USING REAL-WORLD DATA TO EVALUATE COMPARATIVE EFFECTIVENESS COHORTS OF AZITHROMYCIN RELATIVE TO ROFLUMILAST IN INDIVIDUALS WITH UNCONTROLLED CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Sruthi Adimadhyam[1], Laura Hou[1], Inna Dashevsky[1], Rongmei Zhang[2], Yan Li[2], Marie Bradley[2], Efe Eworuke[2], Andrew Clerman[2], Stacy Chin[2], Yunzhao Ren[2], Sally Seymour[2], Kenneth Quinto[2], Judith C. Maro[1], Robert Busch[2]

[1] Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA

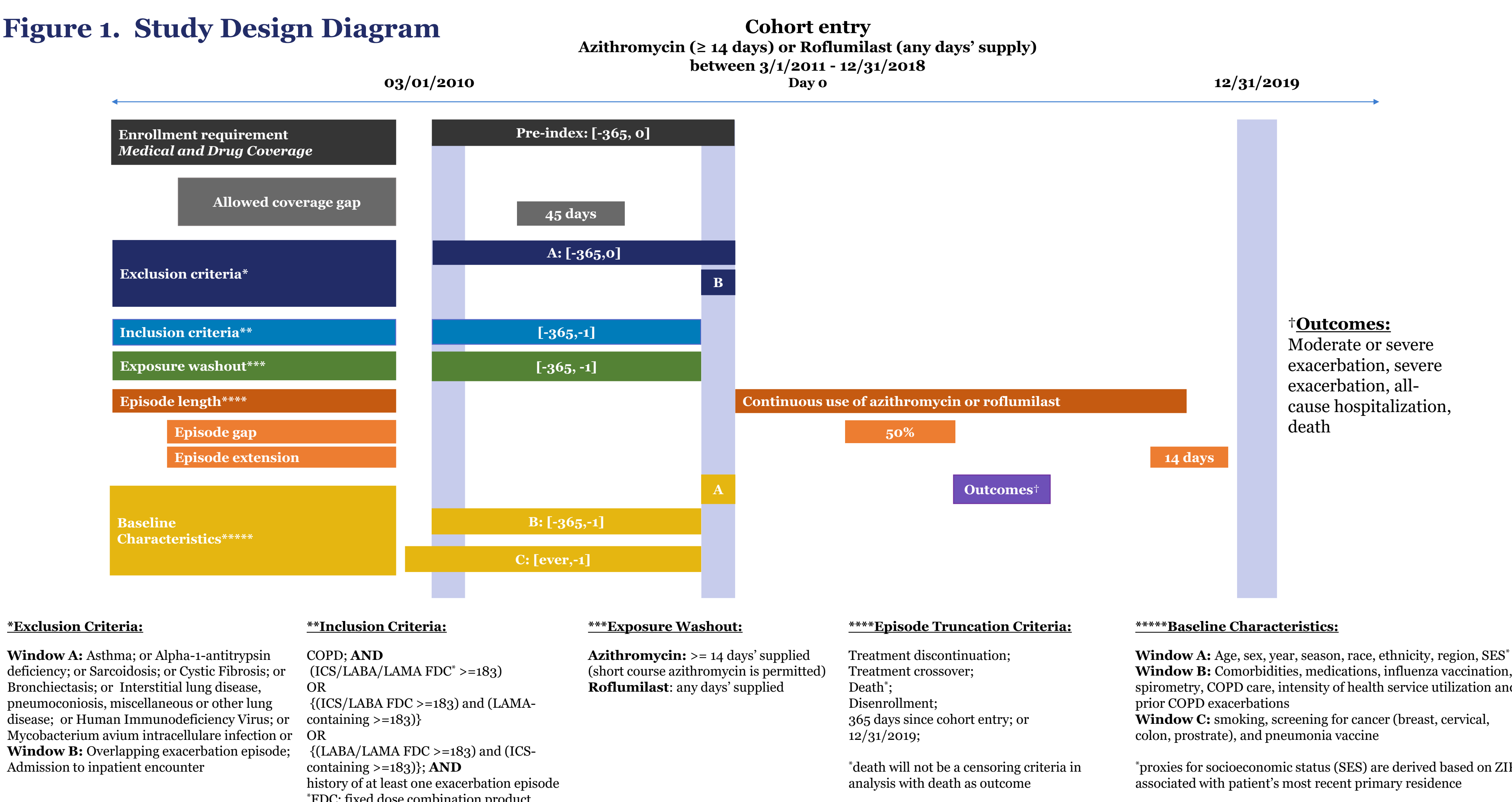[2] United States Food and Drug Administration, Silver Spring, MD, USA

