pcori

A multi-center, randomized, 36-month, parallel-group, non-inferiority, phase III study to compare the effectiveness of 500 mcg QD or alternate regimen of roflumilast (Daliresp) therapy versus 250 mg QD, 500 mg QD three times per week, or alternate regimen of azithromycin therapy to prevent COPD exacerbations (RELIANCE)

RELIANCE

Protocol Version 4.0

08 June 2020

Funded by PCORI PCS-1504-30430

RELIANCE is a U.S.-based pragmatic clinical trial funded by the Patient-Centered Outcomes Research Institute (PCORI) to compare long-term use of roflumilast vs. azithromycin in up to 3,200 patients. It is intended to support hospital efforts to reduce the risk of all-cause hospitalization and reduce pre-mature deaths in individuals with chronic obstructive pulmonary disease (COPD). The COPD Patient Powered Research Network (PPRN) and affiliated investigators will conduct the trial in sites in the U.S.

Both roflumilast and azithromycin have been shown to reduce the risk of COPD exacerbations compared to placebo. However, there has not been a head-to-head comparison of the two medications. So, the relative harms and benefits of the two medications are unknown. Eligible patients will be randomized (1:1) to receive either a prescription for roflumilast or a prescription for azithromycin and will be followed for at least 6 and up to 36 months. The primary endpoint is the combined outcome of all-cause hospitalization or death; the secondary endpoints include premature treatment discontinuation, patient-reported adverse effects, and physical, social, and emotional health. Patients will provide data via an online Participant Portal or via a call center. Baseline and outcome data will also be collected from site medical records and administrative/claims databases.

RELIANCE

Protocol Version 4.0

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PICOTS table

Population N=up to 3,200 randomized over 30 months	Inclusion criteria (must meet all criteria): (1) Patient and treating clinician considering treatment intensification with roflumilast or azithromycin to reduce the risk of COPD exacerbations; (2) Age ≥ 40 years; (3) Current or past smoker of at least 10 pack years; (4) Diagnosis of severe COPD and associated chronic bronchitis; (5) Hospitalized with a diagnosis of COPD exacerbation in the past 12 mos; (6) Current medications include inhaled LAMA, ICS/LABA, or LAMA/LABA; (7) English- or Spanish-speaking. (8) Willing and able to provide a contact telephone number. Exclusion criteria (any criterion): (1) Unable or declines to provide informed consent; (2) Declines to provide social security number (SSN), health insurance claims number, or Tax Payer ID Number (as applicable); (3) History of intolerance to azithromycin or roflumilast that the patient or patient's treating clinician considers sufficiently serious to avoid either treatment option; (4) Current treatment with long-term (more than 30 days) roflumilast or azithromycin (previous treatment with 1 or more doses of azithromycin or roflumilast is not an exclusion criterion, as long as the patient and clinician are seeking treatment intensification options); (5) Known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic; (6) History of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin; (7) Moderate to severe liver impairment (Child-Pugh B or C); (8) Current pregnancy; (9) Any other clinician-determined clinical exclusion as per their clinical practice.
Intervention	Prescription for Azithromycin (250 mg/day, or 500 mg three times per week, or alternate regimen) x 6 to 36 months
Comparator	Prescription for Roflumilast (250 mcg/day x 4 weeks, then 500 mcg/day or alternate regimen) x 6 to 36 months

Outcomes	Primary outcome: All-cause hospitalization or death collected primarily by data provided by patients via the Patient and Call Center Portals, and review of electronic health records (I). Administrative and claims data will be reviewed to evaluate the completeness of ascertainment of the primary outcome. Trial data and National Death Index (NDI) will contribute to primary analyses of primary and secondary outcomes. Trial data, NDI, and Medicare data will contribute to secondary analyses of primary and secondary outcomes. Secondary outcomes: • All-cause individual events: hospitalization, emergency department visit, urgent care visit, death (source: Participant Portal, Investigator PortalEHR, Medicare claims data in a subset, NDI) • Patient-reported outcomes (source: Reference Table: PRO Common Measures, 3.1, Oct 25, 2014) PROMIS measures using the NIH-PROMIS instruments (source: Call Center or Participant Portal): 1. Physical function (Domain: Physical function (alternate), Item code: GLOBAL 06, Item bank: PROMIS Global) 2. Problems with sleep (Domain: Sleep disturbance, Item code: SLEEP20, Item bank: PROMIS Sleep Disturbance) 3. Fatigue (Domain: Fatigue, Item code: 2876R1, Item bank: PROMIS Peds - Fatigue) 4. Anxiety (Domain: Anxiety, Item code: EDANX53, Item bank: PROMIS Emotional Distress-Anxiety) 5. Depression (Domain: Depression, Item code: PEDGLOBAL2, Item bank: PROMIS Peds - Global) • Adverse events: patient report for hearing decrement, diarrhea, nausea, suicidal ideation, other (source: self-report via Call Center or Participant Portal); microbiology cultures in which macrolide-resistant organisms were identified in sputum (sole: EHR) • Medication adherence (source: self-report via Call Center or Participant Portal; Medicare claims data in a subset) • Crossover to alternate study medication (source: self-report via Call Center or Participant Portal, query of clinic staff; Medicare claims data in a subset) • Treatment discontinuation (source: self-report via Call Center or Participant Portal; query of clinic staff; Medicare claims data in a subset) • Out-of-pocket costs for roflumilast or azithromycin (source: self-report via Call Center or Participant Portal) • Weight (source: self-report via Call Center or Participant Portal)
Timing	• Every participant will be followed for a minimum of 6 months ○ Patients will receive a phone call 1 week after randomization, then will complete follow-up at 3 and 6 months after randomization, then, every 6 months until the patient achieves a primary outcome.
Setting	Patients will be identified as they seek care with their clinician (outpatient clinic, telemedicine visit, or hospital)
Study design	Pragmatic, non-inferiority trial using an intention-to-treat analysis to evaluate whether daily azithromycin is non-inferior to daily roflumilast in patients at high risk of COPD exacerbations. We will randomize individual patients to receive prescriptions for roflumilast or azithromycin (1:1 ratio), stratified by site and current smoking status (yes/no).

Contents

1. Study Overview

1.1. Rationale

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease of adults. Cigarette smoking accounts for about half of the attributable risk, but COPD also occurs in non-smokers.[1,2] COPD affects 15 million individuals in the U.S. alone and is associated with worse quality of life and reduced life expectancy.[3,4] COPD is the fourth leading cause of death in the U.S. after heart disease, cancer, and unintentional injury.[5,65] In 2017, COPD accounted for 160,000 deaths in the U.S.[6] In the U.S., COPD is a major cause of health disparities and disproportionately affects women, the elderly, and individuals without a high-school diploma, unable to work or unemployed, or living in households with income less than $25,000/year.[4]

Most of the COPD-related morbidity, hospitalizations, and mortality are due to “exacerbations”, i.e., worsening of respiratory symptoms including difficulty breathing and excess phlegm production. Milder exacerbations may resolve within a week, but more severe exacerbations may last for 3 or more months.[7,8] Each year in the U.S., COPD accounts for eight million office visits, 1.5 million visits to the emergency department (ED), and over 700,000 hospitalizations.[9] Among patients hospitalized for a COPD exacerbation, the 1-month, 3-month, and 12-month re-hospitalization rates are approximately 20%, 30%, and 40%, respectively.[10,11] Mortality among patients hospitalized for COPD exacerbation is 2.5% prior to hospital discharge overall and 30% in those requiring mechanical ventilation.[12,13,14] Among those who survive to discharge, the 1-year mortality varies from 7% to 50% depending on the severity of the COPD exacerbation, comorbid conditions, and level of socioeconomic resources.[4,15,16] In the U.S., annual costs associated with COPD have been increasing and estimated to be $49 billion by 2020.[17] Patients with more frequent or severe COPD exacerbations lose lung function more quickly, do not recover to the pre-exacerbation levels, have a greater decline in health status and a higher likelihood of becoming housebound.[18]

In recognition of the growing burden of COPD exacerbations, the American College of Chest Physicians (ACCP) and Canadian Thoracic Society (CTS) published the first evidence-based guidelines devoted to prevention of COPD exacerbations in 2015.[19] The 2015 ACCP/CTS guidelines report several “Level 1 recommendations” (i.e., evidence indicating that benefits clearly outweighed risks and burden) for preventing COPD exacerbations. There were only

three Level 1 pharmacotherapy options for preventing COPD exacerbations and all of them were inhaled maintenance therapies: inhaled long-acting muscarinic antagonist (LAMA), corticosteroids combined with inhaled long-acting beta-2 agonists [ICS/LABA], and inhaled long-acting muscarinic antagonist combined with LABA [LAMA/LABA].

However, even with inhaled maintenance therapy, many patients continue to have recurrent COPD exacerbations.[20,21,22,23] In such cases, the 2015 ACCP/CTS guidelines suggest initiating **long-term oral macrolide (azithromycin)** (an antibiotic that has immunomodulatory, anti-inflammatory, and anti-bacterial effects)[24] **or oral roflumilast** (a long-acting selective phosphodiesterase-4 inhibitor with anti-inflammatory effects) therapy.[25] Both options are graded as a "Level 2A recommendation" (i.e., evidence is high-quality, but that the "benefits closely balance with risks and burden, therefore, the best action may differ, depending on the circumstances or patient or societal values"). The 2017 European Respiratory Society / American Thoracic Society (ERS/ATS) guidelines offer similar recommendations.[66] Of these two options for treatment intensification, only roflumilast is Food and Drug Administration (FDA)-approved for the prevention of COPD exacerbations.

The results of the systematic reviews and subsequent trials[26,27,28,29,30,33,68,69] comparing the efficacy of azithromycin (ZITHROMAX®) or roflumilast (DALIRESP®) therapy with placebo are summarized in Table 1. Taken together, these studies provide strong evidence about the efficacy of azithromycin or roflumilast as treatment intensification options to help reduce the risk of COPD exacerbations. Further, data from a study of 66,145 COPD patients enrolled in Medicare showed that patients initiated on roflumilast in clinical practice (n=500) have a significantly lower risk of COPD exacerbations ($p<0.001$) and associated hospitalizations ($p=0.009$) than concurrent controls not receiving roflumilast.[31] In a separate observational study of 15,755 patients, patients initiated on roflumilast within 14 days of hospital discharge had a significantly lower likelihood of all-cause 30-day hospitalization ($p=0.02$) compared to historical controls.[32] Data are more limited regarding the effects of azithromycin on hospitalizations from placebo-controlled trials. A small observational study of 220 patients who completed a 12-month treatment period had fewer COPD exacerbations ($p<0.001$), hospitalizations ($p<0.001$), and cumulative annual days of hospital stay ($p=0.01$) compared to the year prior to therapy.[68]

