator exposure status in 30 days before index date

Exposure status	Cases (No. [%])	Controls (No. [%])	Matched unadjusted odds ratio (95% CI)	Matched adjusted odds ratio* (95% CI)
LAMA and LABA dual therapy	144 (13.5)	943 (9.5)	1.49 (1.16 – 1.92)	1.46 (1.12 – 1.91)
LAMA therapy	140 (13.1)	1,333(13.5)	1.0	1.0
LABA therapy	360 (33.7)	3,563 (36.1)	0.98 (0.79 – 1.21)	1.00 (0.80 – 1.24)
Unexposed†	423 (39.6)	4,045 (40.9)	1.03 (0.84 – 1.27)	1.01 (0.81 – 1.26)

Abbreviations CI: confidence interval, LABA: Long-acting beta$_2$-agonist, LAMA: Long-acting muscarinic antagonist, No: Number.

* Adjusted for ethnicity; NZDep06; Charlson comorbidity score; hospital discharge diagnosis before cohort entry of asthma, ACS; hospital discharge diagnosis before cohort entry and (separately) between cohort entry and index date of any ischaemic heart disease, raised blood pressure, dyslipidaemia, heart failure, life-threatening arrhythmia, ischaemic stroke, transient ischaemic attack, diabetes, benign prostatic hypertrophy/bladder outflow obstruction; hospital discharge diagnosis at any time before index date of hyperthyroidism, closed-angle glaucoma, osteoporotic fracture; use in 6 months before cohort entry and (separately) in 6 months before the index date of statin, antiplatelet, blood pressure lowering, non-steroidal anti-inflammatory, and theophylline therapy.

† No long-acting bronchodilator use in 30 days before index date.

e-Table 7. Risk of acute coronary syndrome in relation to long-acting bronchodilator exposure status in 30 days before index date, stratified by total duration of exposure to the currently used regimen between cohort entry and index date[*]

Exposure status	Cases (No. [%])	Controls (No. [%])	Unmatched adjusted odds ratio[†] (95% CI)	Unmatched adjusted odds ratio[‡] (95% CI)
1 – 30 days				
LAMA and LABA dual therapy	62 (16.0)	341 (16.8)	1.12 (0.78 – 1.62)	1.91 (1.44 – 2.53)
LAMA therapy	74 (19.1)	455 (22.4)	1.0	1.0
LABA therapy	252 (64.9)	1,232 (60.7)	1.26 (0.95 – 1.67)	2.15 (1.85 – 2.50)
31 – 60 days				
LAMA and LABA dual therapy	29 (12.9)	290 (15.3)	0.79 (0.49 – 1.28)	0.74 (0.45 – 1.22)
LAMA therapy	49 (21.8)	383 (20.2)	1.0	1.0
LABA therapy	147 (65.3)	1,223 (64.5)	0.94 (0.67 – 1.33)	0.98 (0.69 – 1.39)
61 – 90 days				
LAMA and LABA dual therapy	42 (20.4)	266 (15.6)	1.42 (0.90 – 2.23)	1.34 (0.84 – 2.14)
LAMA therapy	43 (20.9)	382 (22.4)	1.0	1.0
LABA therapy	121 (58.7)	1,061 (62.1)	1.02 (0.70 – 1.47)	1.04 (071 –1.51)
91 – 183 days				
LAMA and LABA dual therapy	80 (17.9)	670 (14.5)	1.19 (0.87 – 1.62)	1.21 (0.88 – 1.66)
LAMA therapy	104 (23.2)	1,029 (22.3)	1.0	1.0
LABA therapy	264 (58.9)	2,909 (63.1)	0.90 (0.71 –1.14)	0.94 (0.73 –1.20)

Exposure status	Cases (No. [%])	Controls (No. [%])	Unmatched adjusted odds ratio† (95% CI)	Unmatched adjusted odds ratio‡ (95% CI)
184 – 365 days				
LAMA and LABA dual therapy	144 (22.3)	1,010 (17.2)	1.48 (1.15 –1.91)	1.46 (1.12 – 1.89)
LAMA therapy	125 (19.3)	1,293 (22.0)	1.0	1.0
LABA therapy	378 (58.4)	3,566 (60.8)	1.10 (0.89 –1.36)	1.18 (0.95 – 1.46)
> 365 days				
LAMA and LABA dual therapy	284 (20.0)	2.015 (15.4)	1.26 (1.06 – 1.50)	1.27 (1.06 – 1.52)
LAMA therapy	283 (19.9)	2,502 (19.1)	1.0	1.0
LABA therapy	855 (60.1)	8,599 (65.6)	0.89 (0.77 –1.02)	0.92 (0.80 -1.07)

Abbreviations CI: confidence interval, LABA: Long-acting beta$_2$-agonist, LAMA: Long-acting muscarinic antagonist, No: Number.