BACKGROUND

- Uncontrolled chronic obstructive pulmonary disease (COPD) with exacerbations despite treatment with inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), and long-acting muscarinic agents (LAMA) is an area of interest for drug development
- Placebo-controlled trials suggest that use of either off-label chronic maintenance azithromycin (CM AZT) or roflumilast (ROF) may demonstrate efficacy on exacerbation endpoints in individuals with uncontrolled COPD[1,2]
- Head-to-head evaluation of the effectiveness of these add-on therapies is lacking

METHODS

- We conducted an active comparator, new user cohort study of CM AZT (>=14 days supplied per dispensing) vs. ROF in individuals with uncontrolled COPD and evidence of maintenance use of ICS+LABA+LAMA in the Sentinel System using administrative claims data from the Centers for Medicare and Medicaid Services (CMS)
- We used propensity scores to perform 1:1 fixed ratio nearest neighbor matching within a caliper of 0.05

Figure 1. Study Design Diagram

*Exclusion Criteria:
Window A: Asthma; or Alpha-1-antitrypsin deficiency; or Sarcoidosis; or Cystic Fibrosis; or Bronchiectasis; or Interstitial lung disease, pneumoconiosis, miscellaneous or other lung disease; or Human Immunodeficiency Virus; or Mycobacterium avium intracellulare infection or
Window B: Overlapping exacerbation episode; Admission to inpatient encounter

**Inclusion Criteria:
COPD; AND
(ICS/LABA/LAMA FDC* >=183)
OR
((ICS/LABA FDC >=183) and (LAMA-containing >=183))
OR
((LABA/LAMA FDC >=183) and (ICS-containing >=183)); AND
history of at least one exacerbation episode
*FDC: fixed dose combination product

***Exposure Washout:
Azithromycin: >= 14 days' supplied (short course azithromycin is permitted)
Roflumilast: any days' supply

****Episode Truncation Criteria:
Treatment discontinuation; Treatment crossover; Death†; Disenrollment; 365 days since cohort entry; or 12/31/2019;
†death will not be a censoring criteria in analysis with death as outcome

*****Baseline Characteristics:
Window A: Age, sex, year, season, race, ethnicity, region, SES†
Window B: Comorbidities, medications, influenza vaccination, spirometry, COPD care, intensity of health service utilization and prior COPD exacerbations
Window C: smoking, screening for cancer (breast, cervical, colon, prostrate), and pneumonia vaccine
†proxies for socioeconomic status (SES) are derived based on ZIP associated with patient's most recent primary residence