Table 1: Efficacy of long-term azithromycin and roflumilast, compared to placebo in clinical trials		
	Oral azithromycin x 3-12 mos.	Oral roflumilast x 12 mos.
FDA-approved indication in COPD	No, no IND required for NIH trials	Yes, 2011, COPD associated with chronic bronchitis
Systematic review and subsequent trials	Herath SC. 2013[26], COLUMBUS, 2014[27], BACE[69]	Chong J., 2013[28], REACT, 2015[29], RE2SPOND, 2016[68]
Treatment regimens in placebo-controlled trials	250 mg/d, 500 mg 3d/wk x 12 mos, or 250 mg/2d x 3 mos	500 mcg/d x 12 mos.
# patients (trials)	1,510 (MACRO[37], n=1,117; COLUMBUS[27], n=92; BACE[69], n=301)	5,036 (M2-124[33], n=1,523; M2-125[33], n=1,568; REACT[29], n=1,945; RE2SPOND[68], n=2,354)
Average reduction in yearly exacerbation rates, as compared to placebo Average reduction in hazard of exacerbation, as compared to placebo	95% confidence intervals MACRO[37] 5-18% COLUMBUS[27] 16-57% 27% reduction, (HR 0.73, 95% confidence interval: 0.53, 1.01); BACE[69])	95% confidence interval 7-19% (M2-124[33], M2-125[33], REACT[29], and RE2SPOND[68])

However, results of post-hoc analyses of two trials (M2-111, M2-112, not listed in Table 1) suggested that the reduction in COPD exacerbations with roflumilast may be limited to patients with COPD associated with chronic bronchitis[34]. Patients with COPD associated with chronic bronchitis are at higher risk of COPD exacerbations compared to patients with COPD without chronic bronchitis.[35] Post-hoc analyses of the MACRO trial, the largest study of azithromycin to prevent COPD exacerbations, suggest azithromycin reduced COPD exacerbations in former smokers (relative hazard vs. placebo: 0.65, p<0.0001) but not in current smokers (relative hazard 0.99, p=0.99).[36] Effect modification by smoking status was noted in exploratory analyses of treatment failure in the BACE study, suggesting lower efficacy among current smokers vs. past smokers using azithromycin after 3 months though the test for interaction by smoking status was not significant (p=0.14).[69] Post-hoc analyses suggest that roflumilast reduces the risk of COPD exacerbations in both past and current smokers[34]. Placebo-controlled clinical trials of chronic azithromycin to prevent COPD exacerbations suggest that azithromycin is generally well-tolerated, though slightly more treatment discontinuations for adverse events occur with

azithromycin (vs. placebo: 26 vs 22%).[27,37,69] The most common reason for premature treatment discontinuation in the MACRO trial was hearing decrement, noted on audiograms performed by study personnel (azithromycin vs. placebo: 25 vs. 20% had hearing decrements, p=0.01). However, hearing returned to baseline levels in a subsequent audiogram in roughly 1/3 of patients whether or not the patient was in the azithromycin or placebo group or if the study treatment was discontinued. Hearing reduction was recorded based on patient report using questionnaires in the BACE trial (azithromycin vs. placebo: 0.7 vs. 4% reported hearing loss, p-value not reported)[69]. No hearing-related adverse events were noted in the COLUMBUS trial, although audiometry tests were not part of the study protocol. Other reasons for treatment discontinuation in the MACRO trial were much less common and did not differ significantly between groups (gastrointestinal, 1-2%; QTc prolongation, tinnitus, allergic reaction, abnormal laboratory test, each <1%). Treatment discontinuation due to adverse effects were uncommon in the COLUMBUS and BACE trials (discontinuation in azithromycin vs. placebo groups: 9 vs. 4%, p=0.33 in the COLUMBUS trial; discontinuation in azithromycin vs. placebo groups: 5 vs. 8%, p-value not reported in BACE), though diarrhea was noted to be more common in the azithromycin group (19% vs. 2%, p=0.02) in the COLUMBUS trial. Mortality was uncommon in the MACRO, COLUMBUS, and BACE trials, and did not differ between groups (azithromycin vs. placebo: 3.2 vs. 3.6%, 0 vs. 4%, 2 vs. 4%, respectively).

There is also uncertainty in the potential long-term risk of promoting macrolide-resistant organisms when instituting chronic macrolides such as azithromycin in clinical populations. Data from the three azithromycin studies (MACRO trial[37], COLUMBUS trial[27], and BACE trial[69]; Table 2) indicate that the prevalence of macrolide-resistant pathogens was already fairly high prior to initiating therapy. In the BACE trial, sputum samples were obtained in fewer than 20% at the end of treatment and follow-up periods in both groups, so no conclusions were made on shifts in bacterial resistance[69]. The incidence of macrolide-resistant pathogens among participants not colonized at baseline were about twice the incidence in the azithromycin vs. the placebo group (81% vs. 41%, P<0.0001) in the MACRO trial[30] and higher in the placebo groups in the COLUMBUS trial[27] (6% vs 24%, P=0.036). Note, however, that in the larger MACRO trial, testing for macrolide resistance was not performed in many patients at baseline or at follow-up, so the true difference in macrolide resistance across groups may be higher or lower than reported.

Table 2: Macrolide resistance

	Study regimens (Study name, journal, year)	Azithromycin 250 mg/day vs. placebo X 12 mos; MACRO trial, NEJM 2011	Azithromycin 500 mg vs. placebo 3x/wk X 12 mos; COLUMBUS trial, Lancet Resp Med 2014	Azithromycin 250 mg every 2 days vs. placebo X 3 mos; BACE trial, AJRCCM 2019
	Azithromycin vs placebo groups, n	558 vs. 559	47 vs. 45	147 vs. 154
Baseline data	**Prevalence of respiratory pathogens, n (%)**	79/558 (14%) vs. 83/559 (15%)	7/22 (32%) vs. 6/20 (30%)	6/109 (5.5%) vs. 2/103 (1.9%)
	Prevalence of macrolide resistance among those with respiratory pathogens, n (%)	23/44 (52%) vs. 28/49 (57%)	5/7 (71%) vs. 4/6 (67%)	37/110 (33.9%) vs. 30/109 (29.1%)
Follow-up data	**Incidence of resp pathogens, n (%)**	66/558 (12%) vs. 172/559 (31%); p<0.0001	4/25 (16%) vs. 12/27 (44%); p=0.03	4/24 (16.7%) vs. 3/22 (13.6%)
	Incidence of macrolide resistance among those with data on newly acquired respiratory pathogens, n (%)	38/47 (81%) vs. 44/108 (41%), p<0.0001	3/4 (75%) vs. 11/12 (92%); p=0.38	0/23 (0.0%) vs. 1/21 (4.8%)

The FDA approved labeling for roflumilast[38] includes a section on "Warnings and Precautions" that discusses concerns about psychiatric events, including suicidality. Treatment with roflumilast is associated with an increase in psychiatric adverse reactions. In 8 controlled clinical trials 5.9% (263) of patients treated with roflumilast 500 mcg daily reported psychiatric adverse reactions compared to 3.3% (137) treated with placebo. The most commonly reported psychiatric adverse reactions were insomnia, anxiety, and depression, which were reported at higher rates in those treated with roflumilast 500 mcg daily (2.4%, 1.4%, and 1.2% for roflumilast versus 1.0%, 0.9%, and 0.9% for placebo, respectively). Instances of suicidal ideation and behavior, including completed suicide, have been observed in clinical trials. Before using roflumilast in patients with a history of depression and/or suicidal thoughts or behavior, the FDA-approved Prescribing Information suggests that clinicians should carefully weigh the risks and benefits of treatment with roflumilast in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with roflumilast if such events occur.

OPTIMIZE was a 12-week randomized double-blind clinical trial in 1,321 patients with severe COPD associated with chronic bronchitis that was used to determine if starting a lower dose

of roflumilast could reduce all-cause treatment discontinuation at 12 weeks.[39] Results of OPTIMIZE indicate that roflumilast 250 mcg per day for the first 4 weeks (then 500 mcg per day X 8 weeks) was associated with a significantly lower risk of all-cause treatment discontinuation than roflumilast 500 mcg per day X 12 weeks (odds ratio 0.66, 95% CI 0.47 to 0.93, p=0.017) and lower rates of adverse events such as diarrhea, nausea, headache, decreased appetite, insomnia, and abdominal pain (odds ratio 0.63, 95% CI 0.47 to 0.83, p=0.001). Initiating roflumilast at 500 mcg every other day X 4 weeks, followed by 500 mcg per day X 8 weeks was associated with a numerically lower, but not significantly different, risk of all-cause treatment discontinuation compared with 500 mcg per day X 12 weeks (20.1% vs. 24.6%, p=0.11).[39] Findings showed the same pattern when comparing treatment emergent adverse effects, adverse events were lower in the groups starting at lower doses of roflumilast versus the group that started at 500 mcg per day dose; for comparison of 250 mcg per day vs 500 mcg per day the rates of treatment emergent adverse events were 45.4% vs 54.2% (P=0.001), respectively, and 48.3% vs 54.2% (P=0.09) for the comparison of 500 mcg every other day vs 500 mcg per day. These results indicate that treatment discontinuations due to adverse effects can be reduced by starting with a lower initial dose of roflumilast. The harms of chronic azithromycin and roflumilast therapy when used in routine clinical settings are not well understood. The RELIANCE study seeks to compare the harms of both medications in "real-world" clinical settings.

In summary, comparisons with placebo indicate that a 12-month course of azithromycin or roflumilast offers a similar opportunity for patients to avoid COPD exacerbations. Observational studies suggest that azithromycin or roflumilast may reduce the risk of severe exacerbations associated with hospitalization. While both therapies are generally well tolerated, treatment discontinuation for adverse effects occurs in 5 to 6% more of patients with either therapy (compared to placebo), leading to uncertainty about the balance of benefits and risks that would occur if used in routine clinical practice settings. The results of the OPTIMIZE study suggest that using a lower starting dose of roflumilast could reduce all-cause treatment discontinuations. The RELIANCE trial is a direct head-to-head comparison of long-term oral roflumilast vs. azithromycin in high-risk patients with COPD to inform decision-making in subgroups defined on the basis of current/past smoking status, and when used for a minimum of 6 and up to 36 months.

