Official Title: ^{129}XE MRI Assessment Of Disease Progression In Patients With Chronic Obstructive Pulmonary Disease Treated With Standard-of-Care Medications With Or Without Daily Open-Label Azithromycin Treatment To Prevent Acute Exacerbation

NCT Number: NCT04353661

Document Date: Protocol Version 5: 29-June-2022

PROTOCOL

TITLE:	**^{129}XE MRI ASSESSMENT OF DISEASE PROGRESSION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE TREATED WITH STANDARD-OF-CARE MEDICATIONS WITH OR WITHOUT DAILY OPEN-LABEL AZITHROMYCIN TREATMENT TO PREVENT ACUTE EXACERBATION**
PROTOCOL NUMBER:	GE42063
VERSION NUMBER:	5
EUDRACT NUMBER:	2020-000852-36
IND NUMBER	148058
NCT NUMBER:	NCT04353661
INTERVENTIONS:	Hyperpolarized ^{129}Xenon MRI Azithromycin
MEDICAL MONITOR:	[redacted], M.D., M.A.S.
SPONSOR:	Genentech, Inc.
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country- or Region-Specific Protocols		
Version	**Date Final**	**Country or Region**	**Version**	**Date Final**
5	See electronic date stamp on title page.	U.K.	4	See electronic date stamp on title page.
4	15 March 2022	U.K.	3	15 March 2022
3	06 August 2021	U.K.	2	06 August 2021
2	11 December 2020	U.K.	1	11 December 2020
1	11 June 2020		—	—

PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol GE42063 has been amended primarily to remove hearing assessment requirements and to implement clarifications. Changes to the protocol, along with a rationale for each change, are summarized below:

- Hearing audiometry requirements for Cohort A have been removed and replaced with alternative hearing disturbance mitigation strategies that more closely align with clinical practice in patients with chronic obstructive pulmonary disease who start azithromycin (Sections 4.1.2, 4.5.5, and 5.1.2.7; Appendix 1).
- Administration of hyperpolarized xenon-129 gas (HP ^{129}Xe) has been revised to align with the study imaging manual (Section 4.3.2.2).
- Management of patients who experience adverse events (including onset or worsening of hearing loss) and the reasons for treatment discontinuation have been updated to reflect current safety profiles related to study treatment (Sections 4.5.5, 4.6.1, 5.1.2.7, and 5.1.3.3; Appendix 1).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.22.6).
- The URL for the Roche Global Policy on Sharing of Clinical Study Information has been updated (Section 9.6).
- Guidance for sites to ensure patients have received a bronchodilator prior to performing the HP ^{129}Xe magnetic resonance imaging scan has been added (Appendix 1).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**^{129}XE MRI ASSESSMENT OF DISEASE PROGRESSION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE TREATED WITH STANDARD-OF-CARE MEDICATIONS WITH OR WITHOUT DAILY OPEN-LABEL AZITHROMYCIN TREATMENT TO PREVENT ACUTE EXACERBATION**
PROTOCOL NUMBER:	GE42063
VERSION NUMBER:	5
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NCT NUMBER:	NCT04353661
INTERVENTIONS:	Hyperpolarized ^{129}Xenon MRI Azithromycin
MEDICAL MONITOR:	[redacted], M.D., M.A.S.
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**^{129}XE MRI ASSESSMENT OF DISEASE PROGRESSION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE TREATED WITH STANDARD-OF-CARE MEDICATIONS WITH OR WITHOUT DAILY OPEN-LABEL AZITHROMYCIN TREATMENT TO PREVENT ACUTE EXACERBATION**
PROTOCOL NUMBER:	GE42063
VERSION NUMBER:	5
EUDRACT NUMBER:	2020-000852-36
IND NUMBER:	148058
NCT NUMBER:	NCT04353661
INTERVENTIONS:	Hyperpolarized ^{129}Xenon MRI Azithromycin
PHASE:	Phase IIa
INDICATION:	Chronic obstructive pulmonary disease
SPONSOR:	Genentech, Inc.

OBJECTIVES AND ENDPOINTS

This study will evaluate magnetic resonance imaging with inhaled hyperpolarized (HP) xenon-129 gas (^{129}Xe MRI) as a prognostic and diagnostic tool in patients with chronic obstructive pulmonary disease (COPD) treated with either azithromycin (AZM) plus standard-of-care COPD medications (long-acting β agonists [LABAs] and/or long-acting muscarinic antagonists [LAMAs], with or without inhaled corticosteroid [ICS] therapy) (AZM + SOC) or standard-of-care COPD medications alone (SOC). Specific objectives and corresponding endpoints for the study are outlined below.

EFFICACY OBJECTIVES

Primary Efficacy Objective

The primary efficacy objective for this study is to characterize the relationship between ^{129}Xe MRI metrics and clinical outcome in patients treated with AZM + SOC versus SOC on the basis of the following endpoint:

- Change in ^{129}Xe MRI ventilation defect percent (VDP) from baseline to Week 24 compared with rate of moderate or severe COPD exacerbations over 48 weeks

  A moderate COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days that lead to treatment with systemic corticosteroids and/or antibiotics.

  A severe COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days that lead to hospitalization or death.

Secondary Efficacy Objective

The secondary efficacy objective for this study is to characterize the relationship between ^{129}Xe MRI metrics and clinical outcome in patients treated with AZM + SOC versus SOC on the basis of the following endpoint:

- Change in ^{129}Xe MRI VDP from baseline to Week 24 and Week 48 compared with absolute change in pre-bronchodilator forced expiratory volume in 1 second (FEV_1; liters) from baseline to Week 24 and Week 48, respectively

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to characterize the relationship between ^{129}Xe MRI metrics and clinical outcome in patients treated with AZM + SOC versus SOC on the basis of the following endpoint:

- Change in ^{129}Xe MRI metrics (VDP, barrier defect percent, and/or RBC defect percent) from baseline to Week 24 and (as appropriate) Week 48 compared with the following:
  - Change in dyspnea, as assessed by the Baseline and Transition Dyspnea Indexes (BDI/TDI), from baseline to Week 24
  - Change in high-resolution computed tomography (HRCT) metrics (parametric response mapping-functional small airway disease [PRM^{fSAD}] and parametric response mapping-emphysema [PRM^{Emph}]) from baseline to Week 24 (if applicable) and Week 48, respectively
  - Change in oscillometry endpoints (including, but not limited to, R5, R20, R5–20, X5, resonance frequency, and reactance area), from baseline to Week 24
  - Absolute change in carbon monoxide diffusing capacity from baseline to Week 24 and Week 48, respectively
  - Change in six-minute walk test (6MWT) distance from baseline to Week 24 and Week 48, respectively
  - Change in health-related quality of life, as assessed by the overall score of the St. George's Respiratory Questionnaire for COPD, from baseline to Week 24 and Week 48, respectively

SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of ^{129}Xe MRI procedures and of AZM + SOC compared with SOC on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the World Health Organization toxicity scale
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results
- Change from baseline in ECG data

EXPLORATORY BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify biomarkers that may provide evidence of changes in disease progression or may increase the knowledge and understanding of disease biology (e.g., association between chronic bronchitis and imaging measures), on the basis of the following endpoints:

- Relative change from randomization visit in biomarker levels in sputum or blood at Weeks 12, 24, and 48
- Relationship between biomarkers in sputum or blood and other biomarker endpoints

STUDY DESIGN

DESCRIPTION OF STUDY

This is a multicenter, open-label, parallel group, randomized study designed to assess the sensitivity of HP ^{129}Xe MRI metrics as measures of disease progression in patients with COPD

treated with SOC medications with or without daily azithromycin treatment. ^{129}Xe MRI will be evaluated as a diagnostic tool that may provide useful images of the functioning of the lung for determining changes in lung function and structure. Approximately 120 patients with a diagnosis of COPD will be enrolled in the study across two cohorts (defined by severity of disease) and three arms. Patients will be followed for 52 weeks, during a 48-week open-label treatment period followed by a 4week safety follow-up period, with assessments performed at baseline and at Weeks 6, 12, 24, and 48. ^{129}Xe MRI images will be compared with standard lung function assessments, including 6MWT to assess functional status, quantitative HRCT to assess lung structure, and questionnaires to assess shortness of breath and quality of life. Patients will be enrolled in the following cohorts:

- **Cohort A**: Approximately 100 patients with COPD Global Initiative for Chronic Obstructive Lung Disease Stage 2–4 (GOLD 2–4), with or without chronic bronchitis, and history of ≥2 acute exacerbations (AEx) within a 12-month period in the prior 24 months will be randomly assigned in a 1:1 ratio to the following treatment arms:

  AZM + SOC: azithromycin (250 mg once a day [QD]) plus other SOC therapy consisting of LABAs and/or LAMAs, with or without ICS therapy

  SOC: SOC therapy consisting of LABAs and/or LAMAs, with or without ICS therapy

  Randomization will be stratified by region (United States vs. United Kingdom/Canada) and by the number of exacerbations in the prior 12 months (2 vs. ≥3).

- **Cohort B**: Approximately 20 patients with COPD GOLD Stage 1 (GOLD 1), with or without chronic bronchitis, and history of ≥1 AEx within a 12-month period in the prior 24 months will be enrolled as an observational cohort into the following arm:

  SOC: SOC therapy consisting of LABAs and/or LAMAs, with or without ICS therapy

Patients who are unable to complete the assessments or meet eligibility requirements during the screening period (from 1 to 28 days) will be permitted to be re-screened once for a total of two times. Patients who re-screen ≤6 weeks after Informed Consent Form completion must repeat only the assessments that triggered the screen failure. Patients who re-screen >6 weeks after Informed Consent Form completion are required to repeat the consent process and all screening assessments except for lung X-rays or HRCT.

The first dose of study drug for applicable patients in Cohort A will be self-administered on the same day as randomization (Visit 2, Day 1) after completion of all scheduled assessments. Thereafter, dosing will be repeated once daily during a 48-week treatment period. Patients will continue on stable doses of their SOC therapy, which must include a long-acting bronchodilator inhaler medication (LABAs and/or LAMAs) with or without additional ICS medication throughout the 48-week treatment period and subsequent 4-week safety follow-up period.

The first assessment of the ^{129}Xe MRI intervention will be performed at Visit 2 (Week 0) for all patients randomized to Cohort A and Cohort B and then repeated at Visit 3 (Week 6), Visit 4 (Week 12), Visit 5 (Week 24), and Visit 7 (Week 48). Safety, efficacy, and patient-reported outcome measures will be assessed throughout the treatment period, as specified in the protocol. Patients in Cohort A will be evaluated for safety for an additional 4 weeks following completion of the treatment period.

One or more interim analyses may be executed at the Sponsor's discretion.

NUMBER OF PATIENTS

Approximately 7 sites will participate to enroll approximately 120 patients with a diagnosis of COPD across two cohorts. Approximately 100 patients with COPD (GOLD 2–4) will be randomized to Cohort A; patients with chronic bronchitis (n ≤60) and without chronic bronchitis (n ≥40) will be randomized across treatment arms. Approximately 20 patients (GOLD 1) will be enrolled in the Cohort B substudy.

TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Age ≥40 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Signed Informed Consent Form (signed before any study procedures are performed)
- Current or former smokers with ≥10 pack years
- mMRC dyspnea score ≥ 1
- Post-bronchodilator FEV_1/forced vital capacity <0.70 at screening (Visit 1) or randomization (Visit 2)
- For patients enrolled in Cohort A: GOLD Stage 2–4 COPD with a history of ≥ 2 moderate/severe exacerbations within a 12-month period in the 24 months prior to screening
- For patients enrolled in Cohort B: GOLD Stage 1 COPD with a history of ≥ 1 moderate/severe exacerbations within a 12-month period in the 24 months prior to screening
- Receiving SOC background drug therapy as per GOLD or British Thoracic Society (BTS) guidance for COPD for 12 weeks prior to screening (Visit 1)
- On an eligible bronchodilator medication (LABA and/or LAMA) ± ICS therapy for ≥ 12 weeks prior to screening (Visit 1)
- Chest X-ray or CT scan within 6 months prior to screening (Visit 1), or during the screening period (prior to randomization [Visit 2]), that confirms the absence of clinically significant lung disease besides COPD
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the study period (all patients) and for 28 days after the final dose of azithromycin (patients enrolled in Cohort A receiving azithromycin)

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  The following are examples of adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of allergy or hypersensitivity to azithromycin
- Significant known respiratory disorders other than COPD that, in the view of the investigator, will affect the trial
- A COPD exacerbation and/or pneumonia within the 4 weeks prior to screening (Visit 1)

- FEV_1 percent predicted less than 25%
- Pregnant or breastfeeding, or intending to become pregnant during the study period (all patients) or within 28 days after the final dose of azithromycin (patients enrolled in Cohort A receiving azithromycin)

  Women of childbearing potential must have a negative serum pregnancy test result at screening.
- Participation in an interventional clinical trial within 4 weeks of screening (Visit 1) or receipt of any investigational medicinal product (IMP) within 30 days or 5 half-lives, whichever is longer
- Use of systemic corticosteroids within 4 weeks (oral or IV) or 12 weeks (intramuscular) prior to screening
- Active tuberculosis requiring treatment within 12 months prior to Visit 1

  Patients who have completed treatment for tuberculosis at least 12 months prior to Visit 1 and have no evidence of recurrent disease are permitted.
- Receiving treatment considered to be palliative (life expectancy $<$12 months)
- Myocardial infarction, unstable angina, or stroke within 12 months prior to screening (Visit 1)
- Clinically significant ECG changes, which in the opinion of investigator warrants further investigation or with a QTc interval $>$ 450 ms
- History of congenital or documented QT prolongation
- Currently receiving treatment with other active substance at doses known to prolong QT interval such as antiarrhythmic of Classes Ia and III, cisapride, and terfenadine
- Electrolyte disturbance (e.g., clinically significant hypokalemia or hypomagnesemia)
- Clinically relevant bradycardia, cardiac arrhythmia, or severe cardiac insufficiency
- History of myasthenia gravis
- For patients in Cohort A: Known *significant* hearing impairment *as indicated by a score of* $\geq$ *26 on the Hearing Handicap Inventory in the Elderly–Screening Questionnaire or as determined by the investigator*
- Impaired hepatic function
- Severe renal insufficiency (estimated glomerular filtration rate $<$ 10 mL/min)
- Concomitant use of ergot derivatives
- Bloodborne infection (e.g., HIV, hepatitis B or C)
- History of *Clostridium difficile* diarrhea
- Ventricular cardiac arrhythmia in the past 30 days
- Claustrophobia, inner ear implants, aneurysm or other surgical clips, metal foreign bodies in eye, pacemaker or other contraindication to MRI scanning

  Patients with any implanted device that cannot be verified as MRI compliant will be excluded.
- Unable to fit into ^{129}Xe vest coil used for MRI
- Deemed unlikely to be able to comply with instructions during imaging
- Evidence, in the opinion of the investigator, of alcohol, drug, or solvent abuse within the prior 12 months
- Medical or psychological conditions which, in the opinion of the investigator, might create undue risk to the patient or interfere with the patient's ability to comply with the protocol requirements
- Diagnosis of malignancy within 5 years of Visit 1 (except for excised localized non-melanoma skin cancer in remission)

END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. The LPLV is expected to occur approximately 52 weeks after the last patient is randomized into the study. This timeframe includes a 48-week treatment period and a 4-week safety follow-up period for Cohort A. The LPLV for Cohort B is expected to occur approximately 48 weeks after the last patient is randomized into the cohort.