RESULTS

Figure 2. Participant Selection Diagram

*Patients can meet multiple inclusion and/or exclusion criteria; therefore, the total number of patients excluded overall for not meeting any cohort selection criteria may not equal the sum of all patients listed in each criterion
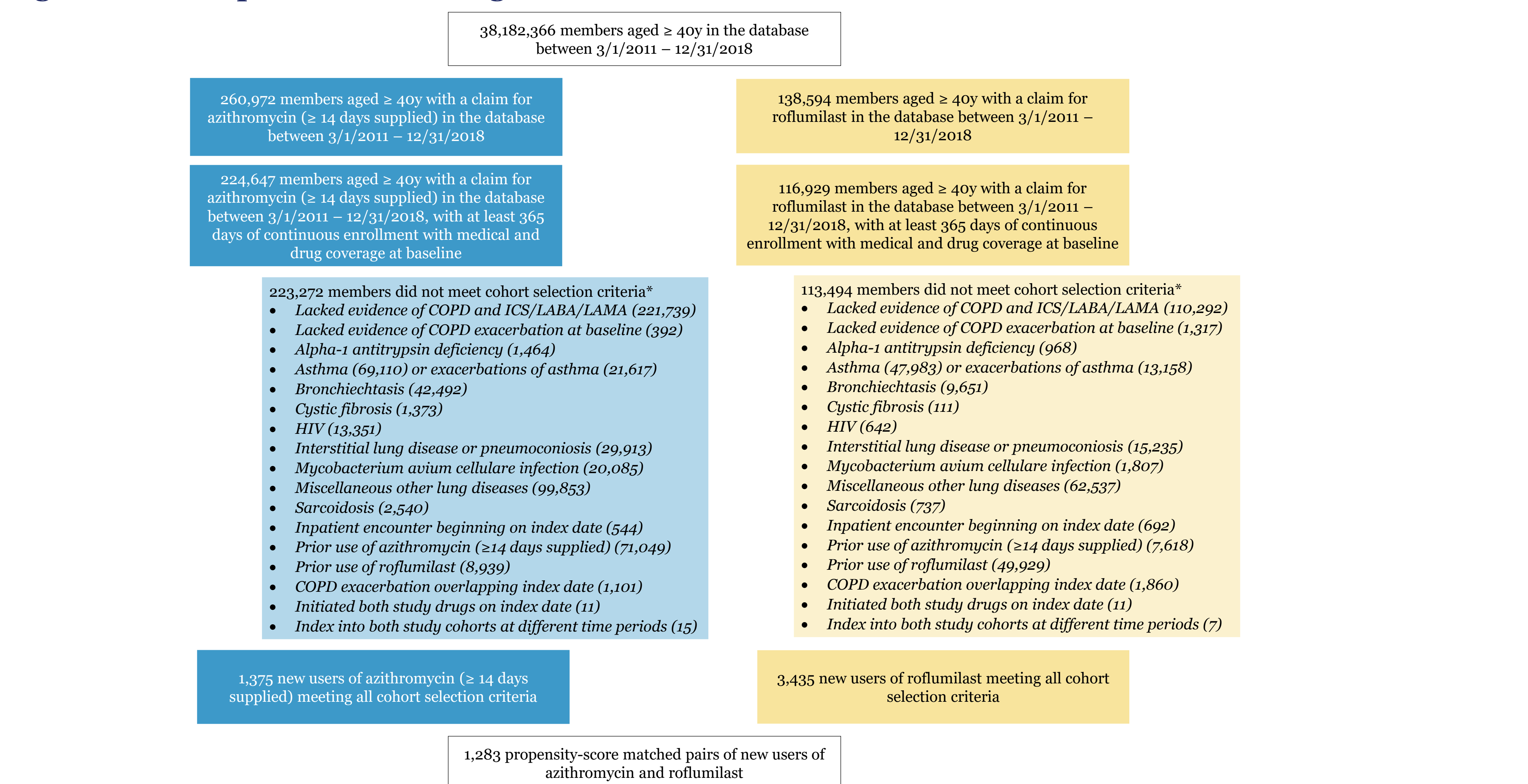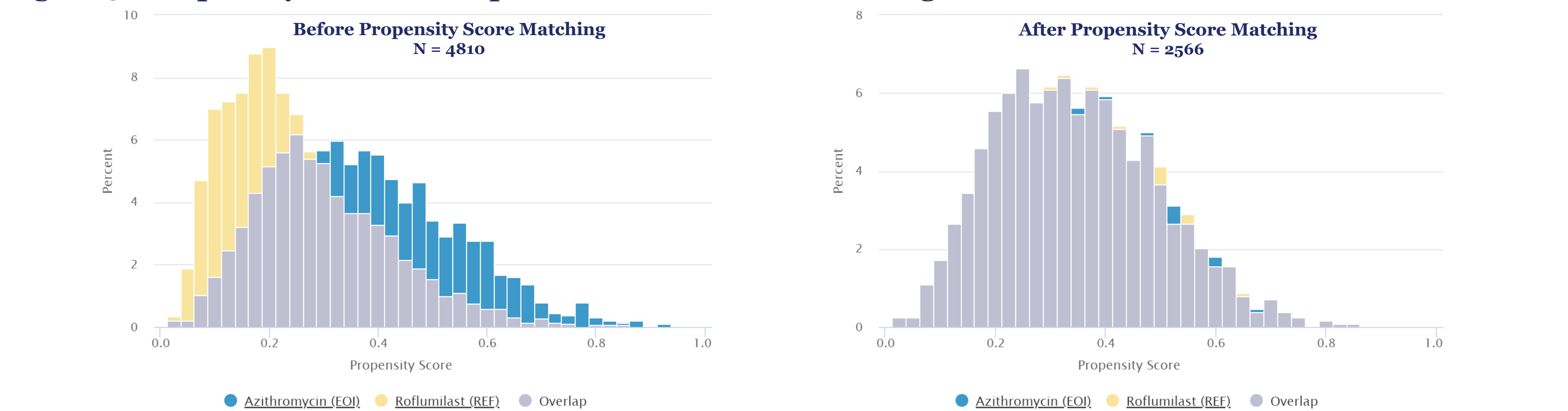
Figure 3. Propensity Score Overlap Before and After 1:1 Matching