1.2. Research Design

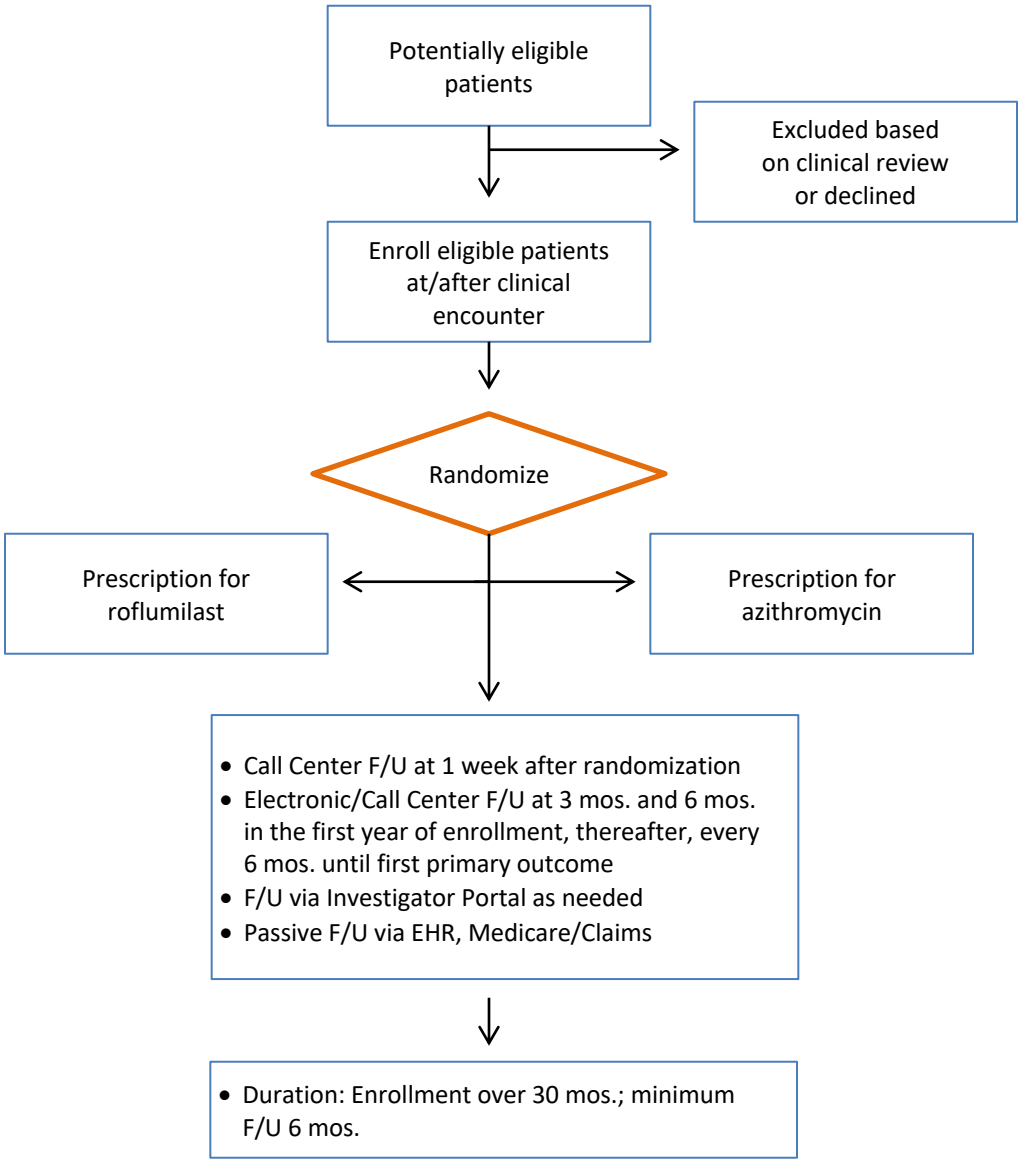
The aims of the RELIANCE study are:

1. Primary aim: To conduct a pragmatic, randomized clinical trial in a high-risk population of patients with COPD and chronic bronchitis to test the hypothesis that azithromycin is non-inferior to roflumilast for prevention of all-cause hospitalizations or death (a primary composite outcome).

   Secondary effectiveness outcomes include all-cause individual events (urgent care visits, emergency department visits, hospitalizations, and death) and other patient-reported measures of physical, mental, and social health.
2. Secondary aim 1: Conduct analyses to evaluate the potential for heterogeneity of treatment effects in current versus former smokers
3. Secondary aim 2: To compare the tolerability of azithromycin vs. roflumilast as assessed by patient-reported adverse events; adherence to assigned treatment (patient-report and claims data); crossover to alternate treatment group (patient-report, query of clinic staff, and claims data); treatment discontinuation (patient-report, query of clinic staff, and claims data); out-of-pocket costs (patient-report); and weight (patient-report).

The trial is a parallel, pragmatic non-inferiority trial with two treatment groups, azithromycin and roflumilast (Figure 1). Up to 3,200 participants will be randomized (1:1) to receive a prescription for one of the two treatments. Treatment assignments will be stratified by site and smoking status (former versus current) using a permuted block design with multiple block sizes. Treatment assignments will be concealed prior to randomization. Once a patient is assigned to receive a treatment, the clinician, Site Coordinator and patient will all be unmasked, i.e., know the treatment.

Figure 1


Potentially eligible patients
Excluded based on clinical review or declined
Enroll eligible patients at/after clinical encounter
Randomize
Prescription for roflumilast
Prescription for azithromycin
• Call Center F/U at 1 week after randomization
• Electronic/Call Center F/U at 3 mos. and 6 mos. in the first year of enrollment, thereafter, every 6 mos. until first primary outcome
• F/U via Investigator Portal as needed
• Passive F/U via EHR, Medicare/Claims
• Duration: Enrollment over 30 mos.; minimum F/U 6 mos.

1.3. Organization of RELIANCE

The organization of the RELIANCE consortium is depicted in Figure 2. The consortium consists of a Clinical Coordinating Center (CCC) led by Jerry Krishnan MD, PhD (Associate Vice Chancellor for Population Health Sciences, Office of the Vice Chancellor for Health Affairs, Professor of Medicine and Public Health, Phone: 312-413-0637), and a Communication Center (CC) led by Hugh Musick, MBA, both at the University of Illinois at Chicago; the COPD Patient Powered Research Network (COPD PPRN), founded by the COPD Foundation and led by Elisha Malanga, David Mannino, MD, Richard Mularski, MD, and Jean Rommes, PhD; the Data Coordinating Center (DCC) at Johns Hopkins University Center for Clinical Trials and Evidence Synthesis led by Robert Wise, MD, Janet Holbrook, PhD, and Elizabeth Sugar, PhD; the FDA Sentinel Operations Center (SOC) led by Kenneth Quinto, MD, Candace Fuller, PhD, and Brad Hammill, PhD; and clinical sites. The leadership for the consortium resides in the Executive Committee (EC), which consists of representatives from each of the resource centers and leaders in the design and conduct of trials of treatments to prevent COPD exacerbations, Richard Albert, MD and Stephen Rennard, MD. The EC relies on input from our funder, the Patient-Centered Outcomes Research Institute (PCORI) located at 1828 L St., NW, Suite 900 Washington, DC 20036; Phone: 202-827-7700), the Stakeholder Advisory Team (STAT), and the Data Safety Monitoring Board (DSMB) to make decisions regarding the design, implementation, and conduct of the trial. An Institutional Review Board (IRB) approved protocol will be provided to PCORI for review prior to distribution to the clinics. The Steering Committee (SC) includes the EC, representatives of each clinical site, and the STAT. The SC will provide overall governance for the trial and voting members will include representatives from the EC, resource centers and clinical centers. The DSMB is composed of 2 pulmonologists, 2 patient advocates, and a biostatistician (see Section 4.7). Intellectual property issues (e.g., authorship, topics for future proposals), if they arise, will be negotiated using current practices of the participating institutions.

The CCC will contract with sites to enroll patients into the RELIANCE study. Each site will have one Principal Investigator and one co-investigator working with colleagues recruited to act as “Clinical Leads”, all of whom are care providers for patients recently hospitalized for a COPD exacerbation at their institution, and one Site Coordinator. Site Coordinators will support the Clinical Leads in identifying and enrolling patients as they receive care for COPD.

Figure 2. RELIANCE Organizational Chart

ORA: 18050802 Date IRB Approved: 4/23/2020 Amendment Date: 7/2/2020

PCORI Program Officer

Lavasani
Barasky
Neu
Giggetts

Clinical Coordinating Center (UIC)

Krishnan
Bracken

RELIANCE Executive Committee

Krishnan (Chair), Albert, Erwin, Fuller, Hamill, Holbrook, Malanga, Mannino, Quinto, Mularski, Rennard, Rommes, Wise

DSMB

Buist (Chair), Bate, Rogatko, Sellers, Tashkin

FDA SENTINEL OPERATIONS CENTER

Fuller, Quinto, Hammill, Toh

Data Coordinating Center (JHU)

Wise (Chair), Holbrook, Roy, Sugar, Shade

COPD PPRN

Mannino (Chair), Mularski, Malanga, Rommes

STAKEHOLDER ADVISORY TEAM

Malanga (Chair) + 10

Communication Center

Musick (Chair), Sculley

Steering Committee

Executive Committee members *plus* Clinical Center leadership

RELIANCE Clinical Centers

KPNW Mularski	**UC Davis** Avdalovic	**MUSC** Strange	**BSW – North** Millard	**Hopkins** Putcha	**Northwestern** Kalhan	**OSU** Diaz	**U of Iowa** Comellas	**Mt Sinai** Braman	**Baystate Health** Pinto-Plata	**UAB** Bhatt
Denver Hospital Hanley		**Duke** Mathews	**Ochsner NO** Seoane	**UPMC** Sciurba	**NorthShore** Bellam	**U of Michigan** Han	**MCW** Bonne		**Case Western** Folz	**U of Arizona** Gerald
		UNC Drummond		**Temple** Criner	**UIC/JBVA** Krishnan/Brillante				**Cleveland Clinic** Hatipoglu	**U of Missouri** Salzman
									Henry Ford Ouellette	**U of Vermont** Dixon
									Providence Lambert	**U of Kansas** Castro

05.2020

1.4. Eligibility Criteria

The eligibility criteria are intended to recruit a diverse group of patients with COPD for whom the 2015 ACCP/CTS and 2017 ERS/ATS guidelines recommend long-term azithromycin or roflumilast as treatment intensification options. Eligibility criteria are intended to select individuals with COPD who can be treated with either medication in clinical practice, with exclusions principally for safety as specified in the FDA Prescribing Information for azithromycin and roflumilast.[40,41] In keeping with the principles of a pragmatic trial, the eligibility criteria will not require assessments outside of standard clinical practice to determine eligibility for the RELIANCE study.[42,43]

Inclusion criteria

- Patient and treating clinician considering treatment intensification with roflumilast or azithromycin to reduce the risk of COPD exacerbations;
- Age ≥ 40 years;
- Current or past smoker of at least 10 pack-years;
- Diagnosis by treating clinician of severe COPD and associated chronic bronchitis;
- Hospitalized with a diagnosis of COPD exacerbation in the past 12 mos.;
- Current medications include inhaled LAMA, LABA/LAMA, or ICS/LABA;
- English- or Spanish-speaking;
- Willing and able to provide a contact telephone number.

Exclusion criteria (any of the criteria below)

- Unable or declines to provide informed consent;
- Declines to provide social security number (SSN), health insurance claims number, or Tax Payer ID Number (as applicable);
- History of intolerance to azithromycin or roflumilast that the patient or patient's treating clinician considers sufficiently serious to avoid either treatment option;
- Current treatment with long–term (more than 30 days) roflumilast or azithromycin (previous treatment with 1 or more doses of azithromycin or roflumilast is **not** an exclusion criterion, as long as the patient and clinician are seeking treatment intensification options and would be willing to use azithromycin or roflumilast, as per randomized treatment assignment.);
- Known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic;
- History of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin;
- Moderate to severe liver impairment (Child-Pugh B or C);
- Current pregnancy;
- Any other clinician-determined exclusion as per their clinical practice.

  The clinicians will be provided the FDA-approved prescribing information for roflumilast and azithromycin. The prescribing information includes a list of warnings and precautions that identifies the potential for adverse effects and is intended to support clinical decision-making that takes into account the risks and benefits of roflumilast and azithromycin for each patient. More information about the warnings and precautions are presented in Section 1.5.

1.5. Warnings and Precautions

The list below is reproduced from the FDA's highlights of prescribing information. Additional details are presented elsewhere in the prescribing information document.