LENGTH OF STUDY

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 30 months.

Total duration of patient participation in Cohort A of the study, from date of randomization (Visit 2, Day 1) through the 48-week treatment period and 4-week safety follow-up period, is approximately 52 weeks. Total duration of patient participation in Cohort B of the study, from date of randomization (Visit 2, Day 1) through the 48-week observation period, will be approximately 48 weeks.

INVESTIGATIONAL MEDICINAL PRODUCTS

The IMPs for this study are azithromycin and HP ^{129}Xe. All patients will continue their COPD therapy as recommended in published COPD guidelines or BTS guidelines. Required COPD inhaler therapy, consisting of LABA and/or LAMA with or without ICS therapy, is considered a non-IMP for this study.

Patients in Cohort A randomized to treatment intervention will receive generic azithromycin 250 mg taken orally QD. Patients will receive a 3-month supply of azithromycin 250-mg tablets at Visit 2 (baseline), Visit 4 (Week 12), Visit 5 (Week 24), and Visit 6 (Week 36) at the study site. Patients randomized to receive azithromycin will receive a maximum of 336 doses with a tablet strength of 250 mg. All patients will be provided with a diary to track daily study treatment and the date of any AEx events.

HP xenon (^{129}Xe) will be administered at *specified timepoints and the total dose bag volume should target 20% of the patient's forced vital capacity* followed by a breath hold of up to 15 seconds. Subsequent ^{129}Xe doses will only be administered once the patient is ready to proceed. Patients will be monitored by a qualified medical professional for the duration of the xenon dose and post-procedural period, as well as the MRI. *Refer to the study imaging manual for details.*

NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Required COPD inhaler therapies, consisting of LABA and/or LAMA with or without ICS therapy, are considered non-IMPs for this study.

STATISTICAL METHODS

PRIMARY ANALYSIS

Details of the analysis are available in the Statistical Analysis Plan, including sensitivity analysis. At a minimum, VDP change at 24 weeks can predict rate of moderate/severe COPD exacerbation over 48 weeks, controlling for treatment assignment. The initial model will be a negative binomial model for exacerbation rate using the intent-to-treat population. As this is an exploratory study, sensitivity analysis is performed for the purpose of confirming signal. If signal is not found using the primary analysis, sensitivity analysis will not be performed.

DETERMINATION OF SAMPLE SIZE

Power calculations for this exploratory study require many assumptions due to lack of available literature on the ^{129}Xe MRI metrics. Further details than those provided in the protocol, including code to generate these calculations, are available in the Statistical Analysis Plan. All calculations were done in R version 3.5.0. The focus of this trial is on estimation, not hypothesis testing.

The main objective of this study is establishing if ^{129}Xe MRI metrics (VDP) are a more sensitive measure of lung function decline and can predict the rate of moderate/severe exacerbation. Approximately 100 patients in Cohort A will be enrolled in this study. A sample size of 100 will enable enough exacerbations to anchor the evaluation of the performance of VDP.

This study is powered (at 77%) to detect a treatment effect due to exacerbation, depending on assumptions. Power calculation was done based on a negative binomial with over-dispersion

of 1.3, with 5% alpha, assuming a mean exacerbation frequency of 2 and observed for 48 weeks. A one-sided test was used and 10% drop-out rate. A further assumption on the azithromycin effect size was needed to establish power—a 35 % reduction rate ratio was used.

This study is powered, depending on assumptions, for the secondary efficacy objectives. To test the sensitivity of VDP metric relative to FEV_1 (coefficient of variation test), a sample size of 100 provides just under 90% power to establish improved coefficient of variation relative to FEV_1 (assumes coefficient of variation of 180% and using a simulation-based power calculation run with MSLR and a p-value of 0.05.)

This study is well powered to test the secondary efficacy objective of establishing the relationship between HRCT metrics and the VDP metric. With a sample size of 100, and assuming a true correlation of 0.25 between the metrics, the study has approximately 75% power to determine if a correlation exists (assuming a multivariate normal with correlation of 0.25 and PRM^{fSAD} mean of 26.6% and SD of 11.6%, and VDP mean of 4.37 and SD of 1.89).

INTERIM ANALYSES

An interim analysis may be performed to assess for changes in VDP and/or other ^{129}Xe MRI metrics relative to other clinical assessments, at the Sponsor's discretion.

Given the exploratory nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by the Sponsor's study team personnel.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWT	six-minute walk test
AECOPD	acute exacerbations of chronic obstructive pulmonary disease
AEx	acute exacerbations
ATS	American Thoracic Society
AX	reactance area
AZM + SOC	azithromycin and standard of care therapy
BDP	barrier defect percent
Borg CR10 Scale	Borg Category-Ration 10 Scale®
BTS	British Thoracic Society
C. difficile	*Clostridium difficile*
CDAD	*Clostridium difficile* associated diarrhea
COPD	chronic obstructive pulmonary disease
COPD-CB	chronic obstructive pulmonary disease with chronic bronchitis
CRO	contract research organization
CRP	c-reactive protein
CT	computed tomography
DDI	drug-drug interaction
DL_{CO}	carbon monoxide diffusing capacity
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FOT	forced oscillometry technique
FVC	forced vital capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HHIE-S	*Hearing Handicap Inventory in the Elderly–Screening Questionnaire*
HIPAA	Health Insurance Portability and Accountability Act
HP	hyperpolarized
HP ^{129}Xe MRI	hyperpolarized xenon magnetic resonance imaging
HRCT	high-resolution computed tomography
ICH	International Council for Harmonisation
ICS	inhaled corticosteroids

Abbreviation	Definition
IM	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
IRC	Independent Review Charter
IxRS	interactive voice or web-based response system
LABA	long-acting β-agonist
LAMA	long-acting muscarinic antagonist
LPLV	last patient, last visit
mMRC	Modified Medical Research Council
MRI	magnetic resonance imaging
N_2O	nitrous oxide
PD	pharmacodynamic
PRM^{Emph}	parametric response mapping-emphysema
PRM^{fSAD}	parametric response mapping-functional small airway disease
PRO	patient-reported outcome
QD	once a day
QTc	corrected QT interval
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RDP	Red blood cell defect percent
SAP	Statistical Analysis Plan
SGRQ-C	St. George's Respiratory Questionnaire-COPD
SMC	Safety Monitoring Committee
SNP	single nucleotide polymorphism
SOC	standard of care
SpO_2	oxygen saturation
ULN	upper limit of normal
VDP	ventilation defect percent
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON COPD

Chronic obstructive pulmonary disease (COPD) has been defined as a clinical syndrome characterized by chronic respiratory symptoms, structural pulmonary abnormalities (airways disease and/or emphysema), and lung function impairment (primarily airflow limitation that is poorly reversible). The characteristic symptoms of COPD are dyspnea, cough, and sputum production (Global Initiative for Chronic Obstructive Lung Disease [GOLD 2019]). The GOLD staging system expresses COPD severity, as reflected by symptoms, history of worsening, requirements for hospital stay, and spirometric measures of lung function and includes stages: GOLD 1 (mild), GOLD 2 (moderate), GOLD 3 (severe), and GOLD 4 (very severe).

COPD is a significant cause of morbidity and mortality worldwide (GOLD 2019). In contrast to other chronic diseases, COPD is increasing in prevalence and is projected to be the third-leading cause of death and disability worldwide by 2030 (GOLD 2019). Worldwide estimation of the overall prevalence of Stage $\geq$2 (moderate) COPD is 10.1% (Buist et al. 2007). COPD is caused by long-term exposure to inhaled noxious gases and particles. Cigarette smoke accounts for more than 90% of cases in developed countries. COPD usually occurs in patients over the age of 40 years and is more common in men.

The costs to society for treating COPD are high, accounting for approximately 3.4% of the total health care budget of the European Union. In the United States, medical costs for treatment of COPD were $32.1 billion in 2010 and are estimated to increase to $49 billion by 2020 (Ford et al. 2015). Acute exacerbations of COPD (AECOPD) are responsible for a large portion of the economic burden, morbidity, and mortality of the disease and are attributed to more than 500,000 hospitalizations and 100,000 deaths in the United States each year.

COPD is a heterogeneous disease, and there are currently no clear methods to identify patients with a high risk of acute exacerbations (AEx), particularly in mild COPD. For example, although patients with a history of exacerbations and/or reduced forced expiratory volume (FEV_1) are considered at higher risk for future adverse outcomes and subsequent disease progression (Donaldson and Wedzicha. 2006; Agusti et al. 2010; GOLD 2019), patients with mild disease also have AEx (Han et al. 2017). To date, the strongest predictor of exacerbation risk is a prior history of exacerbation.

1.2 BACKGROUND ON AZITHROMYCIN TREATMENT FOR COPD AND ^{129}XE MRI IMAGING

The current, guideline-driven treatment options to prevent AECOPD include inhaled corticosteroids (ICSs) with or without oral macrolides such as azithromycin; however, these treatments are not effective for all patients. Development of novel therapies to prevent AEx is hampered by the lack of robust and sensitive surrogate measures of

exacerbations. Due to the low frequency of AEx in patients, interventional trials that use AEx rate as a primary endpoint require a large number of patients and a long period of assessment (i.e., monitoring for 1 year or more). More detailed phenotyping of all patients with COPD—including those at high risk of severe exacerbation according to physiological, biological, genetic, and imaging phenotypes (Kirby et al. 2014; Lowe et al. 2019)—may provide new therapeutic windows of opportunity for targeted treatment.

Several relevant research clinical trials have been published supporting the clinical benefit of long-term macrolide treatment in reducing the rate of AECOPD (Albert et al. 2011; Simpson et al. 2014; Lijuan et al. 2018; Vermeersch et al. 2019). The COPD GOLD 2019 guidelines propose prophylactic macrolide therapy with azithromycin or erythromycin to reduce the risk of exacerbations in patients with moderate or severe COPD prone to exacerbations. However, long-term macrolide treatment could increase the occurrence of adverse events and increase macrolide resistance (Taylor et al. 2015; GOLD 2019 guidelines). While daily azithromycin decreases AECOPD, the response to therapy is unpredictable, even in patients within the same GOLD stage (Han et al. 2014). This is largely related to variable structural damage in different lung units that impair not only ventilation, but also gas exchange. It is necessary to identify these physiological derangements of COPD (i.e., clinical phenotypes) so the pharmacological responses and clinical outcomes can be predicted with more precision. Currently, no single assessment modality provides a comprehensive regional evaluation of lung structure, ventilation, and gas exchange.

Magnetic resonance imaging (MRI) using hyperpolarized (HP) xenon-129 gas (^{129}Xe) is an emerging technology capable of 3D mapping of ventilation and gas distribution in the alveolar space and its uptake in interstitial barrier tissues (“barrier uptake”), as well as its transfer to red blood cells (Driehuys 2012; Joseph 2019). Recent studies comparing healthy smokers, patients with COPD, and non-smokers support the potential of ^{129}Xe MRI to identify multiple physiological lung changes using a single breath-hold (Qing 2019). This allows for discrimination between healthy subjects and healthy smokers prior to loss of lung function assessed by FEV_1 and could become a powerful new measure of early-stage lung disease (Qing et al. 2019; Ruppert 2019). Importantly, this assessment may offer improved sensitivity compared with an AEx endpoint allowing for shorter duration clinical trials.

Few studies have shown any impact of chronic azithromycin treatment on clinically relevant measures of COPD such as FEV_1, or quality of life associated with prophylactic treatment with azithromycin. COPD manifests in a spatially heterogeneous manner, with areas of normal lung in close proximity to areas of small airways disease, fibrosis, and emphysema. Thus, detection of progression and response to therapy requires local assessment of lung structure and function, with the ability to monitor these regions over time. Currently, no single established assessment modality provides a comprehensive regional evaluation of both ventilation and gas exchange. Although high-resolution computed tomography (HRCT) is integral to the diagnosis of COPD/emphysema, it is

poorly suited to monitor therapeutic response. Computed tomography (CT) scans detect structural abnormalities, but the earliest harbinger of changing disease status is lung function. Additionally, CT scans and HRCT scans require use of ionizing radiation. The ability to image both lung function and structure may now be addressed by HP ^{129}Xe MRI.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

^{129}Xe MRI is capable of 3D-mapping ventilation and gas distribution in the alveolar space and its uptake in interstitial barrier tissues ("barrier uptake"), as well as its transfer to red blood cells ("RBC transfer"). Because ^{129}Xe, like oxygen, must traverse the interstitial barrier to reach capillary blood, ^{129}Xe signal in RBCs is exquisitely sensitive to barrier thickness. ^{129}Xe in RBCs has a unique frequency shift, allowing it to reveal interstitial thickening of only a few microns. This high sensitivity to altered blood-gas-barrier in regions of small airways disease and emphysema makes ^{129}Xe MRI uniquely suited to study COPD without the use of potentially harmful ionizing radiation. This has the potential to accelerate clinical trials for COPD by visualizing the therapeutic response on the timescale of months versus years.

This study aims to assess whether change from baseline in ^{129}Xe MRI metrics for ventilation defect percent (VDP), barrier defect percent (BDP), and/or RBC defect percent (RDP) at 24 weeks can predict rate of exacerbation over a 48-week period, and whether baseline ^{129}Xe MRI metrics are prognostic for AEx rate and/or predictive of clinical benefit from daily treatment with azithromycin.

Azithromycin use has been shown to reduce AECOPD, but carries some risk to patients (Taylor et al. 2015). These include a small risk for QT-interval prolongation, hearing loss, and the development of antibacterial resistance. Nonetheless, with adequate safety monitoring (see Section 5.1), reduced risk for recurrent exacerbations may benefit patients' overall quality of life and long-term outcomes.

An assessment has been conducted to determine whether the coronavirus disease 2019 pandemic has any impact on the benefit-risk assessment of this study including, but not limited to, the patient population under study and study treatments (azithromycin and hyperpolarized ^{129}Xe). The safety monitoring and management guidelines and risk mitigation measures provided in the study are considered adequate.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate ^{129}Xe MRI as a prognostic and diagnostic tool in patients with COPD treated with either azithromycin plus standard-of-care COPD medications (long-acting β agonists [LABAs] and/or long-acting muscarinic antagonists [LAMAs], with or without ICS therapy) (AZM + SOC) or standard-of-care COPD medications alone (SOC). Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to characterize the relationship between ^{129}Xe MRI metrics and clinical outcome in patients treated with AZM + SOC versus SOC on the basis of the following endpoint:

- Change in ^{129}Xe MRI VDP from baseline to Week 24 compared with rate of moderate or severe COPD exacerbations over 48 weeks

  A moderate COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days that lead to treatment with systemic corticosteroids and/or antibiotics.

