Comparative Effectiveness of Azithromycin Relative to Roflumilast in Individuals with Uncontrolled Chronic Obstructive Pulmonary Disease Despite Triple Inhaled Therapy

Study Protocol

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The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. These analyses were funded by a contract from the U.S. Food and Drug Administration's (FDA) Office of New Drugs and Office of Medical Policy. This abstract reflects the views of the authors and should not be construed to represent FDA's views or policies.

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1 Contents

2 History of modifications

Version	Date	Modification	Author
V1.0	7/21/2022	Original version	Sentinel Operations Center

3 Introduction

Chronic obstructive pulmonary disease (COPD) affects more than fifteen million individuals in the United States (US)[1,2]. A lower respiratory disease characterized by progressive and irreversible airflow limitation, COPD is associated with significant morbidity and was noted to be the country's 4th leading cause of death in 2018. Cessation of smoking and vaccinations are known to limit progression and reduce serious illness from COPD[3]. While no drug improves mortality in COPD, chronic maintenance pharmacotherapy options for COPD include treatment with inhaled agents such as long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS), as well as oral therapy with roflumilast in a subset of patients with COPD.

Some patients with COPD may experience frequent COPD exacerbations, which are periods marked by an escalation of respiratory symptoms. Moderate COPD exacerbations are defined by disease worsening that requires short-term courses of antibiotics and/or steroids, and studies suggest that a higher frequency of moderate exacerbations is associated with lower quality of life scores[4]. Severe exacerbations are defined by disease worsening that requires inpatient hospitalization for alleviation of symptoms and may result in visits to the emergency department, hospitalizations, or death. Studies suggest that an increased frequency of severe COPD exacerbations is associated with increased mortality[5]. Prevention of COPD exacerbations is both a measure of effectiveness and a safety measure for studies of COPD medications.

Roflumilast is an FDA approved phosphodiesterase-4 (PDE4) inhibitor[6] indicated to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. It is commonly prescribed in clinical practice among a subset of patients with COPD who continue to experience COPD exacerbations and inadequate disease control despite chronic maintenance therapy with ICS, LABA, and LAMA medications.

Azithromycin is a macrolide antibiotic approved by the Food and Drug Administration (FDA) for the treatment of mild to moderate mycobacterial infections[7]. It is not FDA-approved for the maintenance treatment of COPD or for preventing COPD exacerbations, however, due to its purported immunomodulatory and anti-inflammatory effects[8], it is commonly used in clinical practice for this purpose among a similar subset of patients with COPD who continue to experience previous exacerbations and inadequate disease control despite chronic maintenance therapy with ICS, LABA, and LAMA.

Evidence from placebo-controlled clinical trials may suggest that the chronic maintenance use of azithromycin or roflumilast as add-on therapies in this subset of patients with COPD reduces the frequency of moderate-to-severe COPD exacerbations and improves patient quality of life[9–12]. Both medications have adverse event profiles characterized primarily by symptoms of gastrointestinal intolerance. Available efficacy data for azithromycin and roflumilast in this COPD patient population has led to relative equipoise in their clinical context of use, both are conditionally recommended in clinical practice guidelines[13,14] for subsets of COPD patients with exacerbations despite optimized inhaled therapies, and the choice between these two drugs remains an area of open debate and clinical interest.

Currently, however, there are insufficient well-controlled data on head-to-head comparisons of the efficacy or effectiveness of these two drugs to guide prescribers, and the use of chronic maintenance therapy with azithromycin in COPD remains off-label. The relative equipoise and the lack of extant data comparing these two drugs presents an opportunity to evaluate the effectiveness of azithromycin against an approved product, utilizing both observational[15] and randomized trial approaches. RofLumilast or Azithromycin to prevent COPD Exacerbations (RELIANCE) is a US-based, Patient-Centered Outcomes Research Institute (PCORI)-funded,

pragmatic, non-inferiority trial designed to compare the effectiveness of roflumilast vs. azithromycin to prevent hospitalization or death in patients with severe COPD at a high risk for exacerbations[16]. This trial is ongoing with an anticipated completion date in early 2024. Given the degree of equipoise in the choice between these two therapeutic options in clinical practice, analyses from head-to-head comparisons in real-world data sources using a robust, propensity score adjusted, active comparator, new user cohort design may also provide supportive data on the effectiveness of azithromycin versus roflumilast to further inform clinical decision-making.

4 Objective

Our objective is to compare the effectiveness of azithromycin relative to roflumilast in preventing moderate-to-severe COPD exacerbations, all-cause hospitalizations, and severe COPD exacerbations in the first year of treatment among individuals with uncontrolled COPD despite evidence of chronic maintenance therapy with ICS, LABA, and LAMA prior to initiation of treatment with azithromycin or roflumilast.

5 Clinical hypothesis

We hypothesize that azithromycin will be associated with a decreased risk of first moderate-to-severe COPD exacerbation (as measured by time-to-first moderate-to-severe COPD exacerbation), first all-cause hospitalization, and first severe COPD exacerbation compared to roflumilast in the first year of treatment among individuals with uncontrolled COPD who continue to experience exacerbations despite evidence of chronic maintenance inhaled therapy with ICS, LABA, and LAMA.

6 Methods

6.1 Design and data sources

We will conduct a retrospective, propensity score matched, new user[17] observational cohort study using administrative claims data from Medicare. We will supplement this data by also conducting a multi-site study using aggregated data from three additional large national insurers in the Sentinel system. Each contributing data partner has deidentified data on demographic factors, health plan enrollment, and billable clinical encounters for their insured population. Data from billable clinical encounters include diagnoses and procedures recorded in outpatient or inpatient care settings using International Classification of Diseases, Ninth and Tenth Revisions (ICD-9-CM, ICD-10-CM) codes. Data on outpatient pharmacy dispensings (National Drug Codes (NDC), days and amount supplied) and administrations (Healthcare Common Procedure Coding System (HCPCS)) are also included. Data elements at each contributing site are transformed to the Sentinel Common Data Model[18] format version 8 or later by the participating site which are then rigorously evaluated for consistency by the Sentinel Operations Center[19]. Having data in the Sentinel Common Data Model enables the use of privacy-preserving distributed research methods[20].