For azithromycin (version 4/2019)

- Serious (including fatal) allergic and skin reactions: Discontinue azithromycin if reaction occurs.
- Hepatotoxicity: Severe, and sometimes fatal, hepatotoxicity has been reported. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.
- Prolongation of QT interval and cases of torsades de pointes have been reported. This risk, which can be fatal, should be considered in patients with certain cardiovascular disorders including known QT prolongation or history of torsades de pointes, those with proarrhythmic conditions, and with currently taking other drugs that prolong the QT interval.
- Clostridium difficile-associated diarrhea: Evaluate patients if diarrhea occurs.
- Azithromycin may exacerbate muscle weakness in persons with myasthenia gravis.

For roflumilast (version 1/2018)

- Acute bronchospasm: do not use for the relief of acute bronchospasm.
- Psychiatric events including suicidality: advise patients, their caregivers, and families to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Carefully weigh the risks and benefits of treatment with roflumilast in patients with a history of depression and/or suicidal thoughts or behavior.
- Weight loss: monitor weight regularly. If unexplained or clinically significant weight loss occurs, evaluate weight loss and consider discontinuation of roflumilast.
- Drug interactions: use with strong cytochrome P450 enzyme inducers (e.g., rifampicin, phenobarbital, carbamazepine, phenytoin) is not recommended.

Additional notes about exclusion criteria in clinical trials of azithromycin: The exclusion criteria presented in the methods section in three trials evaluating the efficacy of azithromycin are provided here. More detailed information can be found in the published manuscripts, including supplementary materials and appendices that are published with the manuscript. As noted above, while exclusions for RELIANCE are principally for safety as specified in the FDA prescribing information for azithromycin and roflumilast, previous trials, such as the BACE study[69] included some eligibility criteria for scientific purposes in addition to safety precautions.

- MACRO study[37]: asthma, a resting heart rate greater than 100 beats per minute, a prolonged corrected QT (QTc) interval >450 msec, the use of medications that prolong the QTc interval or are associated with torsades de pointes (with the exception of amiodarone), and hearing impairment documented by audiometric testing.

- COLUMBUS study[27]: patients with a history of other clinical significant respiratory diseases (e.g., asthma, cystic fibrosis); presence of bronchiectasis, as assessed by CT scan; maintenance antibiotic treatment; use of more than 10 mg prednisolone a day; allergy to macrolides; pregnancy or lactation in women; liver disease (alanine transaminase or aspartate transaminase concentrations that were two or more times the upper limit of normal); malignant disease of any kind for which the patient received treatment or was being monitored as part of follow-up after treatment; heart failure; and the use of drugs that could adversely interact with macrolides and for which therapeutic monitoring could not be undertaken.

- BACE study[69]: patients with contraindications to azithromycin, respiratory insufficiency requiring mechanical or noninvasive ventilation at the time of randomization, chronic systemic corticosteroid use (>4mg methylprednisolone/day for ≥2 months) and the use of macrolide antibiotics during ≥2 weeks preceding inclusion, presentation of lobar pneumonia.

Additional notes about exclusion criteria in clinical trials of roflumilast: The exclusion criteria presented in the methods section in examples of landmark trials evaluating the efficacy of roflumilast are provided here:

- M2-127 and M2-128 studies[44]: No exclusion criteria are presented in the main report (readers are referred to the web appendix).
- REACT study[29]: COPD exacerbation that was ongoing during the baseline period, or had a diagnosis of asthma or other major lung disease.
- RE2SPOND study[68]: Within the 4 weeks prior to enrollment, patients had a moderate or severe COPD exacerbation and/or COPD exacerbation treated with antibiotics or systemic corticosteroids or a lower respiratory tract infection.

2. Recruitment

We estimate 100 subjects per site will be enrolled over the 30-month enrollment period; this number represents a mean estimate across sites and not site-specific recruitment targets. The overall enrollment goal across all sites is 3,200 participants over a 30-month period. Multiple, simultaneous recruitment strategies will be used. We will work with Clinical Leads to optimize recruitment strategies for individual sites and patient populations. Site Coordinators will confirm that each eligibility criterion is met prior to randomization. The study physician will confirm the patient is a candidate for treatment intensification with azithromycin or roflumilast as part of the eligibility review process. In cases where the study physician is not the patient's primary physician for COPD care, the study team will confirm the patient is a candidate for treatment intensification with the patient's primary physician for COPD care.

Pathways to enrollment will include site-specific approaches that rely on queries to EHR, recruitment from usual clinical activities, registries, or cohort studies. Another pathway will be enrollment of patients hospitalized for a COPD exacerbation in the hospital or just after hospital discharge, potentially as a component of a re-hospitalization reduction program. Hospital readmission programs align well with the objectives of RELIANCE since prevention of re-hospitalization is an important objective for COPD patients, their families, care-providers and payers.[45] At the clinician's discretion, they may enroll patients in the hospital or after hospital discharge who meet study eligibility criteria and are candidates for treatment intensification as recommended by guidelines and meet all study eligibility criteria, in the hospital or after discharge.

We will also utilize queries of EHR records to identify patients hospitalized for COPD in the past year who may be eligible for RELIANCE. The fundamental definition for the COPD phenotype that will be used to query EHR and other databases is described below. Sites will use query results and other sources as well as outreach efforts, e.g., mailings or telephone calls to recruit the patients during scheduled visits. All recruitment materials will be submitted for IRB review prior to use. Prior to contacting the subjects, the research team will reach out to the primary caregiver (defined as the person who provides clinical care for COPD) in person, by phone or e-mail to educate them concerning the study, ascertain agreement with patient's participation, and certify the patient meets eligibility criteria. A waiver of consent and authorization will be requested from the IRB to allow access to the contact information for recruitment; the information will be destroyed after recruitment has ended.

COPD Phenotype is defined as:

- Age 40 years or older, AND
- An ICD-9 discharge diagnosis:
    - Primary diagnosis of COPD COPD (ICD-9 codes: 491.21, 491.22, 491.8, 491.9, 492.8, 493.20, 493.21, 493.22, and 496) OR
    - Primary diagnosis of respiratory failure (ICD-9 codes: 518.81, 518.82, 518.84, 799.1) and a secondary diagnosis of AECOPD (ICD-9 codes: 491.21, 491.22, 493.21, 493.22)

    OR

- An ICD-10 discharge diagnosis:
    - Primary diagnosis of COPD (ICD-10 codes: J41.0, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.9) OR
    - Primary diagnosis of respiratory failure (ICD-9 codes: 518.81, 518.82, 518.84, 799.1) and a secondary diagnosis of AECOPD (ICD-9 codes: 491.21, 491.22, 493.21, 493.22)
    - Secondary diagnosis of AECOPD (ICD-10 codes: J44.0, J44.1)

The COPD PPRN and COPD Foundation's 360Social site will promote awareness of the study among their membership and direct interested patients to RELIANCE sites for enrollment. If accrual is behind schedule, we have the option of increasing the intensity of outreach efforts at existing sites and adding new sites. The RELIANCE study team is prepared to address known barriers to recruitment. These barriers include issues of trust (offset through direct physician engagement rather than strangers), uncertain benefits (both medications have proven track records), disproportionate burden (builds on patient-preferred medication pathway of pills over inhalers and engages routine physician care), and cumbersome reporting procedures (offset by a minimal number of follow-ups and convenience of web portal and call center for data collection of patient-reported outcomes only). All recruitment and outreach materials will be submitted for IRB review prior to use.

2.1. Consent and Randomization

Informed consent and randomization will occur at the point of care using internet-based methods and traditional consent materials supported by treating clinicians and site coordinators. The consent process will adhere to requirements of the governing IRB and state laws. The CC will design and deploy a suite of best practice communication tools for use at enrollment. These tools will include a range of materials, e.g., consent forms, guides for physician-patient conversations and staff instructions, and supporting explanatory materials for patients and their caregivers. Materials will include information about potential adverse effects and out-of-pocket costs. The study tools are designed to work together to support and prepare the physician and staff to efficiently implement the study into routine healthcare environments. Best practice communication tools will help clinical staff organize the conversation with patients and colleagues and set realistic expectations with patients regarding their role and the potential study burden with supporting tools for patients and caregivers. The tools will contain clear instruction for staff and provide background and guidance to help them understand their role and how to facilitate using the study portal for collecting patient data. For patients, tools will include print and online information on COPD management, the RELIANCE trial, and the resources available from the PPRN and COPD Foundation. All patient-facing materials and tools will be submitted for IRB review prior to use.

Consent will be obtained prior to enrollment in the trial. Each patient will then be registered in the RELIANCE Portal by the Site Coordinator. Baseline data will be collected via the Participant Portal or Investigator Portal after the patient signs the consent statement for the trial. Baseline data will include demographic and personal information including social security number and health insurance provider. Eligibility will be confirmed via the Investigator Portal prior to randomization. After eligibility is confirmed, the patient will be randomly assigned to receive a prescription for azithromycin or roflumilast via the Investigator Portal. Once the assignment is released, the clinician, Site Coordinator, and the patient will be unmasked, i.e. will be aware of the treatment assignment. After the treatment assignment has been made, the patient is enrolled in the trial and will be followed regardless of treatment adherence. The clinician will prescribe either azithromycin (250 mg/day daily, 500 mg/day three times per week, or an alternate regimen) or roflumilast (250 mcg/day x 4 weeks, then 500 mcg/day or an alternate regimen) according to the random treatment assignment. Clinicians may tailor the treatment regimen to fit the patient's personal characteristics. Tailoring may include starting with a lower dose or a different dosing schedule. Once the prescription has been dispensed, the Site Coordinator will enter the prescription as written by the clinician into the Investigator Portal.

Remote enrollment

In order to better align with clinical practices, Clinical Centers are permitted to conduct consent and enrollment procedures remotely. For potential participants who meet eligibility criteria, and for whom an in-person or remote (i.e., telemedicine) clinical visit occurred, the clinician will facilitate a handoff to the study team who will reach out to initiate the consent process. Having the option to provide informed consent remotely minimizes risks to potential participants who have telemedicine visits and would be coming to the clinic solely to consent (i.e., patients who come to medical centers for in-person appointments often use public transport, and wait in common waiting areas, increasing their exposure risk to respiratory diseases including the seasonal flu, common cold, and coronaviruses). Please see Appendix 6.2 *Remote Enrollment Pathway* for additional operational details.

2.2. Data Collection

The schedule for data collection schedule is outlined in Table 3. There are no planned in-person study visits outside of normal clinical practice, as was done in another large, pragmatic, comparative effectiveness trial in respiratory disease.[46] Minimal baseline data required for enrollment and randomization will be keyed into the Investigator Portal by Site Coordinators. Follow-up data for the primary outcome (all-cause hospitalization or death) will be collected via the Participant Portal, the RELIANCE Call Center, and ad hoc reporting by Site Coordinators on the Investigator Portal. Medicare administrative/claims data will be collected via a collaboration with the FDA Sentinel Program. Those data along with vital status data from the NDI will be used to assess the completeness of outcome ascertainment.