  A severe COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days that lead to hospitalization or death.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to characterize the relationship between ^{129}Xe MRI metrics and clinical outcome in patients treated with AZM + SOC versus SOC on the basis of the following endpoint:

- Change in ^{129}Xe MRI VDP from baseline to Week 24 and Week 48 compared with absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week 24 and Week 48, respectively

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to characterize the relationship between ^{129}Xe MRI metrics and clinical outcome in patients treated with AZM + SOC versus SOC on the basis of the following endpoint:

- Change in ^{129}Xe MRI metrics (VDP, BDP, and/or RDP) from baseline to Week 24 and (as appropriate) Week 48 compared with the following:
  - Change in dyspnea, as assessed by the Baseline and Transition Dyspnea Indexes (BDI/TDI), from baseline to Week 24
  - Change in HRCT metrics (parametric response mapping-functional small airway disease [PRM^{fSAD}] and parametric response mapping-emphysema [PRM^{Emph}]) from baseline to Week 24 (if applicable; see Section 4.5.11 and Appendix 1) and Week 48, respectively
  - Change in oscillometry endpoints (including, but not limited to, R5, R20, R5–20, X5, resonance frequency [Fres], and reactance area [AX]), from baseline to Week 24
  - Absolute change in carbon monoxide diffusing capacity (DL_{CO}) from baseline to Week 24 and Week 48, respectively

- Change in six-minute walk test (6MWT) distance from baseline to Week 24 and Week 48, respectively
- Change in health-related quality of life, as assessed by the overall score of the St. George's Respiratory Questionnaire for COPD (SGRQ-C), from baseline to Week 24 and Week 48, respectively

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of ^{129}Xe MRI procedures and of AZM + SOC compared with SOC on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the World Health Organization (WHO) toxicity scale
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results
- Change from baseline in ECG data

2.3 EXPLORATORY BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify biomarkers that may provide evidence of changes in disease progression or may increase the knowledge and understanding of disease biology (e.g., association between chronic bronchitis and imaging measures), on the basis of the following endpoints:

- Relative change from randomization visit in biomarker levels in sputum or blood at Weeks 12, 24, and 48
- Relationship between biomarkers in sputum or blood and other biomarker endpoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a multicenter, open-label, parallel group, randomized study designed to assess the sensitivity of HP ^{129}Xe MRI metrics as measures of disease progression in patients with COPD treated with SOC medications with or without daily azithromycin treatment. MRI with inhaled HP ^{129}Xe gas (^{129}Xe MRI) will be evaluated as a diagnostic tool that may provide useful images of the functioning of the lung for determining changes in lung function and structure. Approximately 120 patients with a diagnosis of COPD will be enrolled in the study across two cohorts (defined by severity of disease) and three arms. Patients will be followed for 52 weeks, during a 48-week open-label treatment period followed by a 4-week safety follow-up period, with assessments performed at baseline and at Weeks 6, 12, 24, and 48. ^{129}Xe MRI images will be compared with standard lung function assessments, including 6MWT to assess functional status, quantitative HRCT to assess lung structure, and questionnaires to assess shortness of breath and quality of life. Patients will be enrolled in the following cohorts:

- **Cohort A**: Approximately 100 patients with COPD GOLD Stage 2–4 (GOLD 2–4), with or without chronic bronchitis, and history of ≥2 AEx within a 12-month period in the prior 24 months will be randomly assigned in a 1:1 ratio to the following treatment arms:
  - AZM + SOC: azithromycin (250 mg QD) plus other SOC therapy consisting of LABAs and/or LAMAs, with or without ICS therapy
  - SOC: SOC therapy consisting of LABAs and/or LAMAs, with or without ICS therapy

    Randomization will be stratified by region (United States vs. United Kingdom/Canada) and by the number of exacerbations in the prior 12 months (2 vs. ≥3).
- **Cohort B**: Approximately 20 patients with COPD GOLD Stage 1 (GOLD 1), with or without chronic bronchitis, and history of ≥1 AEx within a 12-month period in the prior 24 months will be enrolled as an observational cohort into the following arm:
  - SOC: SOC therapy consisting of LABAs and/or LAMAs, with or without ICS therapy

Patients who are unable to complete the assessments or meet eligibility requirements during the screening period (from 1 to 28 days) will be permitted to be re-screened once for a total of two times. Patients who re-screen ≤6 weeks after Informed Consent Form completion must repeat only the assessments that triggered the screen failure. Patients who re-screen >6 weeks after Informed Consent Form completion are required to repeat the consent process and all screening assessments except for lung X-rays or HRCT.

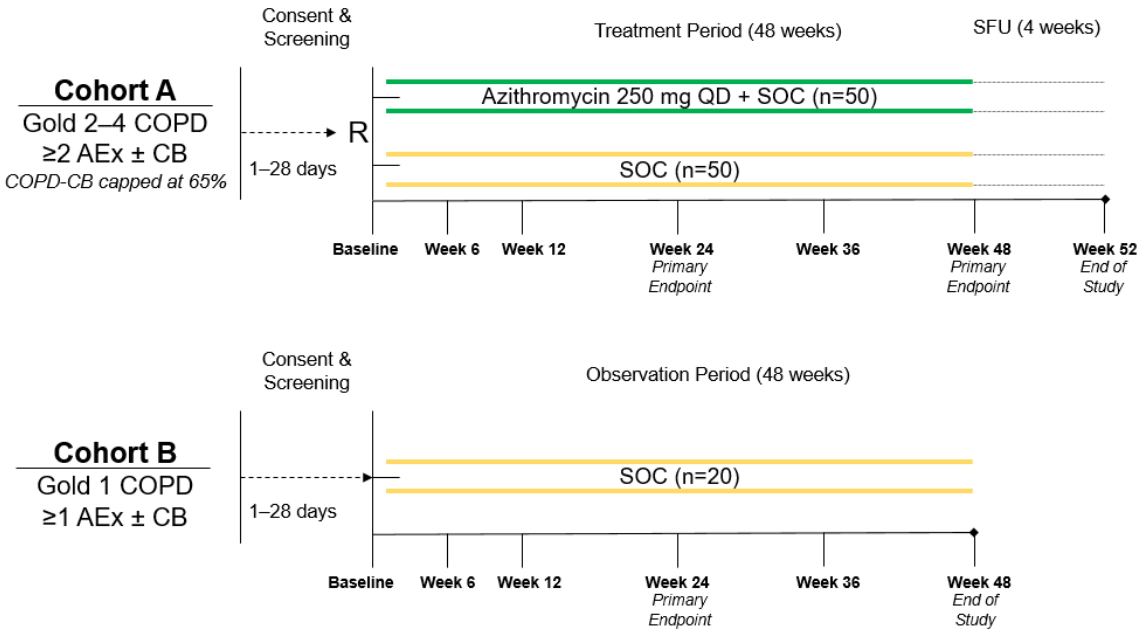
The first dose of study drug for applicable patients in Cohort A will be self-administered on the same day as randomization (Visit 2, Day 1) after completion of all scheduled assessments. Thereafter, dosing will be repeated once daily during a 48-week treatment period. Patients will continue on stable doses of their SOC therapy, which must include a long-acting bronchodilator inhaler medication (LABAs and/or LAMAs) with or without additional ICS medication throughout the 48-week treatment period and subsequent 4-week safety follow-up period.

The first assessment of the ^{129}Xe MRI intervention will be performed at Visit 2 (Week 0) for all patients randomized to Cohort A and Cohort B and then repeated at Visit 3 (Week 6), Visit 4 (Week 12), Visit 5 (Week 24), and Visit 7 (Week 48). Safety, efficacy, and PRO measures will be assessed throughout the treatment period, as specified in Appendix 1. Patients in Cohort A will be evaluated for safety for an additional 4 weeks following completion of the treatment period.

One or more interim analyses may be executed at the Sponsor's discretion.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



AEx = acute exacerbations; CB = chronic bronchitis; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; QD = once a day; R = randomization; SFU = safety follow up; SOC = standard of care.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. The LPLV is expected to occur approximately 52 weeks after the last patient is randomized into the study. This timeframe includes a 48-week treatment period and a 4-week safety follow-up period for Cohort A. The LPLV for Cohort B is expected to occur approximately 48 weeks after the last patient is randomized into the cohort.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 30 months.

Total duration of patient participation in Cohort A of the study, from date of randomization (Visit 2, Day 1) through the 48-week treatment period and 4-week safety follow-up period, is approximately 52 weeks. Total duration of patient participation in Cohort B of the study, from date of randomization (Visit 2, Day 1) through the 48-week observation period, will be approximately 48 weeks.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Populations

There is a high unmet need and limited therapeutic options for patients with intermittent AECOPD and persistent dyspnea, despite adherence with guidelines-based SOC therapy. The definition of COPD exacerbation used in this study is consistent with published guidelines that define a patient population with unmet medical need. Patients having exacerbations despite treatment with ICS and bronchodilator therapy are at increased risk for future exacerbations and adverse health outcomes. A dyspnea score of 1 or more, as defined by the Modified Medical Research Council (mMRC), during screening identifies a patient population with incomplete control of symptoms.

All patients considered for participation in the 48-week azithromycin treatment in Cohort A will have a physician diagnosis of COPD for at least 12 months prior to screening and meet GOLD Stage 2–4 criteria. Patients will be required to have optimal guideline-based SOC treatment (daily for a minimum of 12 weeks prior to randomization). All patients eligible for Cohort A will have a history of ≥ 2 moderate/severe COPD exacerbations within a 12-month period in the 24 months prior to screening.

A separate substudy (Cohort B) will enroll an observational cohort of patients with mild COPD (GOLD 1) and will be required to have optimal guideline-based SOC treatment for a minimum of 12 weeks prior to randomization. Patients must have a history of ≥ 1 moderate/severe AEx within a 12-month period in the 24 months prior to screening and meet all other eligibility criteria. The rationale for this substudy is based on results from large observational studies of COPD that indicate substantial instability in the rate of AEx from year to year, regardless of prior AEx history (Han et al. 2017). This instability potentially limits the clinical value of requiring a threshold of ≥ 2 incidents of AEx in the previous year (Han et al. 2017) as the basis for treatment decisions or patient selection for clinical trials. Furthermore, a large natural history study that explored the association between AECOPD and the change in FEV_1 over a 5-year follow-up period provided convincing data that confirmed a relationship between exacerbations and FEV_1 loss. Additionally, this same study indicated that the impact of AEx on FEV_1 loss is greater in patients with mild COPD (GOLD 1) than in patients with moderate to severe COPD (GOLD 2 or 3) (Dransfield et al. 2017). Collectively, these studies suggest that a threshold of ≥ 2 AEx in the prior year provides limited utility in identifying individual patients at increased risk of AEx, or classifying individuals for treatment decision making and for the basis of patient selection for future clinical trials assessing novel treatments. Therefore, the analysis of patients with mild COPD will help clarify the relationship between lung structure/function and disease status/progression. Initial studies in small cohorts of healthy smokers and patients with COPD suggest that ^{129}Xe MRI has increased sensitivity to detect changes in lung physiology and structure relative to standard clinical measures, including pulmonary function tests (Ruppert 2019).

Patients with GOLD 1 COPD enrolled in Cohort B will be required to be on stable background therapy for a minimum of 12 weeks prior to screening. This cohort of patients will be monitored for changes in disease status and progression based on an assessment of changes in ^{129}Xe MRI metrics relative to the rate of AEx and other standard clinical measures, including lung function activity and PROs.

3.3.2 Rationale for Azithromycin and Control Groups

The selected dose of azithromycin planned for this study is 250 mg/QD. This dosing is supported by the safety and efficacy demonstrated in several research clinical trials and current GOLD guidelines (Albert et al. 2011; Simpson et al. 2014; Cui et al. 2018).

The COPD GOLD 2019 guidelines state that treatment with azithromycin (250 mg/QD or 500 mg three times per week) or erythromycin (500 mg two times per day) for 1 year in patients prone to exacerbations reduces the risk of exacerbations compared with usual care. These dosing recommendations are based on results from several placebo-controlled research clinical trials (Albert et al. 2011; Simpson et al. 2014; Vermeersch et al. 2019). Potential side effects include an increased incidence of bacterial resistance, prolongation of corrected QT interval (QTc), and impaired hearing, which can be monitored in the clinic. Several relevant clinical trial reports support the clinical benefit of long-term macrolide treatment in reducing the rate of AECOPD (Albert et al. 2011). Azithromycin was chosen over other macrolides (e.g., clarithromycin or erythromycin) based on the benefit–risk profile established in several placebo-controlled clinical trials (Cui et al. 2018) and the limited drug-drug interaction (DDI) profile. In contrast to clarithromycin and erythromycin, azithromycin is not metabolized by cytochrome P450 enzymes, specifically cytochrome P450 3A4 (CYP3A4), involved with the metabolism of the largest number of medications (i.e., calcium channel blockers, statins).

In Cohort A, a control group consisting of patients treated only with stable SOC medications will be monitored over the 48-week treatment period to assess for differences in COPD AEx events, pulmonary function, dyspnea symptoms, 6MWT, biomarkers, and safety compared to patients who receive azithromycin plus SOC (AZM + SOC). In Cohort A, patients in both the control and azithromycin arm will continue to receive SOC medication that includes daily long-acting bronchodilator medication with or without ICS. The use of a control group is necessary to assess the differences in ^{129}Xe MRI metrics, exacerbations, pulmonary function, symptoms, and safety compared with patients who receive to azithromycin. In Cohort B, all patients will undergo the same study assessments as patients in Cohort A. All patients will continue to receive SOC for COPD and other allowable medical conditions (with some restrictions; refer to Section 4.4).

3.3.3 Rationale for Biomarker Assessments

Biomarker assessments, before and at various timepoints after azithromycin treatment, will be used to provide evidence of the biologic activity of azithromycin in patients with and without chronic bronchitis, and increase the knowledge and understanding of disease biology. Exploratory biomarker analysis may include, but will not be limited to, analysis of eosinophils, neutrophils, c-reactive protein (CRP), sputum mucins, transcriptomic changes in blood samples, and imaging measures (e.g., PRM^{fSAD}).

A blood sample will be collected for DNA extraction to enable identification of genes related to chronic bronchitis in COPD that may be associated with disease progression or can increase the knowledge and understanding of disease biology.