6.2 Study population

Our population will include patients aged 40 years or older with uncontrolled COPD, despite evidence of chronic maintenance therapy with ICS, LABA, and LAMA in the 365 days prior to initiation of treatment with azithromycin or roflumilast, who newly initiate add-on chronic maintenance treatment with azithromycin or roflumilast between March 1, 2011, and December 31, 2018 (Figure 1). Cohort entry will occur on the index date, which is defined as the date of new use of chronic maintenance azithromycin (first valid dispensing with days-supplied ≥14 days) or roflumilast. Patients will only be allowed to enter the cohort once based on their first valid exposure.

New use will be defined as no prior use of either study drug (azithromycin with ≥ 14 days-supplied or roflumilast) in the 365 days before the index date (baseline period). Chronic maintenance treatment with azithromycin will be defined as dispensings of azithromycin associated with ≥14 days' supply (DS). This ≥14 DS requirement allows for differentiation of chronic maintenance use of azithromycin from episodic use and mitigates misclassification of subjects receiving azithromycin for other acute indications. Short courses of azithromycin of ≤13 DS will be allowed in the baseline period given that short-course azithromycin may be used for COPD exacerbation control or other acute infectious indications.

Uncontrolled COPD will be defined as a history of ≥1 moderate-to-severe COPD exacerbations with evidence of chronic maintenance therapy in the baseline period. Chronic maintenance therapy will be defined as dispensings in the baseline period covering ≥183 DS of each inhaled drug class (i.e., ICS, LABA, and LAMA, as monotherapies or combination products).

Eligible patients will be of age 40 years or older on the index with continuous enrollment in health plans with medical and drug coverage in the baseline period, during which gaps in coverage of up to 45 days will be allowed to account for administrative processes.

Patients will be included if they meet the following criteria evaluated over the baseline period:

- At least one diagnosis of COPD in any care setting; and
- At least 183 days cumulative DS of one of the following medications or combination of medications: 1) ICS/LABA/LAMA combination medication; or 2) an ICS/LABA combination medication and a LAMA-containing medication; or 3) a LABA/LAMA combination medication and an ICS-containing medication or 4) an ICS-containing, a LABA-containing, and a LAMA-containing medication; and
- At least one moderate or severe COPD exacerbation.

Patients will be excluded if they have evidence of any of the following pulmonary conditions evaluated over the baseline period and index date:

- Asthma; or
- Alpha-1-antitrypsin deficiency; or
- Sarcoidosis; or
- Cystic fibrosis; or
- Bronchiectasis; or
- Interstitial lung disease; or
- Pneumoconiosis or miscellaneous other lung diseases.

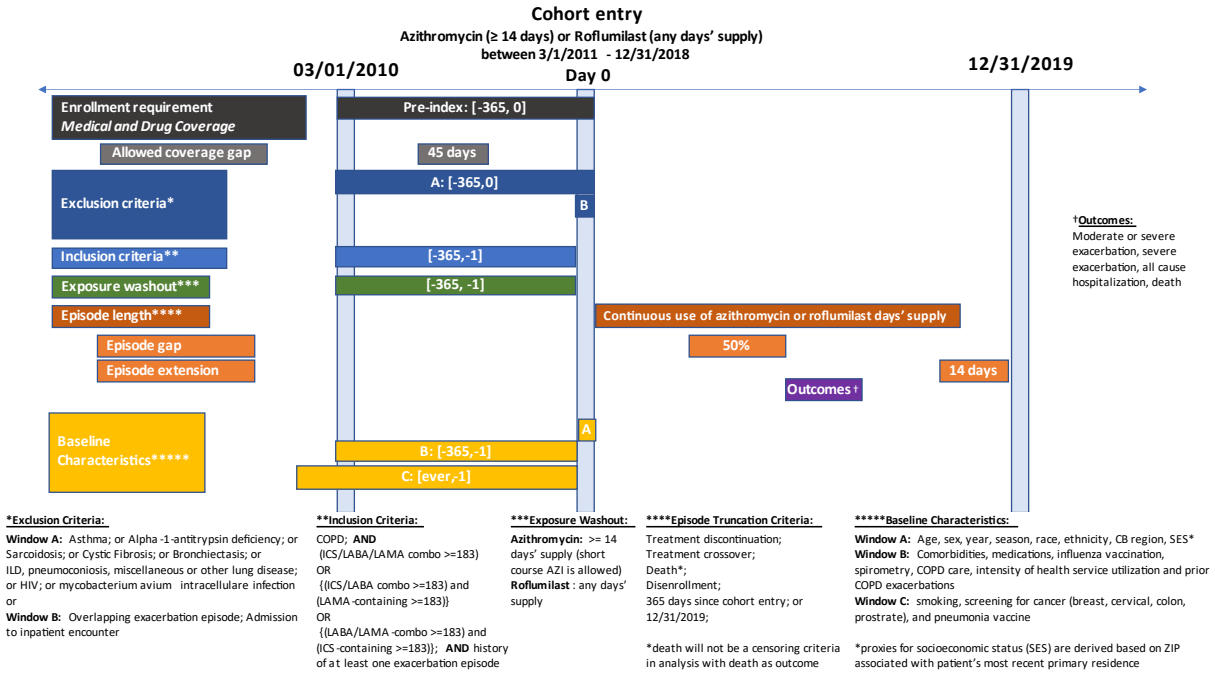
Patients will be excluded if they have evidence of any of the following alternative indications for azithromycin use (e.g., as prophylaxis or treatment) evaluated over the baseline period and index date:

- Human immunodeficiency virus (HIV); or
- Mycobacterium avium intracellulare infection.