Data will be collected directly from the patients via the Participant Portal or the Call Center, if the patients are unable or unwilling to access the Participant Portal. All calls completed by Call Center personnel will be recorded for quality assurance and training purposes using HIPAA-compliant telephony software integrated into the Call Center's Voice Over Internet Phone (VOIP) system. The recordings will be retained throughout the project and up to 3 years after final data analysis and publication is complete. The recordings will be stored locally on a HIPAA-compliant University of Illinois Hospital secure server. The server is maintained by UIH Information Systems Management and adheres to all UIH compliance measures. The recordings will be stored in a private folder accessible only to the PI (Jerry Krishnan) and designated project staff who have a specific project-related need to access. Documentation of security measures used by the telephony software management company has been submitted to the IRB for reference. The recording of these calls for operational purposes is noted in the informed consent form participants will review and sign prior to enrolling. Call Center personnel will be able to view a screen with patient contact information housed within the data management system, i.e., call lists that contain patient's names and phone numbers. In general, there is no need to print protected health information (PHI) data at the Call Center. If a printout is required to complete a specific task, those printouts will be stored in a secure location, locked office or locked file, with access limited to study personnel, and will be destroyed once they are no longer needed or within 24 hours, whichever comes first.

Patients will be queried 1 week after randomization to record if they filled the prescription for the study treatment, and if so, the out-of-pocket cost. Patients will be queried at 3 months and 6 months after randomization during the first year of participation, and then every 6 months until a

primary outcome (hospitalization or death) is observed.

Site Coordinators will be asked to assist in locating patients who are lost to follow-up and in ascertaining or verifying hospitalizations and death. Site Coordinators will also submit data on patient outcomes, such as adverse events, all-cause hospitalization, changes to study medications, medical diagnoses, or other relevant information, and microbiology cultures in which macrolide-resistant organisms were identified in sputum from the EHR via ad hoc and end-of-study reports on the Investigator Portal (Table 3). We will ascertain vital status on all patients via the NDI after follow-up is completed.

In addition, we will work with the FDA Sentinel Operations Center (SOC) to obtain Medicare data regarding the claims for study medications and healthcare utilization for patients enrolled in Medicare.

Table 3: Data collection schedule					
Data item	**Sources (and estimated time for patients)**	**Baseline (BL)**	**1 week**	**3 and 6 mos after randomization, then every 6 mos until primary outcome is recorded or 36 months after start of enrollment, whichever occurs first.**	**End of study**
Informed consent	Investigator Portal	X			
Demographics	Investigator Portal (3 min)	X			
Smoking status	Investigator Portal	X			
	Participant Portal/Call Center (2 min)			X	
PROMIS questionnaires (physical function, sleep disturbance, fatigue, anxiety, depression)	Investigator Portal	X			
	Participant Portal/Call Center (2 min)		X (if not done at BL)	X	
Height, weight	Investigator Portal	X			
	Participant Portal/Call Center (2 min)			X	
Study treatment (adherence, treatment discontinuation, cross-over to alternate medication)	Investigator Portal	X			
	Participant Portal/Call Center (3 min)		X	X (and ad hoc)	
	Claims databases				X
Out-of-pocket costs	Participant Portal/Call Center (2 min)		X	X	
Healthcare utilization	Investigator Portal	X			X
	Participant Portal/Call Center (5 min)		X	X (and ad hoc)	
	Claims databases				X
	National Death Index				X
Adverse events (hearing decrement, diarrhea, nausea, suicidal ideation)	Participant Portal/Call Center (3 min)		X	X (and ad hoc)	
	Claims databases				X
Adverse event (microbiology cultures of macrolide resistant organisms in sputum)	Investigator Portal				X

2.3. Linkage with Medicare Data

Linkage of the RELIANCE trial to Medicare claims data for a secondary analysis will provide additional information regarding use of the study drugs, the primary outcomes and select secondary outcomes that can be assessed with Medicare data, and will also provide an opportunity to test distributed regression methods with vertically partitioned data. In collaboration with the FDA Office of Medical Policy, the Sentinel SOC will work with the Department of Population Health Sciences (DPHS) at the Duke University to link patients enrolled in the RELIANCE trial to Medicare data. The SOC is located at Harvard Pilgrim Health Care Institute and collaborates with the DPHS on specific Medicare linkage activities. The general process for linkage is described below. A more comprehensive Appendix detailing measures to minimize breaches and protect identifiable data, plans for final disposition of identifiers, and movement of direct identifiers will be submitted to the IRB for review prior to the initiation of data transfer.

The general process for Medicare data linkage will be as follows: The DCC will provide SOC a file with direct patient identifiers (i.e., SSN ± Health Insurance Claims Number (HIC/MBI), date of birth, sex) required for Medicare data linkage. SOC will process these data according to CMS requirements, and will submit this information to CMS via encrypted physical media, or other methods required by CMS (or their designee). CMS then will link trial participants to Medicare enrollment file, create a crosswalk file, and extract the requested Medicare data. CMS will then send the extracted Medicare data files to SOC and the DCC. Finally, the DCC will provide SOC with data from the RELIANCE trial required for the distributed regression methods evaluation. We anticipate using enrollment, inpatient claims, and annual Part D medication dispensing data for RELIANCE trial participants enrolled in Medicare to assess the completeness of ascertainment of the primary outcomes (death or all-cause hospitalization) and evaluate adherence to the assigned treatment. In addition, secondary analyses will evaluate other aspects of healthcare utilization, e.g., urgent care and ED visits.

We will make this data linkage twice. The first linkage will be aligned, where possible, with the trial's interim analysis. The second will occur after the trial is completed, in order to receive Medicare data that covers all or most of the trial follow-up period, given the CMS data release schedule. The interim data request is anticipated to occur in 2022 and to include Annual 2019 and 2020 inpatient claims files, enrollment/death files, and Part D prescription drug dispensing files. The final data request is anticipated to occur in 2023 and to include Annual 2021 inpatient claims files, enrollment/death files, and Part D prescription drug dispensing files, as well as Quarterly

2022 (through Q3/2022) inpatient claims files and enrollment/death files. These plans are subject to change, given any changes in Medicare data availability and the trial recruitment timeline. While the Medicare Quarterly files are not considered final and complete by CMS, ordering these files is the only option for obtaining Medicare data covering the final calendar year of the trial.

2.4. Patient Retention Strategies

Patient retention is critical to the success of any trial and we have incorporated several strategies to enhance retention. First, patient burden is minimized by not requiring in-person follow-up visits and collecting information via brief questionnaires (about 15 minutes) administered online (or by the call center) at 3 and 6 months during first year of enrollment, thereafter, every 6 months until the patient achieves a primary outcome. Second, patients often express pride in participating in an important national study that will potentially help others with similar conditions. In this regard, we will give participants regular newsletters and subscriptions to the COPD Foundation's COPD Digest, which will chronicle the study rationale and progress. The COPD Foundation will not have access to participant identifiers. Participants will only receive these materials if they elect to subscribe to the newsletter. Third, participants endorse that they want to be treated with respect as people rather than "guinea pigs." This involves every step of patient engagement with the study, reinforcing the importance of the participants to the overall study goals and general health of patients with COPD, as well as participation of patients in COPD Foundation social networks that support efforts to improve COPD outcomes.

3. Statistical Plan

3.1. Sample Size

RELIANCE is a randomized, pragmatic, comparative effectiveness trial designed to evaluate whether azithromycin is non-inferior to roflumilast in high-risk patients with COPD for prevention of hospitalizations or death. Our choice of a non-inferiority margin of 1.2 was based upon a recently completed clinical trial in COPD, as well as opinions solicited from clinicians and patients[48,49]. In a survey of 48 clinicians, the minimum clinically important difference was identified to be 1.2 or higher by 75% of the survey participants and the margin of 1.2 was the most commonly selected (33%). An online survey of 50 patients conducted by the COPD PPRN identified a range of different effect sizes, which seemed to vary based on the history of previous COPD exacerbations, and hospitalizations, and tolerance for adverse effects. A margin of 1.2 is within the range of interest expressed by patients. The planned recruitment period is 30 months with an additional 6 months of follow-up. A sample size of 3,200 provides 92% power with a 1-sided type I error of 0.025 to establish non-inferiority based upon a log-rank test with a margin of HR = 1.2 (azithromycin: roflumilast) assuming: (1) the true HR = 1, (2) the cumulative percent with an event at 1 year is 30%, and (3) a 5% loss to follow-up per year (14.3% cumulatively). Post-hoc analyses of trials suggest that while roflumilast appears to benefit both past and current smokers, the benefits of chronic azithromycin may be limited to past smokers.[34,50] Accordingly, we will monitor treatment outcomes stratified by current vs. former smoking status and present these results to the DSMB to evaluate the relative safety/efficacy of the two treatments. If the lower bound of the 99% CI for azithromycin exceeds 1.5 at any interim analysis, we will recommend to the SC that the current smoking strata be terminated. The sample size of 3,200 participants provides 89% power to detect a heterogeneous effect based upon smoking status (HR = 1 for roflumilast vs HR = 1.538 for azithromycin for current vs former smokers) assuming a reference cumulative incidence of 30% at one year for current smokers in both treatment groups, equal recruitment to all four subgroups, 5% loss to follow-up per year (14.3% cumulatively) and a two-sided type I error rate. These analyses were computed using PASS software and SWOG Statistical tools, respectively.[51,52]

3.2. Analysis Plan

RELIANCE employs a randomized open-label parallel group trial design to evaluate whether azithromycin is non-inferior to roflumilast in high-risk patients with COPD for prevention of hospitalizations or death.

RELIANCE is designed to compare the effectiveness as opposed to pharmacologic efficacy of roflumilast and azithromycin. We will collect data about patient and clinician practices in the study, including the initial and subsequent dosing regimens, adherence, treatment discontinuations, and cross-overs. These practices plus the pharmacologic efficacy of roflumilast and azithromycin in individual patients will contribute to the observed comparative effectiveness of the two treatment options. The primary analysis will therefore be "as randomized" (commonly referred to as intention-to-treat, ITT), secondary sensitive analyses will include per protocol analyses, i.e., the subgroup of patients who adhere to their assigned treatment.

There is considerable debate about the optimal approach to analysis of non-inferiority trials, as randomized or per protocol. The major concern about as randomized analyses for non-inferiority hypotheses is that if a significant number of patients do not adhere to their assigned treatment, the test treatments may falsely appear to have similar effects thereby introducing a bias favoring a conclusion of non-inferiority. Per protocol analyses, which limits the analyses to the subgroup of patients who adhere to their assigned treatment, are recommended for testing non-inferiority hypotheses primarily to avoid this potential bias. However, per protocol analyses of non-inferiority trials have all the same flaws as they do in superiority trials.[53] For example, if patients discontinue study assigned treatments because of side effects, the potential decreased effectiveness of the treatment is correctly attributed to the assigned treatment in an as randomized analysis but would not be in a per protocol analysis. The preferred approach is to maintain as randomized ITT as the primary analysis and to institute performance measures that ensure the integrity of the trial and provide essential information for interpretation of the results.[54] Per protocol analysis will be a key secondary analysis and will be compared with the as randomized analysis. Data on protocol performance such as treatment adherence, losses to follow-up and missing data will be used to help understand and interpret differences, if any, in the results of the two methods.