3.3.4 Rationale for Non-Standard Clinical Outcome Assessment (^{129}Xe MRI)

MRI using inhaled HP ^{129}Xe gas (^{129}Xe MRI) will be assessed as a new imaging assessment tool that can provide useful images of the functioning of the lung to determine change in lung function and structure; ^{129}Xe MRI provides images of the functioning lung.

More sensitive imaging approaches are vital to monitor the progression of COPD as COPD manifests itself in a spatially heterogeneous manner. In the COPD lung, areas of normal lung are located in close approximation to areas of emphysema and small airway (obstructive) disease. Therefore, it is expected that potential therapeutic responses to slow or halt progression would be regional, thus supporting the need for a sensitive tool that allows for the detection of localized changes on structure and function over time. Advances in 3D pulmonary MRI to image both function and structure now make this possible. HP noble gases, such as ^{3}He and ^{129}Xe (after a single breath mixed with ^{4}He or N_2), provide a way to visualize pulmonary ventilation 3-dimensionally. For inhaled ^{3}He and ^{129}Xe, increased nuclear polarization overcomes their low density compared to tissues and permits imaging their distribution in the airways and airspaces. This can be used to measure apparent diffusion coefficients that estimate gas displacement, as well as to detect structural abnormities in the small airways.

For ^{129}Xe, the fractional solubility of xenon gas in biological tissues has additional applications for measuring gas exchange, alveolar surface area, and capillary blood volume. Because ^{129}Xe, like oxygen, must traverse the interstitial barrier to reach capillary blood, ^{129}Xe signal in RBCs is exquisitely sensitive to barrier thickness and surface area. ^{129}Xe in RBCs has a unique frequency shift, allowing it to reveal loss of surface area manifested as BDP and RDP. The exquisite sensitivity to increased blood-gas-barrier thickness makes ^{129}Xe MRI uniquely suited to study pulmonary function, lung perfusion, and alveolar-to-capillary tissue barrier without ionizing radiation. This has the potential to accelerate clinical trials for COPD by literally visualizing the therapeutic response on the timescale of months versus years.

HP ^{129}Xe MRI has been shown to be safe and well-tolerated in several Phase I clinical trials (Kirby et al. 2012). The safety and sensitivity of HP ^{129}Xe MRI has been evaluated in patients with chronic lung disease, including idiopathic pulmonary fibrosis, asthma, COPD, and pulmonary vascular disease, at one or more of clinical academic centers selected to participate in this trial (Driehuys et al. 2012; Kirby et al. 2012; Svenningsen et al. 2013; Qinga et al. 2014; Ebner et al. 2017; Martin et al. 2017; Stewart et al. 2017; Qing et al. 2019; Weatherley et al. 2019). These studies have enrolled in excess of 200 patients and healthy volunteers and demonstrated that inhalation of up to four 1 L doses of HP ^{129}Xe was well-tolerated, generated no notable changes in measured physiologic parameters, and resulted in no serious adverse events or withdrawals. Patients in this study will be exposed to five 1 L doses of HP ^{129}Xe, and the selected clinical academic centers participating in this trial have the technical experience and infrastructure to conduct this study.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 7 sites will participate to enroll approximately 120 patients with a diagnosis of COPD across two cohorts. Approximately 100 patients with COPD (GOLD 2–4) will be randomized to Cohort A; patients with chronic bronchitis ($n \leq 60$) and without chronic bronchitis ($n \geq 40$) will be randomized across treatment arms. Approximately 20 patients (GOLD 1) will be enrolled in the Cohort B substudy.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Age ≥40 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Signed Informed Consent Form (signed before any study procedures are performed)
- Current or former smokers with ≥10 pack years
- mMRC dyspnea score ≥1
- Post-bronchodilator FEV_1/forced vital capacity (FVC) <0.70 at screening (Visit 1) or randomization (Visit 2)
- For patients enrolled in Cohort A: GOLD Stage 2–4 COPD with a history of ≥2 moderate/severe exacerbations within a 12-month period in the 24 months prior to screening
- For patients enrolled in Cohort B: GOLD Stage 1 COPD with a history of ≥1 moderate/severe exacerbations within a 12-month period in the 24 months prior to screening
- Receiving SOC background drug therapy as per GOLD or British Thoracic Society (BTS) guidance for COPD for 12 weeks prior to screening (Visit 1)

- On an eligible bronchodilator medication (LABA and/or LAMA) ± ICS therapy for ≥ 12 weeks prior to screening (Visit 1)
- Chest X-ray or CT scan within 6 months prior to screening (Visit 1), or during the screening period (prior to randomization [Visit 2]), that confirms the absence of clinically significant lung disease besides COPD
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the study period (all patients) and for 28 days after the final dose of azithromycin (patients enrolled in Cohort A receiving azithromycin)

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  The following are examples of adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of allergy or hypersensitivity to azithromycin
- Significant known respiratory disorders other than COPD that, in the view of the investigator, will affect the trial
- A COPD exacerbation and/or pneumonia within the 4 weeks prior to screening (Visit 1)
- FEV_1 percent predicted less than 25%
- Pregnant or breastfeeding, or intending to become pregnant during the study period (all patients) or within 28 days after the final dose of azithromycin (patients enrolled in Cohort A receiving azithromycin)

  Women of childbearing potential must have a negative serum pregnancy test result at screening.

- Participation in an interventional clinical trial within 4 weeks of screening (Visit 1) or receipt of any investigational medicinal product (IMP) within 30 days or 5 half-lives, whichever is longer
- Use of systemic corticosteroids within 4 weeks (oral or IV) or 12 weeks (intramuscular [IM]) prior to screening
- Active tuberculosis requiring treatment within 12 months prior to Visit 1

  Patients who have completed treatment for tuberculosis at least 12 months prior to Visit 1 and have no evidence of recurrent disease are permitted.
- Receiving treatment considered to be palliative (life expectancy <12 months)
- Myocardial infarction, unstable angina, or stroke within 12 months prior to screening (Visit 1)
- Clinically significant ECG changes, which in the opinion of investigator warrants further investigation or with a QTc interval > 450 ms
- History of congenital or documented QT prolongation
- Currently receiving treatment with other active substance at doses known to prolong QT interval such as antiarrhythmic of Classes Ia and III, cisapride, and terfenadine
- Electrolyte disturbance (e.g., clinically significant hypokalemia or hypomagnesemia)
- Clinically relevant bradycardia, cardiac arrhythmia, or severe cardiac insufficiency
- History of myasthenia gravis
- History of myasthenia gravis
  - For patients in Cohort A: Known *significant* hearing impairment *as indicated by a score of ≥ 26 on the Hearing Handicap Inventory in the Elderly–Screening Questionnaire (HHIE-S) or as determined by the investigator*
- Impaired hepatic function
- Severe renal insufficiency (estimated glomerular filtration rate [eGFR] <10 mL/min)
- Concomitant use of ergot derivatives
- Bloodborne infection (e.g., HIV, hepatitis B or C)
- History of *Clostridium difficile* (*C. difficile*) diarrhea
- Ventricular cardiac arrhythmia in the past 30 days
- Claustrophobia, inner ear implants, aneurysm or other surgical clips, metal foreign bodies in eye, pacemaker or other contraindication to MRI scanning

  Patients with any implanted device that cannot be verified as MRI compliant will be excluded.
- Unable to fit into ^{129}Xe vest coil used for MRI
- Deemed unlikely to be able to comply with instructions during imaging
- Evidence, in the opinion of the investigator, of alcohol, drug, or solvent abuse within the prior 12 months

- Medical or psychological conditions which, in the opinion of the investigator, might create undue risk to the patient or interfere with the patient's ability to comply with the protocol requirements
- Diagnosis of malignancy within 5 years of Visit 1 (except for excised localized non-melanoma skin cancer in remission)

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Patients will be randomized to the treatment arms through the interactive voice/web-based response system (IxRS). After written informed consent has been obtained, patients in Cohort A will be randomized in a 1:1 ratio to one of two open-label treatment arms (azithromycin, 250 mg/QD plus daily SOC medications or daily SOC medications). Patients in Cohort B will continue to receive daily SOC medications.

Permuted block randomization will be performed centrally for Cohort A and stratified by region (United States or United Kingdom/Canada) and prior exacerbation history (2, $\geq$3). During the open-label treatment period, the IxRS will make study treatment kit assignments.

In Cohort A, the number of COPD patients with chronic bronchitis (COPD-CB) will be capped at $\leq$65.

4.3 STUDY INTERVENTIONS AND TREATMENTS RELEVANT TO THE STUDY DESIGN

The IMPs for this study are azithromycin and HP ^{129}Xe. All patients will continue their COPD therapy as recommended in published COPD guidelines (GOLD 2019) or BTS guidelines (NICE 2018). Required COPD inhaler therapies, consisting of LABA and/or LAMA with or without ICS therapy, are considered non-IMPs for this study.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Azithromycin

Azithromycin will be supplied by the Sponsor in the approved 250-mg tablet dosage form. For information on the azithromycin formulation, see the Summary of Product Characteristics for azithromycin.

4.3.1.2 Hyperpolarized ^{129}Xe

^{129}Xe is created by passing a gas mixture of xenon, helium, and nitrogen through the Hyperpolarizer. The gas mixture will be provided by the clinical site and will be hyperpolarized at the clinical site. For information on the gas mixture, see the study imaging manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1. Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Guidelines for treatment interruption or

discontinuation for patients who experience adverse events are provided in Section 5.1.3.

4.3.2.1 Azithromycin

Patients in Cohort A randomized to treatment intervention will receive generic azithromycin 250 mg taken orally (PO) QD. Patients will receive a 3-month supply of azithromycin 250-mg tablets at Visit 2 (baseline), Visit 4 (Week 12), Visit 5 (Week 24), and Visit 6 (Week 36) at the study site. Patients randomized to receive azithromycin will receive a maximum of 336 doses with a tablet strength of 250 mg. All patients will be provided with a diary to track daily study treatment and the date of any AEx events.

4.3.2.2 Hyperpolarized ^{129}Xe

HP xenon (^{129}Xe) will be administered at *specified timepoints and the total dose bag volume should target 20% of the patient's forced vital capacity* followed by a breath hold of up to 15 seconds. Subsequent ^{129}Xe doses will only be administered once the patient is ready to proceed. Patients will be monitored by a qualified medical professional for the duration of the xenon dose and post-procedural period, as well as the MRI. *Refer to the study imaging manual for details.*

HP ^{129}Xe MRI scans will be acquired according to procedures described in the study imaging manual. Scans will be centrally processed and analyzed per the Independent Review Charter (IRC). ^{129}Xe MRI scans will be made available to each participating clinical site when the study has been completed and database has been locked. The study imaging manual and IRC are provided to ensure image acquisition and processing is standardized across all clinical sites.

4.3.3 Standard-of-Care Therapy

All patients will continue the required COPD inhaler therapy for this study that includes bronchodilator medication consisting of LABA and/or LAMA with or without ICS therapy. Refer to the local prescribing information for the formulation, packaging, and handling of these medications. Patients may not be on systemic (oral, IV, or IM) corticosteroids, biologics, or experimental therapeutics for the treatment of COPD. All patients will be provided with a diary to track daily study treatment and the date of any AEx events.

4.3.4 Medical Devices

In this study, the hyperpolarizer and the MRI machines are considered medical devices. Both devices are provided by the site and are not manufactured by or for the Sponsor. The hyperpolarizer and MRI machines are to be operated according to standard institutional practices.

4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to screening (for medications not intended for the treatment of COPD) or 12 weeks prior to screening (for medications intended for the treatment of COPD) to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

Medications known to interact with azithromycin (see prescribing information or summary of product characteristics), in addition to digoxin and cyclosporine, should be used with caution.

Azithromycin should not be taken concurrently with ergot derivatives or simultaneously with antacids.

4.4.1 Permitted Therapy

All patients will continue their COPD therapy as recommended in published COPD guidelines (GOLD 2019 or BTS [NICE 2018]) and adhere to the following:

- Patients must be on stable therapy for at least 12 weeks prior to screening (Visit 1). There should be no anticipated changes in bronchodilator medication during the study.

Patients are permitted to use the following therapies during the study:

- Inhaled bronchodilator and ICS therapy

  Patients may be on more than one bronchodilator with or without ICS therapy.
- Required COPD inhaler therapy for this study: Bronchodilator medication consisting of LABA and/or LAMA
- Additional background COPD therapy during the trial (e.g., phosphodiesterase-4 inhibitors and theophylline), but should remain stable from the start of screening (Visit 1) through completion of the study

From the start of screening (Visit 1) through completion of the study, the doses of bronchodilator medications and ICSs should remain stable. If changes to the background COPD medications are unavoidable, the patient may be switched to another brand or formulation that is equivalent to the medication that the patient was receiving at study entry. All changes to a patient's background medications should be documented in the COPD Targeted Concomitant Medications eCRF.

Rescue Therapy

It is expected that patients will be using short-acting anticholinergic and/or short-acting β-agonist therapy for acute COPD symptoms per existing treatment guidelines.

Combination inhalers (e.g., albuterol/ipratropium) are permitted. Short-acting bronchodilators must be administered via the patient's prescribed inhaler or nebulizer. Any short-acting bronchodilator that is prescribed as COPD rescue medication over the course of the study should be documented in the Concomitant Medications eCRF.

- Systemic corticosteroid use:

  Patients who require any systemic corticosteroids within 4 weeks (oral or IV) or 12 weeks (IM) prior to screening will not be eligible for the trial (see Section 4.1.2).

  The use of systemic corticosteroids is permitted for acute COPD management after randomization. Corticosteroids used for treatment of COPD (e.g., an AEx event as defined in Section 4.5.13) should be documented on the appropriate eCRF. Systemic corticosteroids should not be used other than for COPD exacerbations, but in the event that they are used to treat other medical conditions, this should be documented on the Concomitant Medications eCRF.

4.4.2 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

Medication	Restrictions [a]
COPD Therapies	
Systemic corticosteroids > 10 mg/QD (oral, IV, or IM)	Prohibited within 4 weeks (oral or IV) or 12 weeks (IM) prior to screening and during the screening period Prohibited for treatment of any condition other than COPD exacerbations or life-threatening conditions (e.g., spinal cord compression, cerebral edema) during the study period
Intra-articular corticosteroids > 10 mg	Prohibited within 4 weeks prior to screening, during the screening period, or during the treatment period
Maintenance oral or inhaled antibiotics	Prohibited within 2 weeks prior to screening, during the screening period, or during the treatment period
Investigational therapy (other than protocol-mandated study treatment)	Prohibited within 30 days or 5 half-lives, whichever is longer, prior to initiation of study treatment and during study treatment

IM = intramuscular; IV = intravenous; QD = once a day.