* Sum of all episodes of use between cohort entry and the index date.

† To undertake this secondary stratified analysis it was necessary to break the matching. Estimates are adjusted for the matching factors (date of birth, sex, date of cohort entry, COPD severity).

‡ Adjusted for the matching factors; ethnicity; NZDep06; Charlson comorbidity score; hospital discharge diagnosis before cohort entry of asthma, ACS; hospital discharge diagnosis before cohort entry and (separately) between cohort entry and index date of any ischaemic heart disease, raised blood pressure, dyslipidaemia, heart failure, life-threatening arrhythmia, ischaemic stroke, transient ischaemic attack, diabetes, benign prostatic hypertrophy/bladder outflow obstruction; hospital discharge diagnosis at any time before index date of hyperthyroidism, closed-angle glaucoma, osteoporotic fracture; use in 6 months before cohort entry and (separately) in 6 months before the index date of statin, antiplatelet, blood pressure lowering, non-steroidal anti-inflammatory, and theophylline therapy.

e-Table 8. Risk of acute coronary syndrome in relation to long-acting bronchodilator exposure status in 30 days before index date, stratified by history of ischaemic cardiovascular disease

Exposure status	Cases (No. [%])	Controls (No. [%])	Unmatched adjusted odds ratio* (95% CI)	Unmatched adjusted odds ratio† (95% CI)
History of ischaemic cardiovascular disease‡				
LAMA and LABA dual therapy	327 (11.6)	1,335 (9.7)	1.30 (1.10 1.53)	1.22 (1.04 – 1.44)
LAMA therapy	383 (13.6)	1,975 (14.4)	1.0	1.0
LABA therapy	1,056 (37.4)	4,734 (34.4)	0.90 (0.79 – 1.03)	1.10 (0.96 – 1.25)
Unexposed§	1,061 (37.5)	5,704 (41.5)	0.77 (0.68 – 0.88)	0.88 (0.78 –1.01)
No history of ischaemic cardiovascular disease‡				
LAMA and LABA dual therapy	314 (12.2)	3,257 (8.6)	1.24 (1.06 –1.46)	1.26 (1.06 –1.48)
LAMA therapy	295 (11.5)	4,069 (10.8)	1.0	1.0
LABA therapy	961 (37.4)	13,856 (36.6)	1.10 (0.97 – 1.26)	0.94 (0.82 –1.07)
Unexposed§	1,002 (39.0)	16,633 (44.0)	0.91 (0.80 – 1.04)	0.80 (0.70 – 0.92)

Abbreviations CI: confidence interval, LABA: Long-acting beta$_2$-agonist, LAMA: Long-acting muscarinic antagonist, No: Number.

* To undertake this secondary stratified analysis it was necessary to break the matching. Estimates are adjusted for the matching factors (date of birth, sex, date of cohort entry, COPD severity).

† Adjusted for the matching factors; ethnicity; NZDep06; Charlson comorbidity score; hospital discharge diagnosis before cohort entry of asthma; hospital discharge diagnosis before cohort entry and (separately) between cohort entry and index date of raised blood pressure, dyslipidaemia, heart failure, life-threatening arrhythmia, diabetes, benign prostatic hypertrophy/bladder outflow obstruction; hospital discharge diagnosis at any time before index date of hyperthyroidism, closed-angle glaucoma, osteoporotic fracture; use in 6 months before cohort entry and (separately) in 6 months before the index date of statin, antiplatelet, blood pressure lowering, non-steroidal anti-inflammatory, and theophylline therapy.

‡ History of acute coronary syndrome, other ischaemic heart disease, ischaemic stroke, and/or transient ischaemic attack at any time before the index date.