The primary outcome is the time to first all-cause hospitalization or death. Individuals without an event will be censored at the date of last contact. A Cox proportional hazards model will be used to assess whether azithromycin is non-inferior to roflumilast. Non-inferiority will be achieved if the upper boundary of the confidence interval for the hazard ratio (azithromycin/roflumilast) is

less than 1.2, the non-inferiority margin. The level of the confidence interval will be adjusted from 95% to account for type I error spending during interim efficacy analyses and will match the type I error used in the final analysis. If we achieve non-inferiority, then an additional test for superiority will be performed. The primary analysis will adjust for the stratification variables smoking status (current vs former) through the inclusion of a fixed effect and clinic with a random effect, respectively. A key secondary hypothesis is that the treatment effect will differ for current and former smokers. A test of interaction will be used to assess the heterogeneity of treatment effects (HTE) based upon smoking status (current vs former). Secondary analyses will be performed both adjusting for and investigating the HTE for key baseline characteristics including but not limited 3 pre-specified comparisons: a history of asthma (yes vs no), gender (male vs female) and BMI (obese vs not obese).

Analysis of secondary outcomes by treatment group will employ negative binomial, logistic, linear and Cox proportional hazards models for event rates, binary outcomes, continuous outcomes, and time to event outcomes, respectively. Mixed effects models will be used to model outcomes with repeated measurements over time. Both unadjusted and adjusting models including the stratification variables (clinic and smoking status) as well as clinically important risk factors (e.g. history of asthma, gender, BMI, medication use) will be explored. Summary statistics, model estimates with confidence intervals and p-values will be used to present the findings. A large number of analyses, including HTEs, are planned and caution is necessary in interpreting the results especially since it is generally not possible to pre-specify all potential analyses. The number of secondary analyses explored will be clearly specified and the expected number of false positives will be calculated and included in the presentation of our results. Several methods of adjusting p-values for multiple comparisons exist; however, no clear consensus as to the most appropriate method is available. As recommended by Wang and Lagados, reporting will focus on point estimates and confidence intervals as well as p-values and reports will be considered hypothesis generating.[44]

Performance monitoring is a key component of clinical trials. Our performance monitoring will include site-specific and overall metrics on patient screening, enrollments, retention, missing data, and adherence to treatment. These metrics will be used to assess the internal validity of the trial. External validity will be assessed by evaluation of the characteristics of the screened and enrolled population, the ratio of enrolled to screened participants and comparison of these characteristics to the overall population with COPD. We will rely on published literature as well as CMS data to evaluate the characteristic of US patients with COPD. We will also obtain data from the Master Beneficiary Summary File (via our collaboration with FDA Sentinel).

3.3. Compliance

Compliance will be based upon patient-reported usage. The degree of compliance is an important factor for interpreting the results of the ITT analysis as well as serving the basis for per protocol analyses. However, as noted by Wittes, analyses relying on post-randomization variables are likely to be biased and/or require complex mathematical models with numerous assumptions.[55] Individuals will be classified according to a number of different methods (e.g. any compliance [at least one usage], minimum compliance [above a certain threshold]) for sensitivity analyses. A variety of causal inference techniques, including inverse probability weighting methods similar to those described by Murray and Hernan, will be used to assess the impact of adherence.[56] In addition, prescription data will be available for a subset of patients from Medicare claims files via the collaboration with the FDA Sentinel Program. These data will be compared with the self-reported data to help guide the planned compliance analyses.

3.4. Missing Data

As noted in the IOM Guidelines, prevention is the most important method for handling missing data.[57] The recommended strategies include careful consideration of potential barriers to data collection during the design phase of the trial, including patient and outcome selection. For example, an advantage to our choice of the primary outcome, all-cause hospitalization or death, is that it can be measured and confirmed from numerous sources. The primary source of outcome data will be from patients. In addition, we have planned a number of strategies to limit missing data during the execution of the trial. As noted above, we will rely on several sources of data to ascertain the primary outcome measures of all-cause hospitalization and mortality including patient reports supplemented by administrative data from CMS and the NDI and follow-up data collected by Site Coordinators. For patient-reported outcomes, we will employ several strategies to prevent missing data, including collection of multiple contacts, verification of phone numbers, email addresses, and secondary contacts including relatives or neighbors, and healthcare providers. Patients will be reminded about outstanding questionnaires via emails and texts backed-up with phone calls. Clinical centers will review the EHR periodically and administrative sources will also be used to identify unreported events. If we are unable to contact the patient via those measures, Site Coordinators will be asked to “find” those patients and collect the missing data. We will also employ real-time data performance reporting so that we can monitor trends in missing data to identify problems and develop interventions. Data on treatment adherence and outcomes will be extracted from CMS administrative database on the subset of patients enrolled in Medicare via a collaboration with the FDA Sentinel Program. We will also use the NDI to identify unreported

deaths in the entire study group.

All patients will be accounted for in analyses. For the primary outcome (hospitalization or death), a Cox proportional hazards model will be used. Individuals who are lost to follow-up are censored at the time of the last known contact and so all individuals with follow-up may be included in the analyses. Data collected up until the time of withdrawal will be retained from those participants who do not continue on in the study. Issues with missing data arise if the censoring mechanism is related to the outcome of interest. The range of potential influence will be established by imputing the 'best' and 'worst' case scenarios. Analytic methods will be used to assess the censoring patterns. Based upon these finding, sensitivity analyses using multiple imputation, inverse probability weighting, or a pattern mixture approach will be used.[46,47] For non-time to event outcomes, the primary analysis will be based upon mixed effects models (for replicate measurements over time) or multiple imputation (for single measurements), both of which are robust to data that is missing at random. 'Best' and 'worst' case analyses similar to those used for time-to-event outcomes will also be used to gauge the potential effect of missing data.

Reasons for missing data will be assessed for all data sources. For data collected from clinical centers, the reason for missing data will be collected directly from the clinic, e.g., data not assessed, patient refused or no follow-up for patient at the clinical center. The Call Center will record attempts to remind and collect data for patient-reported outcomes. These will include patient refusal, inability to contact patient, or death. In comparative effectiveness trials where the hypothesis is non-inferiority, treatment cross-overs, treatment cessation, lack of adherence, and loss to follow-up tend to support the inference of non-inferiority between treatment groups. To some extent, these deviations from protocol are the rationale for conducting a "real-world" pragmatic trial. Interpretation of these factors can be assisted by comparison of as randomized and per protocol analyses as well as sensitivity analyses of specified subgroups. However, failure to ascertain the primary outcome, particularly if there is differential data loss between treatment groups is a serious threat to the validity of the trial and there is no analytic technique that can completely overcome this. In this trial, we are proposing to use multiple data streams including EHRs, directly from patients and providers, and from CMS administrative datasets and NDI administrative datasets for the primary outcome, we should be able to have virtually complete ascertainment of hospitalizations and deaths for this largely Medicare population.

3.5. Interim Analysis

A single, formal, interim efficacy analysis will be performed once 50% of the information has been collected (i.e., 684 of the expected 1368 event of hospitalization or death have been observed). The trial will be stopped early only if one of the two treatments is demonstrated to be superior, i.e. it will not stop if the non-inferiority criteria are met. Based upon an O'Brien-Flemming type boundary, the type I error rate would be 0.00305 for the interim analysis and 0.04695 at the final analysis to maintain a global 0.05 error rate over the course of the trial for the superiority comparison.

4. Human Subjects

4.1. Eligibility Criteria

The RELIANCE study is a randomized, multi-center pragmatic clinical trial, comparing the effectiveness of roflumilast vs. azithromycin in up to 3,200 patients with COPD at high risk of exacerbations. The study follow-up will be a minimum of 6 months and maximum of 36 months. Patients will receive a call at week 1, and will answer follow-up questionnaires at month 3 and 6, and thereafter, every 6 months until the patient achieves a primary outcome or the study ends. The eligibility criteria are intended to recruit a representative sample of "patients with severe COPD associated with chronic bronchitis and a history of exacerbations," the FDA-approved indication for roflumilast in the U.S. and consistent with criteria established by the U.S. VA Pharmacy Benefits Management Services, and Medicare Part D benefits.[58,59]

Eligibility criteria will be assessed based on standard clinical procedures with no requirements for specialized assessments, see section 1.4 for individual criteria. Exclusions are principally for safety, based on FDA or 2015 ACCP/CTS guideline or 2017 ERS/ATS guideline recommendations. During informed consent process, participants will be made aware that, should adverse effects occur, discontinuation or switching treatments are options to be discussed with the treating physician, and that they may drop out of the study without disrupting their receipt of routine healthcare. Clinical leads will be asked to exercise clinical judgment in the monitoring and reporting of adverse events to the IRB, FDA, and study through the RELIANCE Investigator. Neither the patient nor clinician will be masked to study treatment.

4.2. Data Sources

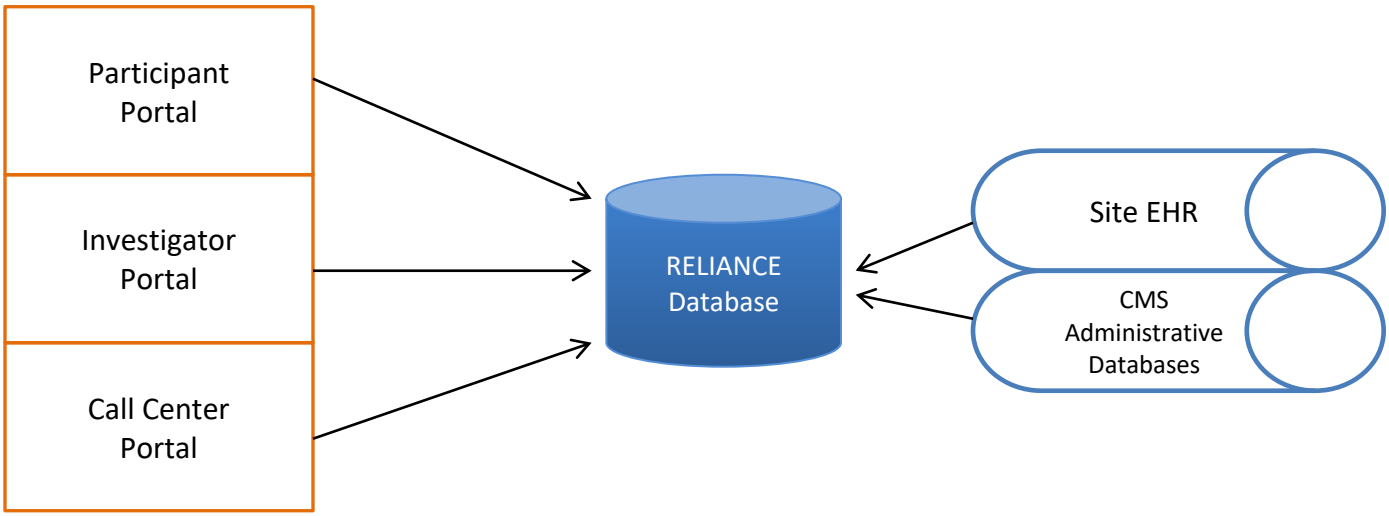
The primary sources of data for RELIANCE are regular interviews of enrolled patients, passive follow-up from EHRs and administrative databases, and ad hoc reporting from sites. Patient-reported outcomes will be collected online via the Participant Portal or, if the patient prefers, via telephone follow-up from the Call Center in English or Spanish, as preferred by the participant. Data on eligibility and occurrence of events will also be reported on the Investigator Portal. Deaths are often not well represented in EHRs, especially out-of-hospital deaths, so the NDI will be queried to determine vital status of all enrolled patients at the end of the trial. Data will also be collected on the subset of patients enrolled in Medicare from CMS administrative databases via collaboration with FDA Sentinel Program. When participants do not respond to regular attempts at contact and no death has been reported, a series of steps will be done to collect data on vital

status including search and outreach by the Site Coordinator.