RESULTS

Table 1: Covariate Balance Before and After 1:1 Matching

	Before Propensity Score Matching			After Propensity Score Matching		
	Azithromycin (n = 1,375)	Roflumilast (n = 3,435)	Standardized Difference	Azithromycin (n = 1,283)	Roflumilast (n = 1,283)	Standardized Difference
Demographic Characteristics						
Age in years, mean (SD)	71.4 (8.7)	69.7 (8.8)	0.19	71.1 (8.7)	70.9 (8.7)	0.03
Age						
40-64 years	19.4%	26.6%	-0.17	20.2%	21.8%	-0.04
65-74 years	48.0%	46.5%	0.03	48.2%	46.3%	0.04
≥ 75 years	32.6%	26.9%	0.13	31.6%	31.9%	-0.01
Sex						
Female	59.3%	58.0%	0.03	58.9%	58.9%	0.00
Male	40.7%	42.0%	-0.03	41.1%	41.1%	0.00
Race*						
American Indian or Alaska Native	M	0.6%	-0.03	M	M	0.00
Asian	M	1.7%	-0.07	M	M	0.02
Black or African American	5.2%	4.3%	0.05	5.1%	5.2%	0.00
Unknown	2.0%	2.3%	-0.03	2.0%	1.6%	0.03
White	91.6%	91.2%	0.01	91.6%	92.0%	-0.02
Hispanic origin						
Yes	M	1.1%	-0.06	M	M	0.02
No	98.0%	97.7%	0.03	98.0%	98.4%	-0.03
Unknown	M	1.3%	0.01	M	M	0.02
Census Bureau Region**						
Midwest	28.7%	26.0%	0.06	28.1%	28.6%	-0.01
Northeast	19.1%	18.8%	0.01	19.0%	20.0%	-0.02
South	34.5%	42.3%	-0.16	35.7%	35.0%	0.02
West	17.7%	12.9%	0.13	17.2%	16.4%	0.02
Proxies for Socioeconomic Status: Average Median Household Income*						
1st Quintile (USD 11,613 - 42,789)	13.4%	20.1%	-0.18	14.2%	13.4%	0.02
2nd Quintile (USD 42,792 - 50,643)	16.2%	18.8%	-0.07	16.1%	17.6%	-0.04
3rd Quintile (USD 50,663 - 58,886)	17.7%	18.3%	-0.02	17.9%	19.0%	-0.03
4th Quintile (USD 58,897 - 74,096)	18.9%	17.8%	0.03	19.1%	18.2%	0.02
5th Quintile (USD 74,098 - 250,001)	24.2%	15.6%	0.22	23.1%	22.8%	0.01
Health Characteristics in the [-365,-1] Days Before Treatment Initiation						
Charlson/Elixhauser combined comorbidity score, mean (SD)	3.1 (2.5)	2.9 (2.4)	0.08	3 (2.5)	3 (2.4)	-0.01
Congestive heart failure	20.1%	24.4%	-0.10	21.3%	20.6%	0.02
Cardiovascular disease****	25.2%	28.8%	-0.08	26.3%	25.6%	0.02
Diabetes	27.5%	32.1%	-0.10	28.6%	29.8%	-0.03
Lung cancer	4.8%	3.3%	0.08	4.5%	4.6%	0.00
Anxiety	30.3%	31.8%	-0.03	30.1%	29.6%	0.01
Major depressive disorder	24.8%	26.6%	-0.04	24.8%	26.0%	-0.03
Cachexia	2.1%	1.5%	0.05	1.9%	2.3%	-0.03
Obesity	14.4%	16.2%	-0.05	15.0%	14.0%	0.03
Obstructive sleep apnea	14.7%	17.8%	-0.09	15.0%	15.0%	0.00
Other (non-lung) cancer	33.5%	27.8%	0.12	32.4%	33.9%	-0.03
Influenza vaccination status	70.0%	67.0%	0.06	69.2%	70.0%	-0.02
Pneumonia	23.6%	22.6%	0.02	23.6%	25.6%	-0.05
Health Characteristics in the [-EVER,-1] Days Before Treatment Initiation						
Pneumococcal vaccination	58.3%	48.8%	0.19	57.3%	56.2%	0.02
Colon cancer screening	37.9%	33.6%	0.09	37.3%	36.8%	0.01
History of smoking	83.4%	82.3%	0.03	83.2%	83.9%	-0.02
COPD Characteristics in the [-365, -1] Days Before Treatment Initiation						
Chronic bronchitis	42.0%	54.7%	-0.26	43.6%	44.1%	-0.01
Emphysematous phenotype	46.5%	35.9%	0.22	45.1%	45.6%	-0.01
Mean number of moderate or severe exacerbations	2.4 (1.6)	2.3 (1.5)	0.05	2.4 (1.6)	2.5 (1.5)	-0.05
Mean number of severe exacerbations	0.3 (0.6)	0.4 (0.7)	-0.06	0.3 (0.6)	0.4 (0.7)	-0.04
Number of antibiotic dispensings (excluding chronic azithromycin)	4.6 (3.8)	3.7 (3.1)	0.25	4.3 (3.4)	4.3 (3.5)	0.02
Number of corticosteroid dispensings	4 (3.8)	3.8 (3.8)	0.06	4 (3.8)	4 (3.9)	-0.01
Oxygen therapy	46.2%	43.9%	0.05	45.3%	45.5%	-0.01
Respiratory failure with intubation and mechanical ventilation*****	1.5%	1.2%	0.03	1.1%	1.6%	-0.04
Medical Product Use in the [-365,-1] Days Before Treatment Initiation						
ACEIs or ARBs	42.4%	48.4%	-0.12	43.6%	43.6%	0.00
Antidepressants	46.2%	48.6%	-0.05	46.6%	47.1%	-0.01
Beta blockers or calcium channel blockers	50.9%	53.9%	-0.06	52.0%	51.0%	0.02
Non-insulin antidiabetic medications	16.0%	18.5%	-0.07	16.8%	16.4%	0.01
Opioids	46.0%	48.4%	-0.05	45.6%	45.7%	0.00
Therapeutic anticoagulants	9.5%	9.8%	-0.01	9.4%	9.5%	0.00
Health Service Utilization Intensity Metrics in the [-365,-1] Days Before Treatment Initiation						
Mean number of ambulatory encounters	24.8 (20)	23.1 (18.4)	0.09	24.5 (20.1)	25 (21.2)	-0.02
Mean number of emergency room encounters	0.6 (1.1)	0.6 (1.1)	-0.03	0.6 (1.1)	0.7 (1.2)	-0.04
Mean number of inpatient hospital encounters	0.5 (0.9)	0.5 (0.9)	-0.06	0.5 (0.8)	0.5 (0.9)	-0.04
Mean number of filled prescriptions	82.9 (51.8)	91.2 (54.3)	-0.16	83.5 (52)	84.7 (50.6)	-0.02
Mean number of unique drug classes dispensed	15 (5.7)	15.3 (5.7)	-0.06	15 (5.8)	14.9 (5.4)	0.02