Patients will be excluded if they have evidence of any of the following outcomes evaluated on the index date:

- Moderate or severe exacerbation episode overlapping with the index date; or
- Any inpatient encounter beginning on the index date.

Figure 1: Illustration of study design



6.3 Baseline characteristics

Demographic and clinical characteristics of our study population will be ascertained on or prior to cohort entry as follows:

On index date [0,0]:

- Demographic characteristics: age, sex, race, ethnicity, calendar season of treatment initiation, calendar year of treatment initiation, census bureau region, and proxies for socioeconomic status[21] including median household income, median property value, and percent unemployment.
- Census bureau region and proxies for socioeconomic status are derived based on ZIP associated with the patients' most recent primary residence. The date associated with ZIP of patients' most recent primary residence may be different than the calendar index date.

Over the baseline period [-365,-1]:

- Anxiety, atrial fibrillation, atrial or ventricular arrhythmias (excluding atrial fibrillation), cachexia, other cancer (non-lung), cardiovascular disease, chronic bronchitis, chronic kidney disease, cirrhosis, congestive heart failure, depression, diabetes, emphysematous phenotype, gastroesophageal reflux disease, hearing loss, hypertension, influenza vaccination, lung cancer, number of pulmonary function tests (spirometry), obesity, obstructive sleep apnea, osteoporosis, oxygen therapy, pneumonia, pulmonary embolism, pulmonary hypertension, history of pulmonary rehabilitation, historic use of antibiotics and oral corticosteroids, prior history of exacerbation episodes, history of respiratory failure with intubation and mechanical ventilation, intensity of health

services utilization including unique drug classes, unique generics, ambulatory, inpatient, and institutional stay encounters, use of antidepressants, anticonvulsants, beta blocker or calcium channel blockers, proton pump inhibitors, opioids, antipsychotics, anxiolytics or hypnotics, medications for dementia, antiparkinsonian agents, benzodiazepine, non-insulin antidiabetic medications, insulin, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), therapeutic anticoagulants, amiodarone, digoxin, diuretics, and the Combined Comorbidity Index[22,23].

In all available history prior to cohort entry [ever, -1]:

- Smoking as identified by evidence of use of smoking cessation therapies or diagnosis/procedure codes indicating tobacco use or nicotine dependence. The algorithm to define smoking will include codes specified by Desai et al.[24] in addition to those identified by the workgroup.
- Health maintenance habits such as pneumococcal vaccination, screening for breast cancer (mammogram), screening for cervical cancer (pap smear), screening for colon cancer (flexible sigmoidoscopy or colonoscopy or CT virtual colonoscopy), and screening for prostate cancer (prostate exam or digital rectal examination or prostate-specific antigen test).

6.4 Outcomes

We will evaluate six outcomes separately in the first year of treatment initiation:

Primary Outcome

1. Time to first occurrence of a moderate-to-severe exacerbation after cohort entry

Secondary Outcomes

2. Time to first occurrence of an all-cause hospitalization after cohort entry
3. Time to first occurrence of a severe exacerbation after cohort entry
4. Frequency of moderate-to-severe exacerbations in the first year of treatment
5. Frequency of severe exacerbations in the first year in the first year of treatment
6. Time to all-cause mortality

For purposes of this study, our definition of moderate exacerbations relies on evidence of an outpatient encounter for COPD or COPD exacerbation, along with evidence of dispensing of antibiotics, steroids, or both, within a specified timeframe. Our definition of severe exacerbation relies on evidence of an inpatient hospitalization encounter for COPD or COPD exacerbation.

Specifically, moderate exacerbations are defined as a COPD diagnosis occurring in an outpatient, emergency department, or ambulatory care setting, within seven days of which there is evidence of at least one of the following:

- New systemic corticosteroid dispensing: comprising ≥3 days' supply of an oral corticosteroid or an injection of corticosteroids without use in the prior 14 days.
- Non-azithromycin antibiotic dispensing (exacerbation dosing): comprising a non-azithromycin antibiotic dispensing of ≥ 3 to <15 days' supply.
- Azithromycin antibiotic dispensing (exacerbation dosing): comprising an azithromycin dispensing with ≥3 to ≤13 days' supply.