[a] The Medical Monitor should be consulted in cases of uncertainty.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medications, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, medication allergies, smoking history, and use of alcohol and drugs of abuse will be recorded at screening. In particular, sites should record whether the patient has any history of anaphylaxis, cancer, cardiovascular disease, eosinophilic disease, inflammatory or autoimmune disease, and surgeries with metal implants. Any history of smoking should be entered on the Tobacco Use History eCRF.

Demographic data will include age (date of birth), sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified visits during the treatment period and as clinically indicated. Limited physical examination includes head, ears, eyes, nose, throat, cardiovascular, respiratory, and dermatologic examinations. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position (resting for at least 5 minutes), temperature, and oxygen saturation. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Hearing Assessment

Patients in Cohort A will complete the *HHIE-S* (Appendix 7) and *be queried on any onset hearing loss, worsening hearing loss, or hearing disturbances at specified timepoints.*

Any patient in Cohort A randomized to azithromycin reporting onset or worsening hearing loss, reporting hearing disturbances, or demonstrating any decline in the interpretation of the HHIE-S score during the study will permanently discontinue azithromycin and be referred for formal audiology testing. Any patient who permanently discontinues azithromycin should be asked to continue all other study assessments, with the exception of azithromycin administration, through the end of the study.

4.5.6 Tobacco Use

At each study visit, the patient will be asked about their tobacco use. Any changes in tobacco use since screening (Visit 1) will be recorded in the eCRF.

4.5.7 Height and Weight

Height and weight will be measured at visits according to the schedule of activities (see Appendix 1). Weight will be determined to the nearest 0.1 kg. For body weight measurements, the patient will wear street clothes without any shoes, outerwear, or accessories.

4.5.8 Chest X-Rays

A chest X-ray must be performed during screening (between Visit 1 and Visit 2), unless a chest X-ray or CT scan has been obtained within 6 months prior to screening (Visit 1) and is available for review by the investigator. The X-ray may be performed locally, but must be reviewed by the investigator prior to randomization at Visit 2.

4.5.9 Spirometry and Forced Oscillometry

Spirometry, including the procedure for bronchodilator testing, which is based on the American Thoracic Society (ATS) and the European Respiratory Society (ERS) Consensus Statement (Graham et al. 2019) and forced oscillometry technique (FOT), will be conducted as per the study pulmonary function manual. Spirometry measures will include pre- and post-bronchodilator FEV_1 and FVC (volume in liters) per Appendix 1. The percentage of predicted FEV_1 and percentage of predicted FVC will

be derived from these volume measurements using the equations derived from the third National Health and Nutrition Examinations Survey (Hankinson et al. 1999). Inhaled bronchodilator therapies that may affect spirometry must be withheld until pre-bronchodilator spirometry measurements are completed. Patients must be made aware that inhaled bronchodilator use is prohibited within a specified window prior to each clinic visit, with the exception of the screening visit (Visit 1), as follows:

- Twice-daily LABA and twice-daily LAMA: within 12 hours prior to spirometry
- Once-daily LABA and once-daily LAMA: within 24 hours prior to spirometry
- Short-acting β-agonist/ipratropium: within 4 hours prior to spirometry

Pre-bronchodilator spirometry should not be performed during the screening visit (Visit 1) if the patient did not withhold bronchodilator medications during the specified time period prior to the screening assessment. The remaining screening assessments should be completed as indicated in Appendix 1.

FOT will be conducted as per the study pulmonary function manual, which is based on the ERS Task Force on Respiratory Impedance Measurements (Oostveen et al. 2003). FOT measures will include resistance at low frequency, 5 Hz (R_5), resistance change (R_{5-20}), AX, and reactance difference inspiration – expiration (ΔX_5).

FOT assessments should be performed shortly before completing the pulmonary function testing assessments.

4.5.10 Gas Exchange-Diffusion Capacity of the Lung for Carbon Monoxide Assessment

DL_{CO} will be conducted as per the study pulmonary function manual, which is based on the 2017 ATS/ERS guidance (Graham et al. 2017).

4.5.11 High-Resolution Computed Tomography

Good-quality pulmonary quantitative HRCT scans (one at full inspiration and one at expiration) performed per the imaging acquisition guidelines provided in the study-specific imaging manual will be obtained at baseline. Alternatively, an acceptable set of scans performed ≤6 months prior to screening and in accordance with study image acquisition guidelines can be used for eligibility determination.

Follow-up HRCT scans will be performed at specified timepoints (see Appendix 1). Ideally, two follow-up HRCT scans will be performed at both Week 24 (Visit 5) and Week 48 (Visit 7). However, if local IRB approves only one follow-up HRCT timepoint, then the HRCT scans should be collected at Week 0 (Visit 2) and Week 48 (Visit 7). Details regarding image acquisition will be provided in the imaging manual.

4.5.12 Hyperpolarized ^{129}Xe MRI

^{129}Xe MRI will be performed at each study visit as indicated in the schedule of activities (see Appendix 1). Details for standardization of image acquisition will be provided in the imaging manual.

To confirm that the ^{129}Xe MRI image acquisition procedure has been harmonized across all clinical research sites, approximately 2 volunteers will be tested at each site prior to randomizing the first patient with COPD. Each volunteer will complete two MRI test sessions within an 8-hour timeframe. The test scans from the volunteers will be analyzed centrally per the study-specific imaging manual. Details regarding test scans will be provided in the imaging manual.

Patients and volunteers will be monitored by a qualified medical professional for the duration of the ^{129}Xe dose and post-procedural period, as well as during the MRI.

4.5.13 Acute Exacerbations of COPD

All patients will be provided with a diary to track daily study treatment and the date(s) of any AEx events. Patients will be required to bring their diaries to study visits. Patients will be asked if they have experienced an AEx during the last month at each study visit.

The investigator will ask directed questions to assess whether the patient experienced any adverse events and any protocol-defined COPD exacerbations since the last study visit.

Given that COPD exacerbations are the key primary endpoint in this study, a dedicated eCRF will be used to record information regarding protocol-defined exacerbation events. A COPD exacerbation must also be reported as an adverse event (or serious adverse event as applicable) as per Section 5.2. Sites should update the COPD Targeted Concomitant Medications eCRF with all medications used for treatment.

4.5.14 Urgent COPD-Related Health Care Utilization

At each study visit after randomization, the investigator will ask directed questions to assess whether the patient has required any urgent COPD-related health care since the last study visit. Urgent COPD-related health care utilization includes any hospitalizations, emergency department visits, and acute care visits (i.e., unplanned clinic visits). A dedicated eCRF will be used to record information regarding any COPD-related hospitalizations, emergency department visits, and/or acute care visits.

4.5.15 Six-Minute Walk Test

The 6MWT will be conducted as per the study 6MWT procedural manual that is based on the 2002 ATS guidelines for the 6MWT (ATS Statement 2002).

For safety reasons, all patients should be clinically stable prior to performing any study-related 6MWT. Supplemental oxygen flow rate will be recorded before every

6MWT. Heart rate, SpO_2, and the Borg Category-Ratio 10 (CR10) Scale® (Appendix 6) will be recorded immediately before and after the procedure. The Borg CR10 Scale is a 1-item assessment that can be used to measure a variety of perceptions and experiences (i.e., perceived exertion, chest pain, dyspnea, and fatigue) (Borg and Borg 2010). The Borg CR10 Scale ranges from 0 (Nothing at all) to 10 (Absolute maximum/Highest possible).

4.5.16 BODE Index

The BODE index is a composite score of other assessments collected in the study.

Body mass index (B), obstruction (O) as measured by FEV_1, dyspnea (D) as measured by the mMRC scale, and exercise endurance (E) as measured by the 6MWT will be assessed as described under the separate sections for each assessment. The standard scoring system will be followed (Celli et al. 2004).

4.5.17 Sputum Induction

Sputum induction will be performed per the study procedure manual. Patients will be pre-medicated with a bronchodilator and then inhale an aerosolized saline solution delivered by an ultrasonic nebulizer to facilitate forcible coughs and sputum expectoration. Peak expiratory flow and FEV_1 will be monitored during sputum induction for safety. Induced sputum will be processed immediately according to the lab manual at the clinical sites to obtain raw and sputolysin-treated sputum samples, as well as sputum cell pellets prepared in a special RNA-protecting solution.

4.5.18 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, and uric acid
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Urinalysis, if clinically indicated as determined by the investigator, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (which may include sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)

Samples for the following laboratory tests will be sent to the Sponsor or a designee for analysis:

- Serum and plasma samples for exploratory research on biomarkers
- Sputum samples for mucin measurements and for exploratory research on biomarkers

Exploratory biomarker research may include, but will not be limited to, analysis of eosinophils, neutrophils, sputum mucins, RNA expression from blood, and single nucleotide polymorphisms (SNPs) of selected genes (e.g., *FAM13A, ATF6*, and other genes related to COPD). Research will not be aimed at distinguishing germline mutations from somatic mutations.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.22), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exception:

- Blood, serum, plasma, and sputum samples collected for biomarker research will be destroyed no later than 10 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on germline mutations, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.19 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be

performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: time of day of recording, heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected through use of Fridericia's formula (QTcF) based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.20 Clinical Outcome Assessments

The SGRQ-C and mMRC will be completed in their entirety by the patient. Each PRO will be collected on paper at the site. Data Collection Methods for Clinical Outcome Assessments PRO instruments will be self-administered at the clinic at specified timepoints during the study (see Appendix 1). At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified. Copies of each questionnaire are provided in Appendix 2 and Appendix 3.

4.5.20.1 St. George's Respiratory Questionnaire for COPD Patients

The impact of COPD on health and well-being, as measured by the SGRQ-C (Meguro et al. 2007), will be assessed by asking patients to recall their COPD-related experiences and to respond to 40 questions included within three domains: symptoms (7 items), activity (13 items), and impacts (20 items). The SGRQ-C does not specify a recall period, with the exception of the item that assesses chest trouble. This item has a recall period of the past year. Lower scores of the SGRQ-C indicate better health-related quality of life. A copy of the assessment is provided in Appendix 2.

4.5.20.2 Modified Medical Research Council Dyspnea Scale

The mMRC scale assesses dyspnea (Bestall et al. 1999). Patients rate how much their breathlessness impacts their mobility. The mMRC is a 5-item scale. A score of "0" (zero) represents the least impairment due to dyspnea and a score of "4" indicates greatest impairment due to dyspnea. There is no recall period for the mMRC. The mMRC is administered at the site on paper. The mMRC is completed at Visit 1 and Visit 2 to determine whether the patient is eligible for this study. The mMRC is also completed throughout the treatment period as a component of the BODE index, as specified in Appendix 1. A copy of the scale is available in Appendix 3.

4.5.21 Optional Blood Samples

Consenting patients will undergo optional blood samples for DNA extraction to enable SNP array to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics. The samples may be sent to one or more laboratories for analysis.

The Informed Consent Form will contain a separate section that addresses optional blood samples. A separate, specific signature will be required to document a patient's agreement to undergo optional blood samples. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the appropriate eCRF.

Genomics is increasingly informing researchers' understanding of disease pathobiology. SNP array is a method that sequences specific subsets of the genome, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

Samples may be used for exploratory biomarker research as described in Section 4.5.18. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.18 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.22 Optional Samples for Research Biosample Repository

4.5.22.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.22.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board/Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.22) will not be applicable at that site.

4.5.22.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to COPD or other respiratory diseases or drug safety:

- Leftover blood, serum, sputum, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.22.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.22.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.22.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.22.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice (GCP) by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment

- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Any Grade 4 adverse event that the investigator determines to be related to study treatment

  This excludes COPD exacerbations, unless they meet one of the other criteria for study treatment discontinuation.
- Pregnancy
- Development of *C. difficile* diarrhea *(for patients in Cohort A randomized to azithromycin)*
- *Any onset hearing loss, worsening hearing loss, hearing disturbance, or decline in the interpretation of the HHIE-S score (for patients in Cohort A randomized to azithromycin)*

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

Patients will return to the clinic for scheduled study visits after the final dose of study drug (see Appendix 1 for additional details).

4.6.2 Patient Discontinuation from the Study

All patients will return to the clinic for final clinical assessments at Week 48. Patients in Cohort B will be discontinued after completing assessment at Week 48 Visit. Patients in Cohort A will be discontinued from the study after a final safety follow-up assessment performed by telephone at Week 52.

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

For Cohort A, participants will be considered to have completed the trial if they complete trial treatment through Visit 7 (Week 48; end-of-treatment visit) and complete Visit 8 (Week 52; safety follow-up visit, which is conducted by telephone).

For Cohort B, participants will be considered to have completed the trial if they continue to participate in the trial through Visit 7 (Week 48).

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Azithromycin is an approved agent to treat patients with a bacterial infection, and the safety profile for both acute and chronic dosing is well characterized in the drug manufacturer's prescribing information. The use of HP ^{129}Xe MR imaging is an investigational diagnostic tool. While there is clinical experience with ^{129}Xe MRI in studies with healthy volunteers, COPD patients, and patients with other chronic lung diseases, its safety profile has not been fully characterized.

The safety plan for this study is designed to ensure patient safety and includes specific eligibility criteria, a Safety Monitoring Committee (SMC), and specific pharmacovigilance monitoring assessments, as detailed below.

A SMC will be used to carefully review the accumulating safety data. The SMC will consist of Sponsor representatives from the following functions: clinical science, drug

safety, biostatistics, and statistical programming and analysis (SPA), and the principal investigator or delegate from each participating clinical study site. The SMC will regularly monitor the safety of the patients in the study and review cumulative data approximately every 6 months.

The anticipated important safety risks are outlined below.

5.1.1 Risks Associated with ^{129}Xe

5.1.1.1 General Anesthesia

Xenon is a general anesthetic when breathed continuously at concentrations $>70\%$ for extended periods of time. Patients may experience transient effects including dizziness, tingling or numbness of the extremities, nausea, smelling of flowers, or a feeling of well-being and euphoria.

Adverse effects may include those listed below and will be monitored closely by medically trained staff throughout the imaging session.

- Sense of analgesia (dizziness, light-headedness, numbness, euphoria, sleepiness, and tingling in extremities)
- Altered heart rate
- Altered gas exchange, SpO_2

5.1.1.2 Hypoxemia

The effect of xenon on the respiratory tract has been the subject of many animal studies. Results showed moderately increased airway resistance with high xenon concentrations (70%) in pigs and dogs with or without methacholine-induced bronchoconstriction (Calzia et al. 1999a), but no effects were seen at a lower xenon concentration (50%) in dogs (Zhang et al. 1995). In a study in pigs (Baumert et al. 2005), where the resistance was corrected for gas viscosity and density, it was concluded that the increase in airway pressure observed in xenon anesthesia can be attributed entirely to its high density and viscosity, and that xenon does not exert any major effects on airway diameter.