§ No long-acting bronchodilator use in 30 days before index date.

e-Table 9. Risk of acute coronary syndrome in relation to long-acting bronchodilator exposure status in 30 days before index date, stratified by ethnicity

Exposure status	Cases (No. [%])*	Controls (No. [%])*	Unmatched adjusted odds ratio† (95% CI)	Unmatched adjusted odds ratio‡ (95% CI)
Māori				
LAMA and LABA dual therapy	72 (10.1)	463 (9.0)	1.26 (0.87 – 1.84)	1.23 (0.84 – 1.82)
LAMA therapy	55 (7.7)	444 (8.7)	1.0	1.0
LABA therapy	254 (35.4)	1,772 (34.6)	1.18 (0.87 –1.61)	1.04 (0.76 –1.43)
Unexposed§	335 (46.8)	2,450 (47.8)	1.13 (0.84 – 1.53)	0.98 (0.72 –1.34)
Non-Māori				
LAMA and LABA dual therapy	553 (12.1)	4,015 (9.0)	1.24 (1.09 – 1.40)	1.25 (1.11 – 1.42)
LAMA therapy	610 (13.3)	5,431 (12.2)	1.0	1.0
LABA therapy	1,725 (37.7)	16,137 (36.2)	0.97 (0.88 – 1.07)	1.01 (0.91 – 1.11)
Unexposed§	1,690 (36.9)	18,983(42.6)	0.81 (0.73 – 0.90)	0.83 (0.75 – 0.92)

Abbreviations CI: confidence interval, LABA: Long-acting beta$_2$-agonist, LAMA: Long-acting muscarinic antagonist, No: Number.

* 105 cases and 1,868 controls for whom ethnicity was not recorded are excluded from this analysis.

† To undertake this secondary stratified analysis it was necessary to break the matching. Estimates are adjusted for the matching factors (date of birth, sex, date of cohort entry, COPD severity).

‡ Adjusted for the matching factors; NZDep06; Charlson comorbidity score; hospital discharge diagnosis before cohort entry of asthma, ACS; hospital discharge diagnosis before cohort entry and (separately) between cohort entry and index date of any ischaemic heart disease, raised blood pressure, dyslipidaemia, heart failure, life-threatening arrhythmia, ischaemic stroke, transient ischaemic attack, diabetes, benign prostatic hypertrophy/bladder outflow obstruction; hospital discharge diagnosis at any time before index date of hyperthyroidism, closed-angle glaucoma, osteoporotic fracture; use in 6 months before cohort entry and (separately) in 6 months before the index date of statin, antiplatelet, blood pressure lowering, non-steroidal anti-inflammatory, and theophylline therapy.

§ No long-acting bronchodilator use in 30 days before index date.

e-Table 10. Risk of acute coronary syndrome in relation to long-acting bronchodilator exposure status in 30 days before index date, stratified by use of inhaled corticosteroid

Exposure status	Cases (No. [%])	Controls (No. [%])	Unmatched adjusted odds ratio* (95% CI)	Unmatched adjusted odds ratio† (95% CI)
ICS exposure				
LAMA and LABA with ICS	612 (20.1)	4,341 (16.2)	1.23 (1.05 – 1.43)	1.23 (1.05 – 1.45)
LAMA with ICS	262 (8.6)	2,254 (8.4)	1.0	1.0
LABA with ICS	1,783 (58.7)	16,836 (62.8)	0.93 (0.81 – 1.12)	0.97 (0.84 – 1.12)
ICS mono-therapy	381 (12.5)	3,385 (12.6)	0.99 (0.84 – 1.17)	1.00 (0.84 – 1.19)
No ICS exposure				
LAMA and LABA, no ICS	29 (1.2)	251 (1.0)	1.05 (0.71 – 1.56)	0.97 (0.65 – 1.47)
LAMA, no ICS	416 (17.6)	3,790 (15.3)	1.0	1.0
LABA, no ICS	234 (9.9)	1,754 (7.1)	1.22 (1.03 – 1.45)	1.19 (1.00 – 1.42)
Unexposed‡	1,682 (71.2)	18,952 (76.6)	0.82 (0.73 – 0.92)	0.83 (0.74 – 0.93)

Abbreviations CI: confidence interval, LABA: Long-acting beta$_2$-agonist, LAMA: Long-acting muscarinic antagonist, No: Number.

* To undertake this secondary stratified analysis it was necessary to break the matching. Estimates are adjusted for the matching factors (date of birth, sex, date of cohort entry, COPD severity).

† Adjusted for the matching factors; ethnicity; NZDep06; Charlson comorbidity score; hospital discharge diagnosis before cohort entry of asthma, ACS; hospital discharge diagnosis before cohort entry and (separately) between cohort entry and index date of any ischaemic heart disease, raised blood pressure, dyslipidaemia, heart failure, life-threatening arrhythmia, ischaemic stroke, transient ischaemic attack, diabetes, benign prostatic hypertrophy/bladder outflow obstruction; hospital discharge diagnosis at any time before index date of hyperthyroidism, closed-angle glaucoma, osteoporotic fracture; use in 6 months before cohort entry and (separately) in 6 months before the index date of statin, antiplatelet, blood pressure lowering, non-steroidal anti-inflammatory, and theophylline therapy.