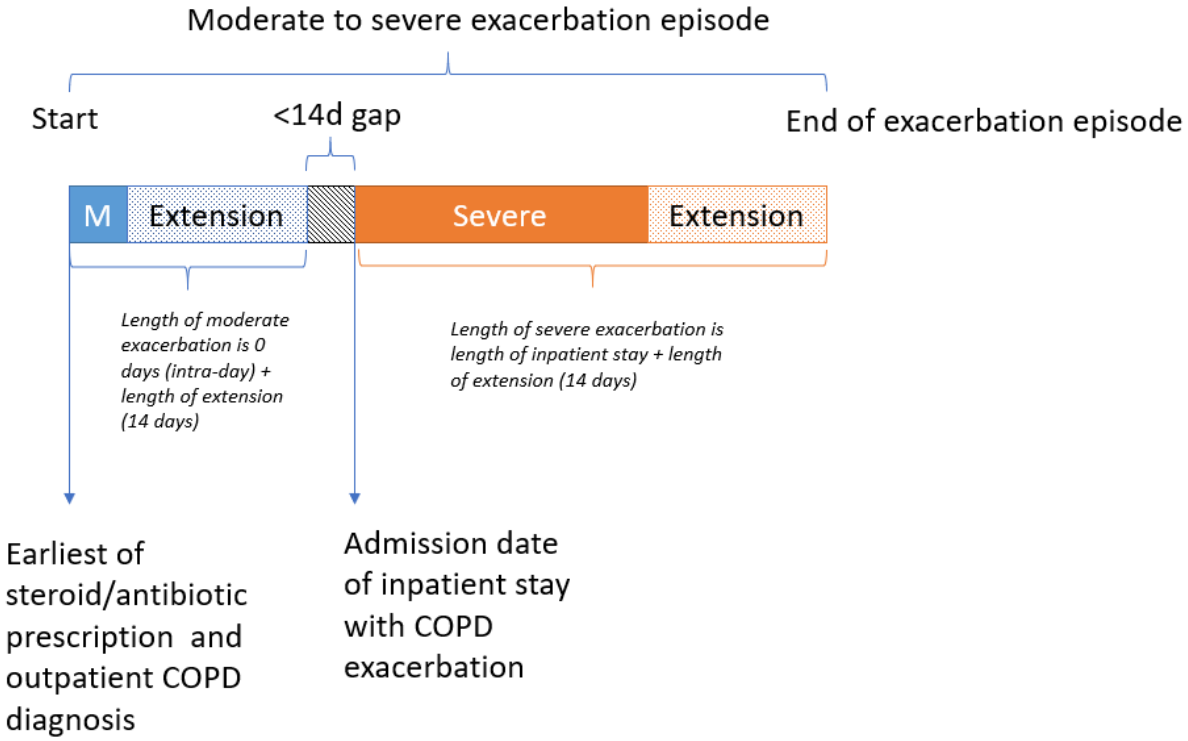
The earlier of the encounter or dispensing events will be used to define the start date of the moderate exacerbation event.

Severe exacerbations are defined as at least one of the following discharge diagnoses in an inpatient care setting, with the admission date designated as the event start date:

- A principal discharge diagnosis of COPD
- Any diagnosis of a COPD exacerbation.
- A principal discharge diagnosis of acute respiratory failure co-occurring with a diagnosis of COPD.

The endpoint of moderate-to-severe exacerbations is a composite endpoint counting both events using the definitions above. Moderate and severe exacerbation events are combined into continuous episodes when appropriate, built by bridging of defining events that were spaced within 14 days together. A 14-day extension was then added to the last exacerbation event. In situations where the criteria for moderate COPD exacerbation event are met and an inpatient hospitalization meeting criteria for severe COPD exacerbation is identified within a timeframe of +/- 14 days, the entire episode will be labeled as a single severe COPD exacerbation, with the first day of the entire episode designated as the event start date. Figure 2 illustrates the method by which moderate-to-severe exacerbation episodes will be built.

Figure 2: Illustration of moderate-to-severe exacerbation episodes



All-cause hospitalizations are defined as an inpatient encounter with any diagnosis codes.

Death is defined as evidence of death by administrative claims (e.g. death recorded in national registry, regional death files, tumor data, or other locally defined sources) or by encounter type

(e.g. discharge disposition of expired), evaluated from Death and Encounter tables of the Sentinel Common Data Model[18].

6.5 Follow-up

All study outcomes will be evaluated within the first year of treatment initiation, separately under 'on treatment' as well as 'intent to treat' style follow-up.

For the outcomes of time to first moderate-to-severe exacerbation, time to first all-cause hospitalization, and time to first severe exacerbation following cohort entry, our primary analysis will be analogous to an "on treatment" design where new users of azithromycin or roflumilast are followed from the day after cohort entry until the earliest occurrence of:

- Outcome event
- Treatment discontinuation (we will bridge together dispensings with gaps less than or equal to 50% of the previous dispensing's days supply and add 14 days to the end of each episode to determine the date of discontinuation)
- Treatment crossover (azithromycin new user initiating roflumilast or vice-versa)
- Disenrollment
- Death
- 365 days since cohort entry
- 12/31/2019 (this stop date was chosen to account for potential changes in medical decision-making, potential changes in risk behaviors of COPD patients, and the potential for resultant changes in observed COPD exacerbation rates due to the COVID-19 pandemic that may have a higher risk of introducing bias by calendar time on study findings)

For the outcomes of frequency of moderate-to-severe exacerbations, frequency of severe exacerbations, and all-cause mortality, our primary analysis will be analogous to an "intent to treat" design where new users of azithromycin or roflumilast are followed from the day after cohort entry until the earliest occurrence of:

- Outcome event
- Disenrollment
- Death*
- 365 days since cohort entry
- 12/31/2019

*Death will not be a censoring criterion in the analysis where death is the outcome.

6.6 Control for confounding

Our cohort is restricted to those with uncontrolled COPD, defined as those with evidence of chronic maintenance therapy with ICS, LABA, and LAMA, and a history of exacerbations at baseline. Further, we compare new users of chronic maintenance azithromycin to new users of roflumilast, a therapy with relative equipoise for this patient population in clinical practice. Taken together, these design choices help to control for confounding by indication and disease severity[17].

Analytically, we will use propensity score adjustment to control for confounding at baseline. At each site, we will estimate the predicted probability of initiating treatment with azithromycin using a multivariable logistic regression model. This propensity score model will include characteristics deemed to confound the relationship between treatment and outcome; or are known to be risk factors for the study outcomes[25]. All covariates in the propensity score model will be measured in the baseline period prior to treatment initiation.