Diffusion hypoxia manifests as a reduction in alveolar oxygen partial pressure and occurs when the administration of the gas mixture is discontinued and room air is breathed. This phenomenon is seen in anesthesia with nitrous oxide (N_2O) and depends on lipid solubility of the gas. As the solubility of xenon is higher than that of N_2, this could theoretically occur after exposure to xenon gas. A study in pigs has been performed to address this question and the arterial partial oxygen pressure was measured during nitrogen wash-in (30% O_2 and 70% N_2) after an initial 30-minute ventilation period with either 70% xenon and 30% O_2, or 70% N_2O and 30% O_2. The changes in arterial partial oxygen pressure were much less in the xenon-treated pigs as compared to that of the N_2O group, demonstrating that diffusion hypoxia is much less likely with xenon than with N_2O, probably due to the low blood solubility of the noble gas (Calzia et al. 1999a).

5.1.2 Risks Associated with Azithromycin

Summary data from Phase III and Phase IV trials indicate that azithromycin is generally well tolerated. The most common adverse events observed were gastrointestinal disorders followed by central nervous system (hearing loss) disorders, and all were typically mild to moderate. Decreased hearing has been reported at low frequency and was reversible. Prolongation of QT interval and cases of torsades de pointes have been reported, with greater incidence in elderly patients.

5.1.2.1 Hypersensitivity

As with erythromycin and other macrolides, serious allergic reactions including angioneurotic edema and anaphylaxis (rarely fatal), Acute Generalized Exanthematous Pustulosis (AGEP), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

5.1.2.2 Hepatotoxicity

Since the liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin. Some patients may have had preexisting hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

5.1.2.3 Ergot Derivatives

In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin; however, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administrated.

5.1.2.4 Superinfection

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms including fungi is recommended.

5.1.2.5 *Clostridium Difficile* Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Strains of *C. difficile* producing hypertoxin A and B contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and

may require colectomy. Therefore, CDAD must be considered in patients who present with diarrhea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents. Patients who develop *C. difficile* diarrhea during the study will be discontinued from treatment.

5.1.2.6 Myasthenia Gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

5.1.2.7 Tinnitus or Hearing Loss

Hearing disturbances including hearing loss, deafness and/or tinnitus, and reports of taste/smell perversion and/or loss have been reported in postmarketing surveillance and in randomized controlled trials assessing benefit/risk profile of azithromycin to prevent AEx in COPD (Albert et al. 2011).

Patients in Cohort A will complete the *HHIE-S* (see Appendix 7) to assess perceived hearing disability. Those with *known significant hearing impairment at screening will be excluded.* Patients who are randomized to the azithromycin arm complaining of worsening tinnitus, *onset hearing loss,* or worsening hearing loss will *permanently discontinue azithromycin and be referred for formal audiology testing.*

5.1.2.8 Elevated Liver Enzymes

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with azithromycin in all patients, then every 12 weeks thereafter. Dosage modifications or interruption may be necessary for liver enzyme elevations. These guidelines should be followed for any patient who may initiate azithromycin treatment, whether as prevention or rescue therapy.

5.1.2.9 Hypersensitivity: Rash, Pruritus, Tongue, or Facial Swelling

The only contraindication listed in the E.U. Summary of Product Characteristics for azithromycin is giving it to patients with known hypersensitivity to macrolide antibiotics.

5.1.2.10 Prolongation of QT Interval

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen with treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin. Physician/Principal Investigators should consider the risk of QT prolongation, which can be fatal when weighing the potential risks and benefits of azithromycin for patients have one or more contraindications

- Known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure
- Co-medications known to prolong the QT interval
- Ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic

ECG testing will be performed during the screening and baseline visits to exclude patients with known risk associated with QT prolongation. ECG testing should be repeated every 6 months to monitor for any significant changes in the QT interval months.

5.1.3 Management of Patients Who Experience Adverse Events

5.1.3.1 Dose Modifications

Reduction in dosing for adverse events is not permitted. Patients who experience certain adverse events considered to be related to study drug should be discontinued from treatment as described in Section 4.6.1.

5.1.3.2 Treatment Interruption

Study treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug. If study treatment has been withheld for two or more consecutive dosing visits because of toxicity, the patient should be discontinued from study treatment. However, if the adverse event(s) that led to withholding dosing shows clear evidence of improvement in the investigator's judgment, treatment may be resumed; the Medical Monitor may be consulted as appropriate.

5.1.3.3 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 1.

Table 1 Management Guidelines

Event	Action to Be Taken
Hepatotoxicity	
ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN or clinical jaundice	• Immediately discontinue study treatment. • Elevations of AST or ALT of > 5 × ULN should be reported as adverse event(s) of special interest to the Sponsor in an expedited manner (see Section 5.3.3). • A hepatology consult is recommended.
Hearing Disturbances	
Any reported onset hearing loss, worsening hearing loss, or hearing disturbance	• Discontinue study treatment. • Refer for formal audiology testing.
QT Prolongation	
Sustained (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 ms and > 60 ms longer than the baseline value	• Unless there is a clear alternative cause other than study drug, discontinue study treatment (see Section 5.1.3.4).[a]
Sustained absolute QTcF that is > 515 ms	• Unless there is a clear alternative cause other than study drug, discontinue study treatment (see Section 5.1.3.4).[a]
An episode of torsades de pointes or a new ECG finding of clinical concern	• Unless there is a clear alternative cause other than study drug, discontinue study treatment (see Section 5.1.3.4).[a]

ULN = upper limit of normal.

[a] In rare circumstances, it may be acceptable to resume azithromycin, provided that any ECG abnormalities have resolved and the patient is appropriately monitored, following discussion with the Medical Monitor. Clinical judgment should be applied.

5.1.3.4 Management of Increases in QT Interval

Azithromycin should be discontinued in patients who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained absolute (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 ms and > 60 ms longer than the baseline value
- Sustained absolute QTcF that is > 515 ms
- An episode of torsades de pointes or a new ECG finding of clinical concern

- Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.
- Management of patients with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended to help in the management of such patients.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for GCP, an adverse event is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An adverse event can, therefore, be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to WHO Toxicity Grading Scale; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.1.3 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.3–5.5. The investigator is also responsible for reporting medical device complaints.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study randomization, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.3.2 for instructions for reporting serious adverse events).

After randomization, all adverse events will be reported until 28 days after the final dose of azithromycin.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.5.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The WHO toxicity grading scale (see Appendix 5) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (<48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

WHO=World Health Organization.

Notes: Developed by the Division of Microbiology and Infectious Diseases.

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 3):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 3 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.3.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 or details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.4) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.3.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.2.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.3.2). This includes death attributed to progression of COPD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of COPD, “Chronic Obstructive Pulmonary Disease progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.5.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of COPD

Medical occurrences or symptoms of deterioration that are anticipated as part of COPD should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of COPD on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of Chronic Obstructive Pulmonary Disease").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3, see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/ECs, drug manufacturers, and health authorities based on applicable legislation.

5.4.1 Emergency Medical Contact

Medical Monitor Contact Information

Genentech Medical Monitor:

Medical Monitor: [redacted], M.D., M.A.S. (Primary)

Telephone Nos.: +1 650-225-2331 (United States)

[redacted] (United States)

Genentech Medical Monitor:

Medical Monitor: [redacted], M.D. (Secondary)

Telephone Nos.: +1 650-866-7684 (United States)

+1 650-826-9469 (United States)

5.4.2 Reporting Requirements for Serious Adverse Events, Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 28 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 28 days after the final dose of azithromycin. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a paper Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), if the event is believed to be related to prior study treatment. These events should be reported through use of the Adverse Event

eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Azithromycin	Single drug covered by prescribing information: Azithromycin E.U. Summary of Product Characteristics
^{129}Xe MRI	Drug device combination covered by combination Investigator's Brochure: HP ^{129}Xe and MRI Investigator's Brochure

HP = hyperpolarized; MRI = magnetic resonance imaging.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

A SMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

Power calculations for this exploratory study require many assumptions due to lack of available literature on the ^{129}Xe MRI metrics. Further details than those provided in the protocol, including code to generate these calculations, are available in the Statistical Analysis Plan (SAP). All calculations were done in R version 3.5.0. The focus of this trial is on estimation, not hypothesis testing.

The main objective of this study is establishing if ^{129}Xe MRI metrics (VDP) are a more sensitive measure of lung function decline and can predict the rate of moderate/severe exacerbation. Approximately 100 patients in Cohort A will be enrolled in this study. A sample size of 100 will enable enough exacerbations to anchor the evaluation of the performance of VDP.

This study is powered (at 77%) to detect a treatment effect due to exacerbation, depending on assumptions. Power calculation was done based on a negative binomial with over-dispersion of 1.3 (COPD BEAT data), with 5% alpha, assuming a mean exacerbation frequency of 2 and observed for 48 weeks. A one-sided test was used and 10% drop-out rate. A further assumption on the azithromycin effect size was needed to establish power—a 35 % reduction rate ratio was used (Seemungal et al. 2008).

This study is powered, depending on assumptions, for the secondary efficacy objectives. To test the sensitivity of VDP metric relative to FEV_1 (coefficient of variation test), a sample size of 100 provides just under 90% power to establish improved coefficient of variation relative to FEV_1 (assumes coefficient of variation observed in Weatherly et al. 2019 of 180% and using a simulation-based power calculation run with MSLR and a p-value of 0.05.)

This study is well powered to test the secondary efficacy objective of establishing the relationship between HRCT metrics and the VDP metric. With a sample size of 100, and assuming a true correlation of 0.25 between the metrics, the study has approximately 75% power to determine if a correlation exists (assuming a multivariate normal with correlation of 0.25 and PRM^{fSAD} mean of 26.6% and standard deviation of 11.6% [Bhatt et al. 2016]). Assumptions of operating characteristics of ^{129}Xe MRI metric, VDP, come from Smith et al. 2018 (mean = 4.37, SD = 1.89).

Exploratory endpoints of RDP and BDP were not evaluated in terms of power. They are purely exploratory and there is no literature on which to base a power calculation.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY OR DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, COPD-CB) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all patients, with patients grouped according to their assigned treatment.

6.4.1 Primary Efficacy Endpoints

The primary efficacy endpoints are detailed in Section 2.1.1.

Details of the analysis are available in the SAP, including sensitivity analysis. At a minimum, VDP change at 24 weeks can predict rate of moderate/severe COPD exacerbation over 48 weeks, controlling for treatment assignment. The initial model will be a negative binomial model for exacerbation rate using the intent-to-treat (ITT) population. As this is an exploratory study, sensitivity analysis is performed for the purpose of confirming signal. If signal is not found using the primary analysis, sensitivity analysis will not be performed.

6.4.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint is detailed in Section 2.1.2.

Details of the analysis are available in the SAP, including sensitivity analysis around alternative timepoints. Establishing greater sensitivity of ^{129}Xe MRI metrics (VDP) will rely on a coefficient of variation test. Establishing correlation of ^{129}Xe MRI metrics (VDP) with HRCT metrics will rely on testing the correlation metric.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints for this study are detailed in Section 2.1.3.

Details of the analysis are available in the SAP, including sensitivity analysis around alternative timepoints. Establishing greater sensitivity of ^{129}Xe MRI metrics (RDP and VDP), will rely on a coefficient of variation test. Establishing correlation of ^{129}Xe MR imaging metrics (RDP and VDP) with other metrics will rely on testing the correlation metric. Prognostic biomarker assessment will be done via linear modeling for primary ^{129}Xe MRI endpoints (RDP, VDP, and BDP).

6.5 SAFETY ANALYSES

The safety analysis population will consist of all patients who received at least one dose of study drug during the 48-week open-label treatment period, with patients grouped according to treatment received (AZM + SOC or SOC).

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs (see Section 2.2).

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to the WHO toxicity grading scale. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 EXPLORATORY ANALYSIS OF PATIENT-REPORTED OUTCOME MEASURES

The PRO measures for this study are as follows:

- SCRQ-C change from baseline to Week 24 and Week 48
- Change in cough and sputum as measured by visual analogue score for dyspnea, cough sputum production (100 mm) from baseline to Week 24 and Week 48

6.7 EXPLORATORY BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies. Exploratory biomarker objectives and endpoints are described in Section 2.3.

Pharmacodynamic (PD) biomarkers (e.g., eosinophils, neutrophils, sputum mucins, and serum CRP) may be assessed to determine pharmacological activity of azithromycin in patients with and without chronic bronchitis. Data will be summarized by absolute levels of the biomarker, as well as absolute and relative changes from levels at randomization visit, for each treatment group. Additional PD analyses will be conducted as appropriate.

Additional exploratory analyses to understand molecular pathways will evaluate the relationship at baseline and longitudinally between biomarkers in sputum, blood (serum, plasma, and RNA from blood) or other biomarker endpoints.

6.8 INTERIM ANALYSES

An interim analysis may be performed to assess for changes in VDP and/or other ^{129}Xe MRI metrics relative to other clinical assessments, at the Sponsor's discretion.

Given the exploratory nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by the Sponsor's study team personnel.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

eCRF and paper patient reported questionnaires including SGRQ-C and mMRC are the primary data collection instruments and are treated as source data. All source data will be entered into the EDC system by site staff.

The Sponsor will provide support for data management of this study, including quality checking of the data in the EDC. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for

the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any collaborating site or location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

Genentech, a member of the Roche group, is the Sponsor of this study. A contract research organization (CRO) may provide clinical operations oversight, including, but not limited to, project management, site management, data quality support, safety reporting, and regulatory activities as specified in the study management plans. The Sponsor will

provide CRO oversight, develop the database and randomization scheme, and conduct statistical programming and analysis. EDC will be utilized for this study.

An IxRS will be used to assign patient numbers, randomize patients into the study through use of a dynamic hierarchical algorithm, and manage site drug supply.

An SMC will be used in this study to provide oversight of safety (see Section 5.1).

Samples for blood and urine chemistry including pregnancy tests will be analyzed at the local laboratory. Samples for PD biomarkers, tests will be sent to the Sponsor for analysis.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication

of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res 2010;11:122.

Albert R, Connett J, Bailey W, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365: 689–98.

American Thoracic Society (ATS) Statement. Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.

Baumert JH, Hecker KE, Hein M, et al. Effects of xenon anaesthesia on the circulatory response to hypoventilation. British J Anaesthesia. 2005;95:166–71.

Bestall JC, Paul EA, Garrod R. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54:581–6.

Bhatt XP, Soler X, Wang X, et al. Association between functional small airway disease and fev1 decline in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2016;194:178–84.

Borg G, Borg E. The Borg CR Scales® Folder. Hasselby, Sweden: Borg Perception; 2010.

Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD study): a population-based prevalence study. Lancet 2007;370:741–50.

Calzia E, Stahl W, Handschuh T, et al. Respiratory mechanics during xenon anesthesia in pigs: comparison with nitrous oxide. Anesthesiology 1999a;91:1378–86.

Celli BR1, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350:1005–12.

Cui Y, Luo L, Li C, et al. Long-term macrolide treatment for the prevention of acute exacerbations in COPD: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis 2018;13:3813–29.