Data will be collected from various sources as outlined throughout the protocol (Participant Portal, Call Center Portal, Investigator Portal, EHR, and CMS administrative databases). The DCC will coordinate integration of these data throughout the study into the RELIANCE Database, which is housed at the DCC. The DCC will have real-time access to data keyed on the Investigator, Patient, and Call Center Portals. Follow-up data will be available to the DCC in real time and will be downloaded weekly. There will be intensive reviews of the Patient, Call Center, and Investigator Portal data on a weekly basis to review for missing data requiring follow-up from the patient, Call Center agent, or Investigator/Coordinator. The full database will be downloaded weekly to run reports on recruitment, retention, and missing data. These reports will be reviewed each week at the DCC and every other week during Executive Committee webinar meetings. Data queries will then be issued to sites and/or the Call Center for completion.

Please see Table 3, *Data Collection Schedule* for additional information on data collected from each source, and section 2.3. *Linkage with Medicare Data* for an overview of data transmission between CMS Administrative Databases and the RELIANCE databases.

Figure 3: RELIANCE Data Sources Overview



4.3. Potential Risks

During this study, participants will continue to receive their usual care for COPD as per their treating physician. There are no additional evaluation procedures that patients will undergo to participate in the study. Patients will be asked to provide some information on their health history and current health status that is routinely collected in the process of medical care of patients with COPD. There are no significant physical risks from these procedures. As with all medical information, there is always the risk of psychological distress if PHI is not held confidential within the wishes of the participant. In order to minimize this risk, EHRs are held in HIPAA-2 compliant password-protected databases, and written information is stored in locked files or file-rooms when not attended by study personnel. Medical information is provided to treating sources consistent with HIPAA guidelines. If any medical illness requiring treatment is discovered during the collection of data for the course of this study protocol, individuals will be referred to their primary care providers for further evaluation and treatment.

Potential risks associated with this study are primarily those associated with the drugs under study, both of which are routinely used in clinical practice for this indication. As detailed in section 1.1, in completed trials of azithromycin for prevention of COPD exacerbations the most common reason for premature treatment discontinuation in the MACRO trial was hearing decrement, noted on audiograms performed by study personnel (azithromycin vs. placebo: 25 vs. 20% had hearing decrements, p=0.01).[37] Interestingly, hearing returned to baseline levels in a subsequent audiogram in roughly 1/3 of patients regardless of which group the patient was assigned to, azithromycin or placebo group, or if the study treatment was discontinued. Though no statistical test was reported and audiometry tests were not performed, self-reported hearing reduction in the BACE trial, was greater in the placebo group (4 vs 1% azithromycin).[69] No hearing-related adverse events were noted in the COLUMBUS trial, although audiometry tests were not part of the study protocol. Premature treatment discontinuation, noted in the MACRO trial due to adverse effects, was more common in the azithromycin group (33 vs. 28% placebo), however in the BACE trial it was more common in the placebo group (8 vs. 5% azithromycin).[27,37,69] Macrolide resistance was also more common in the azithromycin group (81 vs. 41% placebo, p <.0001).[69] Other reasons for treatment discontinuation were less common and not significantly different between the azithromycin and placebo groups. These included: gastrointestinal, 1-2%; QTc prolongation (1 vs. 0.7% placebo), tinnitus, hearing decrements, allergic reaction, abnormal laboratory test, each <1%.[69] In the BACE trial, there was no significant differences for positive sputum cultures with newly acquired pathogens, nor for

macrolide-resistant bacteria during follow-up.[37]

Macrolides (including azithromycin) are known to cause ventricular arrhythmias that could be fatal, but the incidence for long-term azithromycin use to prevent COPD exacerbations is unknown. On the basis of results published in an observational study using claims data, the FDA re-iterated the importance of carefully reviewing patient-level risk factors (history of prolonged QT interval, comorbid condition, or arrhythmogenic potential of other co-therapies) when using azithromycin. [60,61] The incidence of arrhythmias with macrolides in the absence of additional risk factors is estimated to be very low, perhaps <1 in 100,000 individuals.

In a Cochrane review of placebo-controlled efficacy trials of roflumilast, premature treatment discontinuation due to adverse effects was more common with roflumilast than with placebo (15 vs. 9%, p<0.05; 9,511 patients).[28] The most common adverse effects that were also more common in the roflumilast group included diarrhea (10 vs. 3%, p<0.05), nausea (5 vs. 1%, p<0.05); weight loss (8 vs. 2%, p<0.05), psychiatric disorders (7 vs. 4%, p<0.05; includes anxiety, depression); and sleep disturbances/insomnia (3 vs. 1%, p<0.05). Mortality was low in the trials of roflumilast, with no significant difference between groups (roflumilast vs. placebo: 2 vs. 2%). A similar increase in adverse effect-associated treatment discontinuation was noted in comparative trials of up to 12 months in the REACT, RESPOND[2] and M2-124 and M2-12533 studies (12 vs. 8% placebo). The most common adverse effects that were also more common in the roflumilast group included diarrhea (17 vs. 6% placebo), weight loss (9 vs. 3% placebo). The OPTIMIZE study found that premature treatment discontinuation can be reduced by initiating treatment with a 4-week course of 250 mcg/day of roflumilast before dose-escalation to 500 mcg/day.

4.4. Data Confidentiality

All participant information will be protected using standard physical and electronic approaches to PHI (e.g., study IDs, locked file cabinets, password protect files, encryption) in compliance with HIPAA Privacy and security rules. Only authorized study staff will have access to study data and study reports will not contain any identifiable information.

4.5. Data Security

Data will be collected, stored, and transferred in compliance with HIPAA Privacy and security rules. All portions of the Data Management System (DMS) will be password-protected using user-specific personal identification numbers (PINs) and strong passwords. Once the user is logged in, all subsequent activities are stamped with the user's PIN and date-time stamp. Data will be encrypted while in-transit using secure sockets layer (SSL) and 128 or 256-bit public key encryption. Data will also be encrypted for storage on dedicated servers maintained in guarded, key lock-entry facilities with appropriate fire suppression and redundant power.

There will be four primary sources of data: (1) Investigators/Coordinators at sites will key data into a dedicated data system; (2) Call Center staff will interview patients by telephone and key data into a dedicated data system; (3) Participants may opt to enter their follow-up data into a dedicated data system; and (4) FDA Sentinel Program will provide data on hospitalizations and vital status from Medicare claims files.

The DMS security system permits differing levels of system access controlled by the database administration such that only certified data entry personnel may access the distributed data entry system and access patient identifiers, including birthdate, SSN and HIC/MBI, the number assigned to individuals by Medicare. Access will be provided to limited to personnel. For example, Call Center personnel will have access to a patient's name and contact information but will not be able to access SSN or HIC.

Only the DCC and the database developers will have access to all patient data. As stated above, UIC Call Center will have access to patient identifiers, e.g., name, phone and address, but will not have edit access to Insurance ID or SSN. However, if a patient fails to provide complete information at enrollment (i.e. HIC or SSN), Call Center personnel will be prompted to collect those data. Call Center personnel require access to patient contact information in order to conduct follow-up interviews. Call Center personnel will also have access to facilitate communications with clinical sites regarding adverse events, outcome assessments, or lost-to-follow-up assessments.

4.6. Potential Benefits of the Proposed Research to the Patients and Others

We do not anticipate any direct benefits of participating in the study. The results of the trial will contribute to practice-based evidence needed to inform future clinical decision-making.

4.7. Data Safety Monitoring Plan

The study will be reviewed initially by the IRB at each participating site who will then document their intent to rely on the single IRB of record (CHAIRb at UIC). CHAIRb will be responsible for ongoing review of the trial. Any participating sites who do not cede review to CHAIRb will obtain approval by their local IRB. We will submit continuing reviews annually and adverse event reports to the single IRB and each local IRB per their guidelines.

This study will use an independent DSMB that will include 5 individuals who are not affiliated with any of the participating investigators. Members include two pulmonologists with expertise in COPD, Sonia Buist, MD (Chair) and Donald Tashkin, MD, a statistician with expertise in clinical trials, Andre Rogatko, PhD, and a patient advocate and caregiver, Debra Sellers and Margaret Bates, respectively. The DSMB will convene twice per year during the course of the study. The DSMB will make an affirmative decision at each meeting whether to continue, either according to the existing protocol or with necessary amendments, or terminate the study (e.g. futility, safety, or efficacy based on interim analyses). In general, the DSMB will be provided data grouped by treatment without identified treatment groups (i.e., masked to treatment assignment). If the DSMB requests, for the purpose of competent deliberation, to see the treatment assignments (by group or individual), these will be provided by the RELIANCE DCC biostatistician.

4.8. Inclusion of Women and Minorities

We will not exclude patients on the basis of sex or race/ethnicity. Given the linkage of RELIANCE with sites in a number of geographic locations, we expect our study population to approximate the demographic distribution of COPD among hospitalized individuals in the U.S. (87% White, 7.5% Black, 0.8% Asian, 0.2% American Indian, rest other; 4.5% Hispanic; 56% Women, 44% Men).[62] Because the prevalence of hospitalization or ED visit for COPD in the past 12 months is more common among Blacks and Hispanics than among White (25 vs. 21 vs. 18%), and in women than in men (20 vs. 17%),[4] we will target a higher proportion of these higher risk groups. Thus, we propose 70% White, 15.5% Black, 10% multi-race, 3% Asian, 1% American Indian/Alaskan Native, and 0.5% Hawaiian; 10% Hispanic; 60% women, 40% men. Children and adults under 40 years of age are excluded from the trials because patients are unlikely to develop COPD related to smoking before the age of 40 years.

5. Data Sharing and Dissemination

For the purposes of sharing and disseminating the research data, all direct identifiers and any indirect identifiers that could be used in conjunction with other publicly available information to identify individuals will be removed from the study data. All RELIANCE intervention-participating patients will be assigned a study subject pseudo identifier. Quantitative data will be organized into the structure of a portable file with all data clearly defined. The DDC will be responsible for providing data to other investigators. The DCC will establish a data use agreement prior to distribution of limited or de-identified datasets to DPHS, SOC, or any other entities such as trial sites. The DCC will also enter into a joint DUA with Duke DPHS, SOC, and the DCC with CMS for the Medicare claims data.

We will make the data and associated documentation available to users under a data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes and not to identify any individual participant; (2) evidence of local IRB approval at the users institution; (3) a commitment to securing the data using appropriate methodology and technology; and (4) a commitment to destroying or returning the data after analyses are completed. Should other researchers in the U.S. request our data, we propose to transmit analytic files via a HIPAA-secure website.

Final findings will be disseminated in multiple ways. Manuscripts will be finalized and submitted for publication in peer-reviewed journals. PCORI will have an opportunity to review manuscript prior to submission. In addition to journal articles, dissemination of results will take place through presentations and project reports.