The following covariates will be included in the propensity score model:

- **Demographic factors**
  - Age
  - Sex
  - Race
  - Census Bureau region based on ZIP code
  - Proxies of socioeconomic status based on ZIP code
    - Percent unemployment
    - Median household income
    - Median property value
- **Factors related to time of treatment initiation**
  - Calendar year
  - Calendar season
- **Comorbidities**
  - Combined Comorbidity Index[22,23]
  - Specific comorbidities
    - Pulmonary hypertension
    - Chronic bronchitis
    - Emphysema
    - Obstructive sleep apnea
    - Pulmonary embolism
    - Pneumonia
    - Obesity
    - Cachexia
    - Gastroesophageal reflux disease
    - Chronic kidney disease
    - Diabetes
    - Hypertension
    - Coronary artery disease/Cardiovascular disease
    - Congestive heart failure
    - Lung cancer
    - Other cancer (i.e., non-lung cancer)
    - Atrial fibrillation
    - Atrial or ventricular arrhythmias (excluding atrial fibrillation)
    - Osteoporosis
    - Anxiety
    - Major Depressive Disorder
- **Medications**
  - Number of unique drug classes
  - Number of unique generic drugs
  - Specific concomitant medication class use
    - Antidepressants
    - Anticonvulsants
    - Beta-blockers or calcium-channel blockers
    - Proton pump inhibitors
    - Opioids
    - Antipsychotics
    - Anxiolytics/hypnotics
    - Benzodiazepines
    - Medications for treatment of dementia

    - Medications for treatment of parkinsonism
    - Insulin
    - Non-insulin diabetes medications
    - Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers
    - Therapeutic anticoagulants
    - Amiodarone
    - Digoxin
    - Diuretics
- **Health maintenance habits**
    - Screening for colon cancer (Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy)
    - Screening for breast cancer (Mammograms)
    - Screening for cervical cancer (Pap smear)
    - Screening for prostate cancer (Prostate exam/DRE or prostate-specific antigen test)
    - Influenza vaccination
    - Pneumococcal vaccination
- **Proxies for COPD severity and overall morbidity burden**
    - Frequency of pulmonary function tests in prior year (spirometry code days)
    - Evidence of prior smoking
    - Evidence of supplemental oxygen use
    - Pulmonary rehabilitation in the prior year
    - Number of antibiotic dispensings in prior year
    - Number of corticosteroid dispensings in prior year
    - Number of severe exacerbations in prior year
    - Respiratory failure with intubation and mechanical ventilation in prior year
    - Number of ambulatory encounters in prior year
    - Number of inpatient encounters in prior year
    - Any institutional stay encounters in prior year (e.g., long-term acute care hospital, acute rehabilitation center, nursing home)

At each site, patients in the azithromycin and roflumilast cohorts will be matched 1:1 on their propensity score within a caliper of 0.05 using optimal nearest neighbor matching without replacement, meaning that each new user of roflumilast within a given site will be matched once, at most, to a new user of azithromycin at the same site.

Success of propensity score matching to control for confounding will be evaluated by examining covariate balance for the aggregated cohort at baseline before and after matching using standardized differences[26]. We will use a threshold of 10% to detect meaningful differences at baseline between new users of azithromycin and roflumilast.

We will use different specifications of the propensity score model in the primary (Medicare) and supplementary (aggregate of three large national insurers) analyses to account for varying sample size at each site. We anticipate Medicare to yield the largest sample size and will therefore accommodate a propensity score model with an extensive list of covariates listed above to control for confounding. We expect to run a more parsimonious specification, a subset of the list of covariates above, at the smaller sites.

We will conduct a beta-test of our pre-specified propensity score model to examine the distribution of propensity scores in Medicare data. The purpose of this beta-test is to evaluate covariate balance at baseline before and after matching with propensity score. This beta-test

will not include any treatment effect estimates. We may remedy any potential propensity score model misspecification prior to the final analysis.

6.7 Statistical analysis

6.7.1 Time-to-event outcomes

Incidence rates for moderate-to-severe COPD exacerbations, severe COPD exacerbations, all-cause hospitalizations, and death will be determined by dividing the number of events observed over the total follow-up time in each exposure. We will use case-centered logistic regression[27] models which are equivalent to the Cox Proportional Hazards model to estimate the hazard ratio and 95% confidence intervals for the crude, unconditional, and conditional matched analyses. We will report results from the unconditional matched analyses as primary results.

6.7.2 Frequency outcomes

Event rates for moderate-to severe exacerbation events and severe exacerbation events within the first year of treatment will be determined by totaling the number of exacerbation events in each exposure and dividing it by the total follow-up time in each exposure[28,29]. Frequency of exacerbations will be analyzed as an over-dispersed count outcome using negative binomial regression. These regression models will be run at each site with and without stratification by the matched pair to generate conditional and unconditional estimates. Incidence rate ratios and 95% confidence intervals from Medicare data will inform the primary analysis. In supplementary data, effect estimates from each site will be combined at the Sentinel Operations Center using fixed and random effects meta-analysis[30].

6.8 Sensitivity and subgroup analyses

6.8.1 Sensitivity analyses

We cannot rule out the possibility that drug discontinuation may differ between the two exposure groups and may be related to the study outcomes. We will therefore conduct a sensitivity analysis evaluating each outcome under an "intent to treat" style follow-up where patients will be followed up from the day after cohort entry until the earliest occurrence of the outcome, death, disenrollment, 365 days after treatment initiation, or 12/31/2019.

Residual confounding remains a possibility despite inclusion of multiple, clinically relevant covariates in our primary propensity score model. We will therefore conduct a sensitivity analysis using a high-dimensional propensity score (hdPS) with 300 empirically determined covariates in addition to the pre-specified covariates[31] mentioned above to assess the effect of more robust control of residual confounding on our outcomes. Empirical selection of covariates will be based on codes present in the patients' records from 365 to 1 day prior to cohort entry. One hundred codes each from seven domains (drug class, ICD-9-CM diagnosis, ICD-10-CM diagnosis, ICD-9-CM procedure, ICD-10-CM procedure, Current Procedural Terminology (CPT), HCPCS) will be considered and the top 300 as ranked by the Bross bias formula will be selected for inclusion in the propensity score model along with other pre-specified covariates. Resulting high dimensional propensity score will be used to perform 1:1 nearest neighbor matching without replacement within a caliper of 0.05.