‡ No long-acting bronchodilator or ICS use in 30 days before index date.

e-Table 11. Absolute risk of acute coronary syndrome in relation to exposure category, overall and stratified by ethnicity

Exposure category	Number of cases*	Person-years of exposure	Crude incidence rate per 1,000 person-years (95% CI)	Age- and sex-adjusted incidence rate per 1,000 person-years (95% CI)†
Overall				
LAMA and LABA dual therapy	645	18,461	34.9 (32.3 – 37.7)	25.1 (20.5 – 29.6)
LAMA therapy	679	19,095	35.6 (32.9 – 38.3)	22.4 (18.3 – 26.4)
LABA therapy	2025	100,527	20.1 (19.3 – 21.0)	16.0 (15.2 – 16.7)
Unexposed‡	2073	143,209	14.5 (13.9 – 15.1)	12.9 (12.3 – 13.4)
Māori				
LAMA and LABA dual therapy	72	2,453	29.4 (23.0 – 37.0)	27.4 (18.3 – 36.6)
LAMA therapy	56	2,040	27.5 (20.7 – 35.6)	36.1 (27.0 – 45.2)
LABA therapy	254	11,877	21.4 (18.8 – 24.2)	22.6 (19.2 – 26.0)
Unexposed‡	335	19,173	17.5 (15.7 – 19.4)	20.6 (17.7 – 23.5)
Non-Māori				
LAMA and LABA dual therapy	557	15,499	35.9 (33.0 – 39.1)	24.2 (18.9 – 29.5)
LAMA therapy	610	16,456	37.1 (34.2 – 40.1)	22.2 (17.3 – 27.0)
LABA therapy	1733	84,089	20.6 (19.7 – 21.6)	15.5 (14.7 – 16.3)
Unexposed‡	1700	117,159	14.5 (13.8 – 15.2)	12.2 (11.6 – 12.8)

Abbreviations CI: confidence interval, LABA: Long-acting beta$_2$-agonist, LAMA: Long-acting muscarinic antagonist.

* 23 cases for whom controls could not be found are included in all the analyses. 105 cases for whom ethnicity was not recorded are excluded from the analysis stratified by ethnicity.

† Standardised to the total New Zealand population.

‡ No long-acting bronchodilator use in 30 days before index date.

e-FIGURE LEGENDS

e-Figure 1. Example to illustrate how an individual's dispensing data were summarised as continuous episodes of use of specific drugs and drug classes

For each member of the study cohort, we combined the dispensing data related to individual drugs into continuous episodes of use and censored episodes at the earliest of the following: an ACS event, death, or 31 December 2013. Next, we summarised the continuous episodes of use of individual drugs into continuous episodes of use of drug classes (LAMA, LABA, LABA/ICS combination products); we also summarised continuous episodes of use of ICS products. The figure shows (i) how an individual's dispensing data relating to specific LABA drugs were summarised as continuous episodes of use (Step 1), and (ii) how continuous episodes of use of specific LABA drugs were then summarised as a continuous episode of use of LABA as a drug class (Step 2). The same process was used for LABA/ICS, LAMA, and ICS products.

e-Figure 2. Example to illustrate how an individual's dispensing data were summarised as continuous episodes of therapeutic regimens and exposure categories

We combined the data regarding continuous episodes of use of drug classes into continuous episodes of use of nine mutually exclusive therapeutic regimens, and then grouped them into four broad exposure categories: LAMA and LABA dual therapy, LAMA therapy, LABA therapy, and ICS mono-therapy. The example shows how concurrent episodes of use of drug classes were combined into mutually exclusive therapeutic regimens (Step 3) and then grouped into broad exposure categories (Step 4). The following four exposure categories were used in the primary ACS analysis and most of the secondary analyses: LAMA and LABA dual therapy

(LAMA and LABA *with* or *without* ICS), LAMA therapy (LAMA *with* or *without* ICS), LABA therapy (LABA *with* or *without* ICS), and ICS mono-therapy (ICS *without* LAMA or LABA) (see Table 1). Seven broad exposure categories were used in the secondary analyses stratified by ICS use (see e-Table 1).

e-Figure 3. Example to illustrate classification of user status on the index date