Donaldson GC, Wedzicha JA. COPD exacerbations .1: Epidemiology. Thorax 2006;61:164–8.

Dransfield MT, Kunisaki KM, Strand MJ, et al. Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2017;195:324–30.

Driehuys B, Martinez-Jimenez S, Cleveland Z, et al. Safety and tolerability of hyperpolarized ^{129}Xe MR imaging in healthy volunteers and patients. Radiology 2012;262:279–89.

Ebner L, He M, Virgincar RS, et al. Hyperpolarized ^{129}Xenon magnetic resonance imaging to quantify regional ventilation differences in mild to moderate asthma. Invest Radiol 2017;52:120–7.

Ford ES, Murphy LB, Khavjou O, et al. Total and state-specific medical and absenteeism costs of COPD among adults aged 18 years in the United States for 2010 and projections through 2020. Chest 2015;147:31–45.

[GOLD 2019] Global Strategy for the Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease: 2019 [cited: 15 February 2020]. Available from: http://goldcopd.org.

Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J 2017;49:1600016.

Graham BL, Steenbruggen L, Miller MR, et al. Standardization of spirometry 2019 update an official american thoracic society and european respiratory society technical statement. Am J Respir Crit Care Med 2019;200:e70–e88.

Han MK, Quiberra PM, Carretta EE, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. Lancet Respir Med 2017;5(Suppl 8):619–26.

Han MK, Tayob N, Murray S, et al. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. Am J Respir Crit Care Med 2014;189:1503–8.

Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. Am J Respir Crtl Care Med 1999;159:179–87.

Joseph G. Joseph G. Mammarappallil4, EM, et al. Identification of gas exchange phenotypes using hyperpolarized 129Xe MRI in patients with chronic obstructive pulmonary disease (COPD). Am J Respir Crit Care Med 2019;199:A1122.

Kirby M, Pike D, Coxson HO, et al. Hyperpolarized (3)He ventilation defects used to predict pulmonary exacerbations in mild to moderate chronic obstructive pulmonary disease. Radiology 2014;273:887–96.

Kirby M, Svenningsen S, Owrangi A, et al. Hyperpolarized 3He and 129Xe MR imaging in healthy volunteers and patients with chronic obstructive pulmonary disease. Radiology 2012;265:600–10.

Lowe KE, Regan EA, Anzueto A, et al. COPDGene® 2019: Redefining the diagnosis of chronic obstructive pulmonary disease. Chronic Obstr Pulm Dis 2019;6:384–99.

Martin TN, Rahman N, Nickol AH, et al. Chronic obstructive pulmonary disease: lobar analysis with hyperpolarized 129Xe MR imaging. Radiology: 2017;282:857–68.

Meguro M., Barley EA, Spencer S, et al. Development and validation of an improved COPD-specific version of the St. George Respiratory Questionnaire. Chest 2007;132:456–63.

NICE Guideline Updates Team (UK) (editors). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. London: National Institute for Health and Care Excellence (UK); 2018 Dec.

Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J 2003;22:1026–41.

Qing K, Tustison NJ, Mugler JP III, et al. Probing changes in lung physiology in COPD using CT, perfusion MRI, and hyperpolarized Xenon-129 MRI. Acad Radiol 2019;26:326–34.

Qinga J, Mugler JP III, Altes TA, et al. Assessment of lung function in asthma and COPD using hyperpolarized ^{129}Xe chemical shift saturation recovery spectroscopy and dissolved-phase MRI. NMR Biomed 2014;27:1490–1501.

Ruppert, K, Qing K, Patrie JT, et al. Using hyperpolarized Xenon-129 MRI to quantify early-stage lung disease in smokers. Acad Radiol 2019;26:335–6.

Seemungal TA, Tom M A, Wilkinson MA, et al. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. Am J Respir Crit Care Med 2008;178:1139–47.

Simpson JL, Powell H, Baines KJ, et al. The effect of azithromycin in adults with stable neutrophilic COPD: a double blind randomised, placebo controlled trial. PlosOne 2014;9(8):e105609.

Smith L, Marshall H, Aldag I, et al. Longitudinal assessment of children with mild cystic fibrosis using hyperpolarized gas lung magnetic resonance imaging and lung clearance index. Am J Respir Crit Care Med 2018;197:397–400.

Stewart NJ, Horn FC, Norquay G, et al. reproducibility of quantitative indices of lung function and microstructure from ^{129}Xe chemical shift saturation recovery (cssr) mr spectroscopy. Magn Reson Med 2017;77(6):2107–13.

Svenningsen S, Kirby M, Starr D, et al. Hyperpolarized (3)He and (129)Xe MRI: differences in asthma before bronchodilation. J Magn Reson Imaging 2013;38(6):1521–30.

Taylor SP, Sellers E, Taylor BT. Azithromycin for the Prevention of COPD Exacerbations: The Good, Bad, and Ugly. Am J Med. 2015;128:1362.e1–6.

Vermeersch K, Gabrovska M, Aumann J, et al. Azithromycin during acute COPD exacerbations requiring hospitalization (BACE): a multicentre, randomized, double-blind, placebo-controlled trial. Am J Respir Crit Care Med 2019;200(7):857–68.

Weatherly ND, Stewart NJ, Chan HF, et al. Hyperpolarised xenon magnetic resonance spectroscopy for the longitudinal assessment of changes in gas diffusion in IPF. Thorax 2019;74:500–2.

World Health Organization. The Global Burden of Disease [resource on the Internet]. 2017 [cited: 12 December 2017]. Available from: http://www.who.int/respiratory/copd/en/.

Zhang P, Ohara A, Mashimo T, et al. Pulmonary resistance in dogs: a comparison with nitrous oxide. Can J Anaesth 1995;42:547–53.

Appendix 1
Schedule of Activities

	Screening	Treatment Period					End of Tx	Safety Follow-Up [a]	ET [b]	UV
Visit No.	1	2 [c]	3	4	5	6 [d]	7	8 [e]		
Week (Window, days)	–28 to –1	0 (± 4)	6 (± 4)	12 (± 7)	24 (± 7)	36 (± 7)	48 (± 7)	52 (± 7)		
Informed consent [f]	x									
Randomization		x								
Demographic data [g]	x									
General medical history and baseline conditions [h]	x									
Smoking history	x									
Tobacco use	x	x	x	x	x	x	x		x	x
Vital signs [i]	x	x	x	x	x	x	x		x	x
Weight	x	x	x	x	x	x	x		x	x
Height	x									
Complete physical examination	x									
Limited physical examination [j]		x	x	x	x	x	x		x	x
Single ECG [k]	x	x			x		x		x	
HHIE-S [l]	x			x	*x*		x			
Pregnancy test [m]	x	x	x	x	x	x	x		x	
Annual COPD exacerbation rate [n]	x									
SGRQ-C [o]		x		x	x		x		x	x

Appendix 1: Schedule of Activities

	Screening	Treatment Period					End of Tx	Safety Follow-Up [a]	ET [b]	UV
Visit No.	1	2 [c]	3	4	5	6 [d]	7	8 [e]		
Week (Window, days)	–28 to –1	0 (± 4)	6 (± 4)	12 (± 7)	24 (± 7)	36 (± 7)	48 (± 7)	52 (± 7)		
mMRC Dyspnea [p]	x	x	x	x	x		x		x	x
Hematology [q]	x	x	x	x	x	x	x		x	x
Chemistry [r]	x	x	x	x	x	x	x		x	x
Urinalysis [s]	x	x			x		x		x	x
Pre-bronchodilator spirometry [t]	x	x			x		x			
Post-bronchodilator spirometry	x	x	x	x	x		x		x	x
Forced oscillometry technique		x	x	x	x		x		x	x
DL_{CO}/KCO	x	x	x	x	x		x		x	x
^{129}Xe MRI session [u]		x	x	x	x		x		x	
X-ray [v]	x									x
HRCT [w]		x			(x)		x			
6-minute walk test [x]		x			x		x			
Serum for biomarkers		x		x	x		x		x	x
Plasma for biomarkers		x								
Sputum for biomarkers [y]		x		x	x		x			x
Blood for RNA analysis		x					x		x	
Blood for specific DNA SNP analysis (optional) [z]		x								

^{129}Xe MRI—Genentech, Inc.

Appendix 1: Schedule of Activities

	Screening	Treatment Period					End of Tx	Safety Follow-Up [a]	ET [b]	UV
Visit No.	1	2 [c]	3	4	5	6 [d]	7	8 [e]		
Week (Window, days)	–28 to –1	0 (± 4)	6 (± 4)	12 (± 7)	24 (± 7)	36 (± 7)	48 (± 7)	52 (± 7)		
Concomitant medications	x	x	x	x	x	x	x	x	x	x
AEx		x	x	x	x	x	x	x	x	x
Health care utilizations [aa]		x	x	x	x	x	x	x	x	x
Adverse events [bb]		x	x	x	x	x	x	x	x	x
Study drug Rx (3-month supply) [cc]		x		x	x	x				
Patient diary review [dd]			x	x	x	x	x			

6MWT = six-minute walking test; AEx = acute exacerbations; BORG CR10 Scale = Borg Category-Ratio 10 Scale®; COPD = chronic obstructive pulmonary disease; CT = computed tomography; DL_{CO} = carbon monoxide diffusing capacity; ET = early termination; FEV_1 = forced expiratory volume; *HHIE-S = Hearing Handicap Inventory in the Elderly–Screening Questionnaire;* HRCT = high-resolution computed tomography; IRB = Institutional Review Board; KCO = carbon monoxide transfer coefficient; mMRC = Modified Medical Research Council; MRI = magnetic resonance imaging; PRO = patient-reported outcome; Rx = prescription; SGRQ-C = St. George's Respiratory Questionnaire—COPD; SNP = single nucleotide polymorphism; SOA = Schedule of Activities; *SOC = standard of care;* SpO_2 = oxygen saturation; Tx = treatment; UV = unscheduled visit.

[a] Safety follow-up will take place via telephone interview for adverse events, health care utilization, and change in medications.

[b] The ET visit applies to patients who discontinue study drug prematurely.

[c] All baseline assessments at Visit 2 must be completed prior to the first dose of study drug (azithromycin). Azithromycin will only be dispensed to patients randomized to study drug in Cohort A.

[d] Patients in Cohort B will be assessed by telephone call from site staff. Assessments limited to changes in concomitant medications, AEx, health care utilizations, and adverse events occurring between Week 24 and Week 36.

[e] Limited to patients in Cohort A only.

[f] Written informed consent for participation in the study must be obtained before performing any study-specific tests or evaluations.

[g] Demographic data will include age (date of birth), sex, and self-reported race/ethnicity.

[h] Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, medication allergies, smoking history, and use of alcohol and drugs of abuse, will be recorded at screening. In particular, sites should record whether the patient has any history of anaphylaxis, cancer, cardiovascular disease, eosinophilic disease, inflammatory or autoimmune disease or surgeries with metal implants. Any history of smoking should be entered on the Tobacco Use History eCRF.

[i] Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position (resting for at least 5 minutes), temperature, and oxygen saturation.

[j] Limited physical examination includes head, ears, eyes, nose, throat, cardiovascular, respiratory, and dermatologic examinations.

[k] ECGs must be performed prior to any scheduled spirometry measurements, vital sign measurements, or blood draws.

[l] Required hearing *questionnaires* are limited to Cohort A.

[m] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[n] Annual COPD exacerbation rate is determined by a continuous 12-month period within the 24 months prior to screening where a COPD exacerbation is defined by symptomatic worsening of COPD requiring use of systemic corticosteroids and/or antibiotics for at least 3 days, a single depot injectable dose of corticosteroids will be considered.

[o] PRO questionnaires must be administered prior to the completion of other non-PRO assessments and before the patient receives any disease status information or study drug during that visit.

[p] mMRC (Appendix 3) must be administered prior to the completion of other non-PRO assessments and before the patient receives any disease status information or study drug during that visit.

[q] Includes hemoglobin, hematocrit, platelet count, WBC count, RBC count, and differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells).

[r] Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, and uric acid.

[s] If clinically indicated as determined by the investigator. Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (which may include sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[t] Pre-bronchodilator spirometry. Except for Visit 1, patients must withhold inhaled bronchodilator use within the specified window (see Section 4.5.9). The pre-bronchodilator spirometry measurements should not be performed during the screening visit (Visit 1) if the patient did not withhold bronchodilator medications during the specified time period prior to the screening assessment. For safety reasons, spirometry may be omitted if the patient is having an acute COPD exacerbation event at the time of the scheduled visit.

[u] *Sites should ensure that the patient receives a bronchodilator (either daily SOC medication or short-acting bronchodilator on visits where pre-bronchodilator spirometry is performed) prior to performing the ^{129}Xe MRI assessment.*

[v] A chest X-ray must be performed or scheduled at Visit 1 unless a chest X-ray or CT scan has been obtained within 6 months prior to Visit 1 and is available for review by the investigator. The X-ray may be performed locally but must be reviewed by the investigator prior to randomization at Visit 2. If a chest X-ray (or CT scan) is not available in the 6 months preceding Visit 1 or a chest X-ray cannot be completed during screening, the patient will not be eligible for the study.

[w] An HRCT should be performed at baseline (Visit 2) unless an acceptable set of inspiratory and expiratory scans have been performed within 6 months of screening per imaging manual guidelines. Follow-up sets of scans at Weeks 24 and 48 will be performed as indicated in the SOA if acceptable by site IRB; if determined to be unacceptable by site IRB, a single follow-up set of scans at Week 48 is acceptable.

[x] For safety reasons, the 6MWT may be omitted if the patient is unable or unwilling to perform the test. Heart rate, SpO_2, and the Borg CR10 Scale (Appendix 6) will be recorded immediately before and immediately after the procedure.

[y] Sputum induction will be performed per the study procedure manual. Subjects will be pre-medicated with a bronchodilator and then inhale an aerosolized saline solution delivered by an ultrasonic nebulizer to facilitate forcible coughs and sputum expectoration. Peak expiratory flow and FEV_1 will be monitored during sputum induction for safety. Induced sputum will be processed immediately according to the lab manual at the clinical sites to obtain raw and sputolysin treated sputum samples, as well as sputum cell pellets prepared in a special RNA-protecting solution.

[z] Blood samples for DNA are optional and should only be obtained from patients who provide written informed consent to participate.

[aa] The investigator will ask directed questions to assess whether the patient has required any urgent COPD-related health care since the last study visit. Urgent COPD-related health care utilization includes any hospitalizations, emergency department visits, and acute care visits (i.e., unplanned clinic visits). See Section 4.5.14 for additional details.

[bb] All adverse events, including serious adverse events and adverse events of special interest. *Patients in Cohort A randomized to azithromycin will additionally be queried on any onset or worsening hearing loss or hearing disturbances.*

[cc] 3-month drug supply limited to Cohort A. Completion of all Visit 2 baseline assessments required to be completed prior to dispensing first dose of azithromycin.