6.8.2 Subgroup analyses

Roflumilast is FDA-approved for a specific chronic bronchitis phenotype of COPD, while azithromycin is not FDA-approved for chronic maintenance use in COPD and carries no labeling information regarding use in COPD patient populations. This discrepancy has the potential to limit use of roflumilast – but not azithromycin use – to a specific subgroup of COPD patients in a systematic way. While the likely overlap between subjects meeting clinical criteria for a chronic bronchitis phenotype and uncontrolled COPD by our definition is substantial, we will

conduct a subgroup analysis to assess the effect in the subgroup with documentation of chronic bronchitis in the baseline period.

In addition, subgroup analyses will be performed for the following demographic categories, where possible:

- Age (40-64, 65-74, and 75 or above)
- Sex (male, female)

Subgroups will be created from the overall matched population and patients in each subgroup will be re-matched 1:1 using the original propensity score.

6.9 Multiple comparisons

We chose to implement a pre-specified hierarchical testing strategy for strict control of Type I error in the presence of multiple relevant clinical questions and multiple hypothesis tests.

6.9.1 Analysis of the primary effectiveness endpoint

The time-to-first moderate-to-severe COPD exacerbation in the on-treatment analysis population will be compared between subjects receiving azithromycin and roflumilast as the primary effectiveness endpoint (see Null and Alternative hypothesis equations, below). This hypothesis will be tested using a two-sided test at an α of 0.05. If the null hypothesis is not able to be rejected, all subsequent hypothesis tests in the hierarchy will be considered exploratory. The null hypothesis for this analysis states that there is no difference between the time-to-first moderate-to-severe COPD exacerbation in the on-treated analysis population comparing azithromycin versus roflumilast. The alternative hypothesis is that such a difference is present.

H_o: time-to-first moderate-to-severe COPD exacerbation among those dispensed azithromycin = time-to-first moderate-to-severe COPD exacerbation among those dispensed roflumilast

H_a: time-to-first moderate-to-severe COPD exacerbation among those dispensed azithromycin ≠ time-to-first moderate-to-severe COPD exacerbation among those dispensed roflumilast

Only if rejection of the null hypothesis is demonstrated for the primary efficacy endpoint can the result of the test be declared statistically significant, and hierarchical testing of the next endpoint in the secondary endpoint hierarchy proceed using the same rules (e.g., $\alpha = 0.05$, if null hypothesis not rejected then all subsequent tests in the hierarchy considered exploratory), in the order defined below:

6.9.2 Secondary effectiveness endpoint testing hierarchy

- Time to first all-cause hospitalization in the on-treatment analysis
- Time to first severe exacerbation in the on-treatment analysis
- Frequency of moderate or severe exacerbation in the intent-to-treat analysis
- Frequency of severe exacerbation in the intent-to-treat analysis
- Time to all-cause mortality (i.e., death) in the on-treatment analysis

We will report effect estimates and confidence intervals for all outcomes regardless of the results of hypothesis testing.

6.9.3 Additional exploratory effectiveness endpoints

Additional endpoints will be analyzed in an exploratory fashion, without formal hypothesis testing. Effect estimates and confidence intervals will be reported for the following:

- Time to first moderate or severe exacerbation in the intent-to-treat analysis
- Time to first all-cause hospitalization in the intent-to-treat analysis
- Time to first severe exacerbation in the intent-to-treat analysis
- Time to all-cause mortality (i.e., death) in the intent-to-treat analysis

6.10 Multi-site distributed analysis

Our primary analysis is conducted using data from a single site (Medicare). We will supplement this data by also conducting a multi-site study using aggregated data from three additional large national insurers in the Sentinel system.

The Sentinel Operations Center will distribute common analytic programs to Medicare and three other large national insurers separately. Each site will execute the analytic program against their data locally behind institutional firewalls. Sites will return summary and effect estimate data to the Sentinel Operations Center where results will be aggregated via meta-analysis, reviewed, and shared with the FDA. Inverse variance weighted meta-analysis using DerSimonian-Laird's fixed and random effects models will be used to pool effect estimates from multiple sites[30]. All analyses will be conducted using the Sentinel Query Request Package version 11.3.0 with the Propensity Score Analysis module[32] and additional custom programming to meet the study objectives. Data will be analyzed using SAS 9.4 (SAS Institute, Cary, NC).

The data generated from this study will not be publicly available. Sentinel uses a distributed data approach in which Data Partners maintain physical and operational control of their own electronic health data after transforming it into a common data model. Sentinel does not save, maintain, or post individual level datasets to preserve patient privacy.

6.11 Small cell redaction

Medicare is one of the four participants in this multi-site distributed cohort study. Sentinel follows the small cell suppression policy enacted by the Centers for Medicare and Medicaid Services (CMS) for all aggregated reports containing Medicare data. This policy stipulates that any cell containing a count value of >0 and <11 or any cell that can be used to derive a value of <11 cannot be reported directly[33]. The Sentinel Operations Center may consider combining categories to prevent small cell counts where applicable and meaningful.

7 Sample table and figure shells

Sample table and figure shells presented below are for the purpose of representation only and will be refined over time.