M: represents data <11 suppressed due to small cell suppression policy
* There were no individuals with self-reported race Native Hawaiian or Other Pacific Islander or Multi-Racial
** There were no individuals in the matched cohort with region US Territories or Unknown
*** 132/135 azithromycin/roflumilast new users had missing data on average median household income prior to matching; 123/116 azithromycin/roflumilast new users had missing data on average median household income post matching
**** Defined as myocardial infarction, stroke, heart failure, angina or transient ischemic attack
***** Defined as evidence of respiratory failure and intubation and mechanical ventilation in the 365 days prior treatment initiation

CONCLUSIONS

- Among a target population with COPD, we used propensity score matching to identify a well-balanced study population among whom measures of effectiveness may be estimated with minimal known confounding.
- Limitations of our study include potential misclassification due to the use of unvalidated event definitions from administrative claims data; our study also only evaluated insured patients within a CMS population.
- We intend to generate estimates of effectiveness of chronic use of azithromycin relative to roflumilast based on clinical endpoints of COPD exacerbations and all-cause hospitalization in the propensity-score matched cohort
- Well-designed observational studies using real-world data can generate informative comparisons to guide investigations of comparative effectiveness.

REFERENCES

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2. Herath SC et al. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2018;2018(10):CD009764.

ACKNOWLEDGEMENTS/DISCLOSURES