6. Appendix

6.1. Protocol change log

Protocol version 3.1 (14 August 2019) to version 4.0 (08 June 2020)	
Section #/title	**Change**
Multiple	• Administrative changes for consistency (e.g, consistent use of hyphens; use of acronym after initial introduction of entity; use of "Participant Portal" rather than "Patient Portal"); • Correction of grammar/typos.
PICOTS table	• Added inclusion criterion (see *Eligibility Criteria* section below for rationale); • Added "or Taxpayer ID Number" after Social Security Number for consistency with other documents; • Corrected item code of two PROMIS measures for documentation purposes; • Included "telemedicine visit" in Setting to reflect current modes of care delivery.
Figure 1.	• Added 1-week follow-up timepoint for consistency with Table 3 and other documents.
1.3 Organization of RELIANCE	• Updated UIC Communication Center lead from Kim Erwin to Hugh Musick.
1.4 Eligibility Criteria	• Added eligibility criterion, "Willing and able to provide a contact telephone number"; • Included "or Taxpayer ID Number" after SSN for inclusivity. *Rationale: Willingness to provide a telephone number was implied given all follow-up for the study is completed by telephone. This is consistent with messaging in the consent form as well. We are including this criterion for clarity across documents.*
2.1 Consent and Randomization	• Added remote enrollment (this section was included to match the level of detail in other sections, additional detail can be found in the Appendix 6.2). *Rationale: We have been approved for remote enrollment during the COVID-19 precaution period (approved 5/12/20). As the epidemiology of COVID-19 evolves, various sites in different locations across the US may cycle in and out of COVID-19 precautions. We seek approval from CHAIRb to provide sites flexibility based on local conditions consistent with patient care, and to avoid the need to submit frequent requests for modifications to the IRB.*
2.2 Data Collection	• Clarified that we are not collecting the name and address of the participant's pharmacy;

	• Included “medical diagnoses” for consistency with consent form other documents. *Pharmacy information was originally planned when we were planning to collect pharmacy data, but due to budget constraints by the funder, we were not able to include this.*
Table 3.	• Sources and timing of data collection were corrected to align with current data capture. *Based on input from a patient advisor during final form development, the study team decided to shift some data collection from enrollment to the first follow-up call to limit participant burden, as enrollment was originally designed to occur in a clinical setting.*
Appendix	• Added protocol change log; • Added *Remote Enrollment Proposal.*

6.2. Abbreviations

ACCP	American College of Chest Physicians
ATS	American Thoracic Society
BMI	Body mass index
CCC	Clinical Coordinating Center
CDM	Common Data Model
CMS	The Centers for Medicare and Medicaid Services
COPD	Chronic obstructive pulmonary disease
CTS	Canadian Thoracic Society
DCC	Data Coordinating Center
DMS	Data Management System
DSMB	Data Safety Monitoring Board
EC	Executive Committee
EHR	Electronic Health Record
FAQ	Frequently Asked Question
FDA	Food and Drug Administration
F/U	Follow up
HICN	Health Insurance Claim Number
HTE	Heterogeneity of Treatment Effects
ICD	International Classification of Diseases
ICS	Inhaled corticosteroids
IRB	Institutional Review Board
ITT	Intention-to-treat
THE	Heterogeneity of treatment effects
LAMA	Long-acting anti-muscarinic
LABA	Long-acting beta-agonist
PCORI	Patient Centered Outcomes Research Institute
PHI	Protected Health Information

PPRN	Patient Powered Research Network
STAT	Stakeholder Advisory Team
SC	Steering Committee
SOC	Sentinel Operations Center
SSN	Social Security Number
SWOG	Southwest Oncology Group

6.3. Remote Enrollment Pathway

Background

For several months the RELIANCE study team has been considering improving our alignment with current clinical practice by implementing a remote enrollment pathway. We have heard from several of our large network-affiliated sites (e.g., Kaiser Permanente, University of Pittsburgh, University of Kansas Medical Center), that implementing the option of remote enrollment could lead to more participant satisfaction and allow the study team to adhere more closely with current clinical practices.

With our proposal, we are requesting approval from CHAIRb to obtain informed consent from patients via telephone/remote visits (e.g., telehealth). *Written informed consent* would be obtained from each participant enrolled, the initial discussion of the potential need for treatment intensification with either azithromycin or roflumilast would still come from the patient's treating clinician, and all key aspects of the protocol would remain in effect.

We brought this concept to a patient advisor who represents the COPD patient population, having the condition herself, who simply said "this is the future of care, and research enrollment." The patient liked that the remote consent option could make enrollment "far more flexible", and more convenient for patients. She noted this also provides patients who are interested but may not have the time during/after their clinic visit, the opportunity to participate.

We also sought input from one of our sites, Kaiser Permanente, a large health network where 52% of the more than 100 million patient encounters each year are now "virtual visits", and whose research team currently offers remote enrollment for other studies. We asked specifically what feedback they have received from patients. They noted that overwhelmingly, patients appreciate the convenience and the content/substance of the conversation that can be had in the comfort of their home. They also noted that patients seem to appreciate the option of having the consent discussion over the phone. If anyone needs more time to decide, they can follow-up at a later time, just like they would in clinic.

Summary

Potential participants may be seen at one of several clinics affiliated with our large academic medical centers. Having the ability to obtain informed consent via telephone/remotely could provide more patients the opportunity to participate by alleviating the logistical barrier of study staff not being present at all clinics, while simultaneously accommodating patient schedules.

For potential participants who otherwise meet eligibility criteria and for whom a clinician visit that satisfies the study criteria recently occurred, or for whom the clinic visit was conducted remotely in accordance with institutional practices (i.e., telehealth visit), *the clinician will facilitate a handoff to the study team member* who will reach out to initiate the consent process. Having the option to provide informed consent remotely minimizes risks to potential participants who have telemedicine visits and would be coming to the clinic solely to consent. The option for in-person informed consent will be provided to participants.

Process + details

There are three ways in which remote enrollment pathway may be employed:

1. The patient is seen in-person by their clinician in a clinic at which a coordinator is present. After having a conversation with their clinician about the need for treatment intensification for their COPD, the patient expresses interest in the study but does not have time to stay for the consent process and baseline surveys.
2. The patient is seen in-person by their clinician in a clinic affiliated with a RELIANCE clinical center, but a coordinator is not physically present. After having a conversation with their clinician about the need for treatment intensification for their COPD, the patient expresses interest in the study.
3. The patient is seen by their clinician for a telehealth visit as per institutional policies.

In each of the pathways above, the treating clinician will provide the introduction to the study after assessing a patient's clinical requirement for treatment intensification. If the patient expresses interest, and the clinician believes the patient is a good candidate, the treating clinician will provide a warm handoff to the study team. In some cases, depending on clinic flow and current practice, this may be documented in a note within the electronic health record, in other cases, it may be physical introduction, or a telephone call to the research team.

In the remote enrollment pathways, potential participants will be consented by RELIANCE study staff (i.e., research coordinators) located at RELIANCE-affiliated clinical centers remotely/via telephone. Staff who are completing the informed consent process with participants have been listed as study personnel, and have completed appropriate HIPAA/CITI training, as well as a RELIANCE protocol exam.

As we try to improve the flexibility of the consent process while maintaining the rigor and value, we are paying special attention to the subtle changes that will be made for remote consenting. As mentioned above, the option for in-person informed consent will be provided for participants.

We reviewed the process with several large medical centers currently using telephone-based consent (e.g., Kaiser Permanente Northwest), as well as the literature on this topic. In a Danish randomized controlled trial the researchers compared the effect of providing study information (including obtaining consent) by telephone versus the standard face-to-face consultation.[1] They found no difference in the comprehension between the two groups, or in the number of participants who sought more information after being informed. The researchers did not record the reasons for nonparticipation in the trial, however, they noted, "our impression is that the majority of those declining to participate did so because they preferred to be informed by telephone. Nonparticipants gave various reasons for this, e.g., it would take too much time to attend a consultation, logistical problems, and busy or inflexible schedules. This observation is in accordance with the findings of a recent Cochrane meta-analysis on improving the recruitment to

randomized controlled trials".[1] Other recent studies have also found the use of the telephone in the informed consent process to be feasible.[2-6]

For each method described above, potential participants will receive a copy of the IRB approved consent form *prior* to the consent discussion. The copy of the consent form will be provided by mail ahead of the call, email (based on participant preference), or handed to the participant during a clinic visit.

Steps for obtaining informed consent remotely

When obtaining informed consent remotely/via telephone, the following steps will be taken:

1. Study staff and patient have consent discussion remotely/by telephone;
2. The content of the consent discussion is identical to that of an in-person consent discussion, the patient is given time and opportunity to ask questions during the process and at the end of the conversation;
3. At the conclusion of the consent discussion, if the patient wants to take part in the study, they are instructed to sign and date the consent form in the “Signature of Participant” field, and mail/return it to the study staff using pre-paid postage provided by the study team;
4. Upon receipt of the patient-signed consent form the study team member who conducted the consent discussion signs and dates the consent as the “Person Obtaining Consent,”;
5. Once both parties’ signatures are on the consent form study activities can commence (i.e., the Coordinator may complete enrollment questionnaires with the participant);
6. Study staff will mail/return a copy of the fully signed consent form and study documents (e.g., *Follow-up support tool, v11.21.19*) to the patient for their records and retain the original in the site's study files;
7. The consent discussion, subsequent receipt of the patient-signed consent form, and final signing of the consent form by the study staff member who held the consent discussion will be documented in the patient record to account for the date discrepancy on the consent form between the participant signature and study staff signature,
8. Additionally, the consent note within the file will articulate the telephone conversation and consent process. If there are additional requirements per institutional policy (e.g., inputting a consent note into the patient record), these will be followed.

Script for introduction to telephone consent

Hello my name is [study staff], may I please speak to [patient name]?

No -> Ok, is there a better time to reach them?

Yes -> Hello [patient], I am calling from [medical center/hospital name] regarding the COPD study your lung doctor, Dr. [insert clinician name], mentioned called RELIANCE. Is this a good time to talk about the study?

No -> Ok, is there a better time to call back?

If Yes -> Ok, great. RELIANCE is a study for people with COPD. The goal of RELIANCE is to compare two medicines that are already commonly prescribed for COPD. You are eligible for the study because your doctor was considering prescribing one of the medicines for your COPD already, and neither you nor your doctor had a preference for one medicine. Today, doctors don't know which medicine might work better for different types of people. The goal of RELIANCE is to learn which medicine works best for which types of people with COPD. Are you interested in hearing more about what participating in the study might be like?

No-> Ok, thank you for your time.

Yes-> Great. If you think you want to participate in the study, we will review the study consent form which includes details about the study and participation together by phone. If, after reviewing the consent form together, you need more time, we can talk again another day. Otherwise, I will ask you to sign the form and mail it back to me. If you choose to join, your participation may last for 6 months to 3 years. During this time, the study team will call you every 3-6 months to complete a survey. This will take 15-20 minutes to complete by phone. Does this sound like something you are interested in?

No -> Ok, thank you for your time.

Yes -> Ok, great. Do you have the consent document that [was mailed to you recently *OR* was provided during your clinic visit] available so we can review this together?

No -> Coordinator will either offer to mail or email a copy and call the patient back.

Yes -> Ok, great. Lets begin [Coordinator will review the consent form with the participant as they would in person], following steps 1-8 above.

In the absence of visual cues when completing the consent and to assess attention and understanding, the Coordinator will ask a few questions to assess comprehension.

1. *Should you continue to seek care from your lung doctor throughout the duration of the study?*
2. *How frequently will the study team contact you to complete a survey while you are in the study?*
3. *If you want to stop the medicine and your lung doctor agrees, can you still continue in the study?*

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