Sample table 1: Aggregated baseline characteristics of new users of azithromycin or roflumilast selected between March 1, 2011 and December 31, 2018 in select Sentinel Data Partners, before and after 1:1 propensity score matching

	Before Matching			After Matching		
	Azithromycin	Roflumilast	Standardized Difference	Azithromycin	Roflumilast	Standardized Difference
Characteristic	**N (%)**	**N (%)**		**N (%)**	**N (%)**	
Number of unique patients			--			--
Demographics						
Mean Age in years						
40-64 years						
65-74 years						
>=75 years						
Sex: Female						
…						

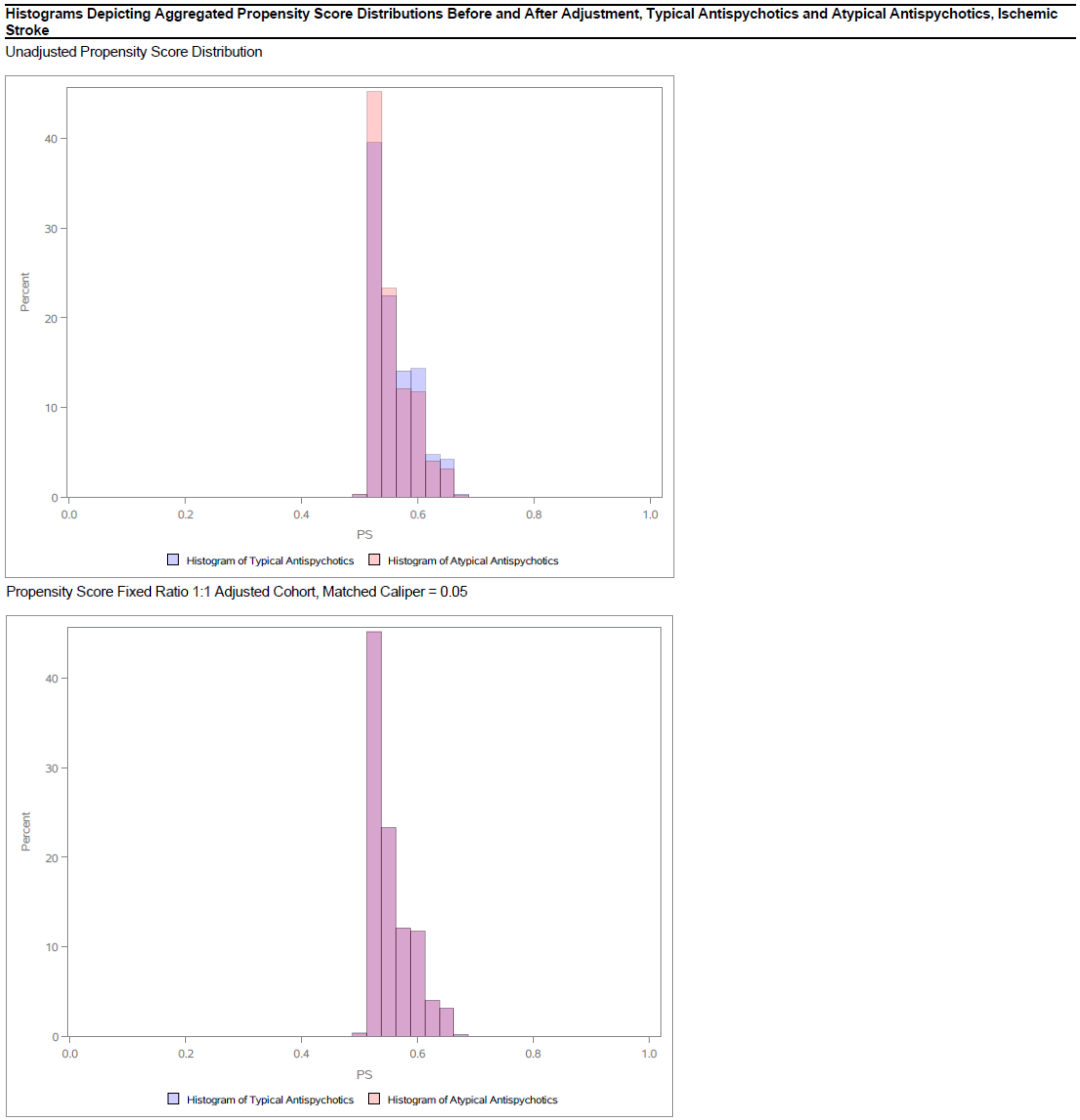
Sample table 2: Unadjusted and adjusted effect estimates for time-to-event outcomes under <style of follow-up: on treatment or intent to treat>among new users of azithromycin or roflumilast selected between March 1, 2011 and December 31, 2018 in select Sentinel Data Partners

Exposure	New Users	Person-Years at Risk	Average Person-Days at Risk	Average Person-Years at Risk	Number of Events	Incidence Rate per 1,000 Person-Years	Incidence Rate Difference per 1,000 Person-years	Hazard Ratio (95% Confidence Interval)	Wald p-value
Before 1:1 Propensity Score Matching									
Azithromycin									
Roflumilast								(Ref)	
After 1:1 Propensity Score Matching (Conditional Analysis)									
Azithromycin									
Roflumilast								(Ref)	
After 1:1 Propensity Score Matching (Unconditional Analysis)									
Azithromycin									
Roflumilast								(Ref)	

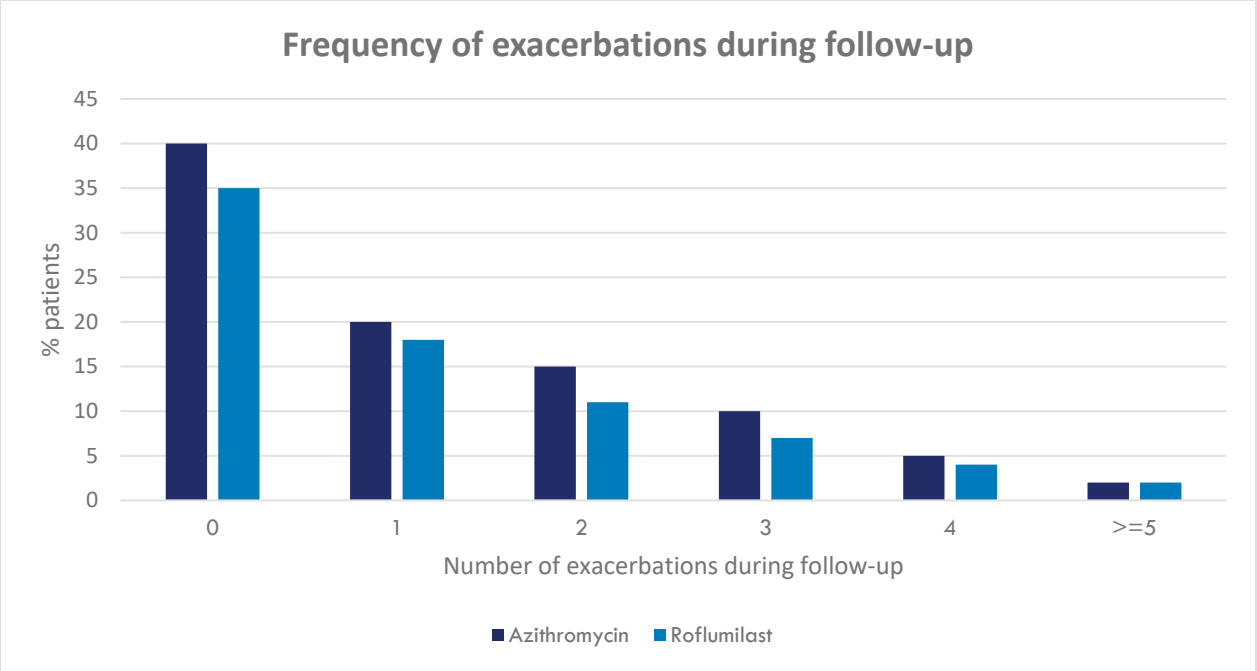
Sample table 3: Unadjusted and adjusted effect estimates for frequency outcomes observed during <style of follow-up: on treatment, intent to treat> among new users of azithromycin or roflumilast selected between March 1, 2011 and December 31, 2018 in select Sentinel Data Partners

Exposure	New Users	Person-Years at Risk	Number of Events	Incidence Rate per 1,000 Person-Years	Incidence Rate Ratio (95% Confidence Interval)	p-value
Before 1:1 Propensity Score Matching						
Azithromycin						
Roflumilast					(Ref)	
After 1:1 Propensity Score Matching (Conditional Analysis)						
Azithromycin						
Roflumilast					(Ref)	
After 1:1 Propensity Score Matching (Unconditional Analysis)						
Azithromycin						
Roflumilast					(Ref)	

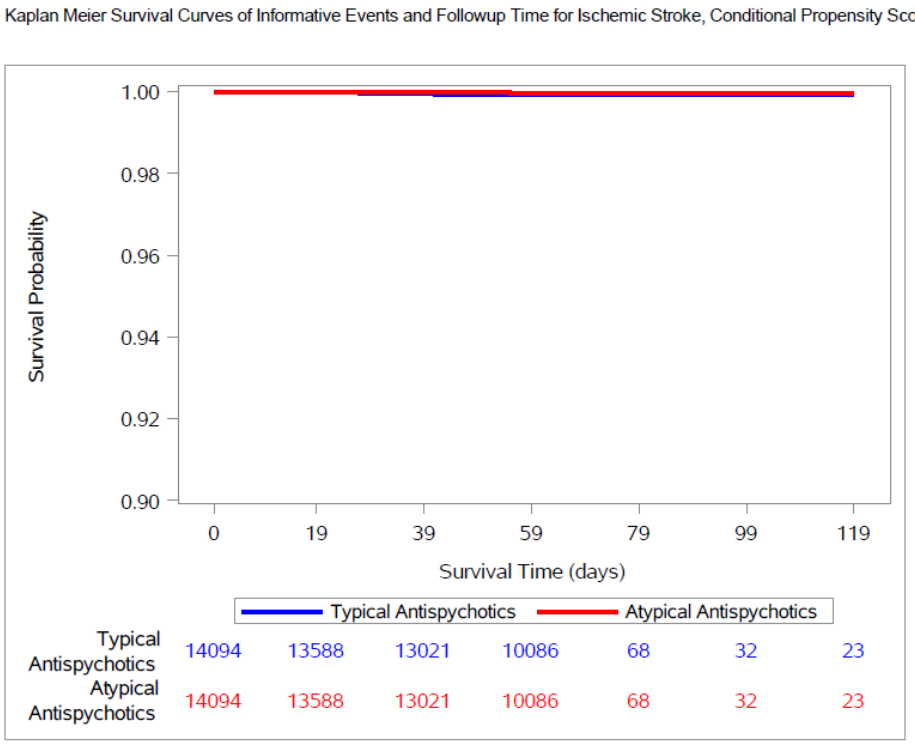
Sample figure 1: Distribution of propensity scores in new users of azithromycin and roflumilast, before and after 1:1 propensity score matching (figures generated with synthetic data for a use case example)



Sample figure 2: Frequency of moderate-to-severe or severe exacerbations during <style: on treatment or intent to treat>follow-up period (figure generated with mock data)



Sample figure 3: Kaplan-Meier curves for study outcomes (figure shown here is generated with synthetic data for a use-case example and does not reflect the title or content of the planned figure. Planned figure will be generated for pertinent time-to-event study outcomes displayed for the study arms of azithromycin and roflumilast)



8 Human subjects considerations

This Sentinel analysis is deemed a public health surveillance activity conducted under the authority of the Food and Drug Administration and, accordingly, is not subject to Institutional Review Board oversight[34–36].

9 Documentation of amendments and deviations

Any changes made to this protocol after its publication will be documented here.

Version	Date	Modification	Author

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