[dd] Patients will be instructed to complete a diary that will be reviewed at study visits.

Appendix 2
St. George's Respiratory Questionnaire for COPD Patients

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
for COPD patients

(SGRQ-C)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life.
We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

ID: _____

Date: _____/_____/_____ (dd/mm/yy)

Before completing the rest of the questionnaire:

Please select one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

Version: 1st Sept 2005

P.W. Jones, PhD FRCP
Professor of Respiratory Medicine,
St. George's University of London,
Cranmer Terrace
London SW17 ORE, UK.

Tel. +44 (0) 20 8725 5371
Fax +44 (0) 20 8725 5955

Appendix 2: St George's Respiratory Questionnaire for COPD Patients

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have.

Please select **ONE** box for each question:

Question 1. I cough:

- most days a week ☐ a
- several days a week ☐ b
- only with chest infections ☐ c
- not at all ☐ d

Question 2. I bring up phlegm (sputum):

- most days a week ☐ a
- several days a week ☐ b
- only with chest infections ☐ c
- not at all ☐ d

Question 3. I have shortness of breath:

- most days a week ☐ a
- several days a week ☐ b
- not at all ☐ c

Question 4. I have attacks of wheezing:

- most days a week ☐ a
- several days a week ☐ b
- a few days a month ☐ c
- only with chest infections ☐ d
- not at all ☐ e

UK/ English version COPD 2/7

continued...

SGRQ-C - United Kingdom/English
SGRQ-C_AU1.0_eng-GBorl.doc

Question 5. How many attacks of chest trouble did you have during the last year?

3 or more attacks	☐ a
1 or 2 attacks	☐ b
none	☐ c

Question 6. How often do you have good days (with little chest trouble)?

no good days	☐ a
a few good days	☐ b
most days are good	☐ c
every day is good	☐ d

Question 7. If you have a wheeze, is it worse in the morning?

no	☐
yes	☐

St. George's Respiratory Questionnaire
PART 2

8. ***How would you describe your chest condition?***

Please select ***ONE***:

Causes me a lot of problems or is the most important problem I have	☐ a
Causes me a few problems	☐ b
Causes no problem	☐ c

9. ***Questions about what activities usually make you feel breathless.***

For each statement please select ***the box*** that applies to you these days:

	True	False	
Getting washed or dressed	☐	☐	a
Walking around the home	☐	☐	b
Walking outside on the level	☐	☐	c
Walking up a flight of stairs	☐	☐	d
Walking up hills	☐	☐	e

St. George's Respiratory Questionnaire
PART 2

10. ***Some more questions about your cough and breathlessness.***

For each statement please select ***the box*** that applies to you these days:

	True	False	
My cough hurts	☐	☐	a
My cough makes me tired	☐	☐	b
I am breathless when I talk	☐	☐	c
I am breathless when I bend over	☐	☐	d
My cough or breathing disturbs my sleep	☐	☐	e
I get exhausted easily	☐	☐	f

11. ***Questions about other effects that your chest trouble may have on you.***

For each statement please select ***the box*** that applies to you these days:

	True	False	
My cough or breathing is embarrassing in public	☐	☐	a
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐	b
I get afraid or panic when I cannot get my breath	☐	☐	c
I feel that I am not in control of my chest problem	☐	☐	d
I have become frail or an invalid because of my chest	☐	☐	e
Exercise is not safe for me	☐	☐	f
Everything seems too much of an effort	☐	☐	g

St. George's Respiratory Questionnaire
PART 2

12. ***These are questions about how your activities might be affected by your breathing.***

For each statement please select ***the box*** that applies to you because of your breathing:

	True	False	
I take a long time to get washed or dressed	☐	☐	a
I cannot take a bath or shower, or I take a long time	☐	☐	b
I walk slower than other people, or I stop for rests	☐	☐	c
Jobs such as housework take a long time, or I have to stop for rests	☐	☐	d
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐	e
If I hurry or walk fast, I have to stop or slow down	☐	☐	f
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐	g
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐	h

13. ***We would like to know how your chest trouble <u>usually</u> affects your daily life.***

For each statement please select ***the box*** that applies to you because of your breathing:

	True	False	
I cannot play sports or games	☐	☐	a
I cannot go out for entertainment or recreation	☐	☐	b
I cannot go out of the house to do the shopping	☐	☐	c
I cannot do housework	☐	☐	d
I cannot move far from my bed or chair	☐	☐	e

St. George's Respiratory Questionnaire

14. ***How does your chest trouble affect you?***

Please select ***ONE***:

- It does not stop me doing anything I would like to do ..... ☐ a
- It stops me doing one or two things I would like to do..... ☐ b
- It stops me doing most of the things I would like to do..... ☐ c
- It stops me doing everything I would like to do..... ☐ d

Thank you for filling in this questionnaire.

Before you finish, would you please check to see that you have answered all the questions.

Appendix 3
Modified Medical Research Council Dyspnea Scale

Modified Medical Research Council Dyspnea Scale

Please select the statement that best describes you with respect to your COPD.

Grade

0 _ "I only get breathless with strenuous exercise."

1 _ "I get short of breath when hurrying on the level or up a slight hill."

2 _ "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level."

3 _ "I stop for breath after walking 100 yards or after a few minutes on the level."

4 _ "I am too breathless to leave the house."

Grade ..... ☐

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Appendix 4
Six-Minute Walk Test

The Six-Minute Walk Test (6MWT) will be conducted as per the study 6MWT Procedural Manual that is based on the 2002 American Thoracic Society (ATS) guidelines for the Six-Minute Walk Test (ATS Statement 2002).

Absolute contraindications to the 6MWT include unstable angina or myocardial infarction during the previous month.

Relative contraindications to participation in the 6MWT include:

- Resting heart rate $>$ 120 per minute
- Systolic blood pressure $>$ 180 mmHg
- Diastolic blood pressure $>$ 100 mmHg

Supplemental oxygen flow rate will be recorded before every 6MWT. Heart rate, oxygen saturation (SpO_2), and the Borg Category Ratio 10 (CR10) Scale® will be recorded immediately before and after the procedure.

6MWT procedures will occur with the patient receiving the O_2 flow rate as determined by the screening oxygen titration protocol. Patients that are prescribed a different oxygen requirement either at rest or with exercise should be placed on the flow rate determined during the titration protocol. SpO_2 should be measured before all study-related 6MWTs after the patient has been at rest for 5 minutes while receiving their titrated O_2 requirement. Any patient who has an SpO_2 of $<$ 85% after 5 minutes should not undergo the procedure during that visit.

SpO_2 should not be monitored during the 6MWT procedure. Patients should immediately stop the 6MWT procedure if any of the following occur:

- Chest pain
- Light headedness
- Intolerable dyspnea
- Leg cramps
- Staggering
- Diaphoresis
- Pale or ashen appearance
- Mental confusion or headache

Appendix 5
WHO Toxicity Grading Scale

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
HEMATOLOGY				
Hemoglobin	9.5–10.5 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	< 6.5 g/dL
Absolute neutrophil count	1000–1500/mm^3	750–999/mm^3	500–749/mm^3	<500/mm^3
Platelets	75,000–99,000/mm^3	50,000–74,999/mm^3	20,000–49,000/mm^3	<20,000/mm^3
PT	1.01–1.25 × ULN	1.26–1.5 × ULN	1.51–3.0 × ULN	>3 × ULN
aPPT	1.01–1.66 × ULN	1.67–2.33 × ULN	2.34–3 × ULN	> 3 × ULN
Fibrinogen	0.75–0.99 × LLN	0.50–0.74 × LLN	0.25–0.49 × LLN	< 0.25 × LLN
Fibrin split product	20–40 μg/mL	41–50 μg/mL	51–60 μg/mL	> 60 μg/mL
Methemoglobin	5%–9.9%	10.0%–14.9%	15.0%–19.9%	> 20%
LIVER ENZYMES				
AST (SGOT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
ALT (SGPT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
GGT	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
ALP	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Amylase	1.1–1.5 × ULN	1.6–2.0 × ULN	2.1–5.0 × ULN	> 5.1 × ULN
CHEMISTRIES				
Hyponatremia	130–135 mEq/L	123–129 mEq/L	116–122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146–150 mEq/L	151–157 mEq/L	158–165 mEq/L	> 165 mEq/L or mental status changes or seizures
Hypokalemia	3.0–3.4 mEq/L	2.5–2.9 mEq/L	2.0–2.4 mEq/L or intensive replacement Rx required or hospitalization required	< 2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6–6.0 mEq/L	6.1–6.5 mEq/L	6.6–7.0 mEq/L	> 7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55–64 mg/dL	40–54 mg/dL	30–39 mg/dL	<30 mg/dL or mental status changes or coma
Hyperglycemia (note if fasting)			251–500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4–7.8 mg/dL	7.7–7.0 mg/dL	6.9–6.1 mg/dL	< 6.1 mg/dL or life-threatening arrhythmia or tetany

Appendix 5: WHO Toxicity Grading Scale

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Hypercalcemia (correct for albumin)	10.6–11.5 mg/dL	11.6–12.5 mg/dL	12.6–13.5 mg/dL	> 13.5 mg/dL life-threatening arrhythmia
Hypomagnesemia	1.4–1.2 mEq/L	1.1–0.9 mEq/L	0.8–0.6 mEq/L	< 0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0–2.4 mg/dL	1.5 –1.9 mg/dL or replacement Rx required	1.0 –1.4 mg/dL intensive Rx or hospitalization required	< 1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	1.1–1.5 × ULN	1.6–2.5 × ULN	2.6–5 × ULN	> 5 × ULN
BUN	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	> 10 × ULN
Creatinine	1.1 × 1.5 × ULN	1.6–3.0 × ULN	3.1–6 × ULN	> 6 × ULN or required dialysis
URINALYSIS				
Proteinuria	1+ or < 0.3% or <3 g/L or 200 mg–1 g loss/day	2 –3 + or 0.3%–1.0% or 3–10 g/L or 1–2 g loss/day	4+ or > 1.0% or > 10 g/L or 2–3.5 g loss/day	nephrotic syndrome or > 3.5 g loss/day
Hematuria	Microscopic only	Gross, no clots	Gross+ clots	Obstructive or required transfusion
CARDIAC DYSFUNCTION				
Cardiac rhythm		Asymptomatic, transient signs, no Rx required	Recurrent/persistent; no Rx required	Requires treatment
Hypertension	Transient inc. > 20 mm; no Rx	Recurrent, chronic, > 20 mm, Rx required	Requires acute Rx; no hospitalization	Requires hospitalization
Hypotension	Transient orthostatic hypotension, no Rx	Symptoms correctable with oral fluids Rx	Requires IV fluids; no hospitalization required	Requires hospitalization
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no Rx	Symptomatic effusion; pain; EKG changes	Tamponade; pericardiocentesis or surgery required

Appendix 5: WHO Toxicity Grading Scale

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Hemorrhage, blood loss	Microscopic/occult	Mild, no transfusion	Gross blood loss; 1–2 units transfused	Massive blood loss; > 3 units transfused
RESPIRATORY				
Cough	Transient; no Rx	Treatment associated cough; local Rx	Uncontrolled	
Bronchospasm, acute	Transient; no Rx < 80%–70% FEV_1 (or peak flow)	Requires Rx normalizes with bronchodilator; FEV_1 50%–70% (or peak flow)	No normalization with bronchodilator; FEV_1 25%–50% (or peak flow retractions)	Cyanosis: FEV_1 < 25% (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	Mild discomfort; no limits on activity	Some limits on eating/drinking	Eating/talking very limited	Requires IV fluids
Nausea	Mild discomfort; maintains reasonable intake	Moderate discomfort; intake decreased significantly; some activity limited	Severe discomfort; no significant intake; activities limited	Minimal fluid intake
Vomiting	Transient emesis	Occasional/moderate vomiting	Orthostatic hypotension or IV fluids required	Hypotensive shock or hospitalization required for IV fluid therapy
Constipation	Mild	Moderate	Severe	Distensions with vomiting
Diarrhea	Transient 3–4 loose stools/day	5–7 loose stools/day	Orthostatic hypotension or > 7 loose stools/day or required IV fluids	Hypotensive shock or hospitalization for IV fluid therapy required
NEURO & NEUROMUSCULAR				
Neuro–cerebellar	Slight incoordination dysdiadochokinesis	Intention tremor, dysmetria, slurred speech; nystagmus	Locomotor ataxia	Incapacitated
Mood	Mild anxiety or depression	Moderate anxiety or depression and therapy required	Severe anxiety or depression or mania; needs assistance	Acute psychosis; incapacitated, requires hospitalization

Appendix 5: WHO Toxicity Grading Scale

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Neuro control	Mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	Moderate confusion/agitation some limitation of ADL; minimal Rx	Severe confusion/agitation needs assistance for ADL; therapy required	Toxic psychosis; hospitalization
Muscle strength	Subjective weakness; no objective symptoms/signs	Mild objective signs/symptoms; no decrease in function	Objective weakness function limited	Paralysis
OTHER PARAMETERS				
Fever: oral, > 12 hours	37.7°C –38.5°C or 100.0°F –101.5°F	38.6°C –39.5°C or 101.6°F –102.9°F	39.6°C –40.5°C or 103°F –105°F	> 40°C or > 105°F
Headache	Mild, no Rx therapy	Transient, moderate; Rx required	Severe; responds to initial narcotic therapy	Intractable; required repeated narcotic therapy
Fatigue	No decrease in ADL	Normal activity decreased 25%–50%	Normal activity decreased > 50% can't work	Unable to care for self
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema	Anaphylaxis
Local reaction	Tenderness or erythema	Induration < 10 cm or phlebitis or inflammation	Induration > 10 cm or ulceration	Necrosis
Mucocutaneous	Erythema; pruritus	Diffuse, maculopapular rash, dry desquamation	Vesiculation, moist desquamation, or ulceration	Exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery

ADL = activities of daily living; FEV_1 = forced expiratory volume in 1 second; LLN = lower limit of normal; Rx = treatment; ULN = upper limit of normal.

Appendix 6
Borg Category Ratio 10 Scale®

Instruction. Use this rating scale to report how strong your perception is. It can be exertion, pain or something else. First look at the verbal expressions. Start with them and then the numbers. Of these ten (10) or "Extremely strong", "Maximal" is a very important intensity level. This is the most intense perception or feeling you have ever had.

If your experience or feeling is "Very weak", you should say "1", if it is "Moderate", say "3". Note that "Moderate" is "3" and thus weaker than "Medium", "Mean" or "Middle". If the experience is "Strong" or "Heavy" (it feels "Difficult") say "5". Note that "Strong" is about half of "Maximal". If your feeling is "Very strong", choose a number from 6 to 8. If your perception or feeling is stronger than "10", - "Extremely strong", "Maximal" – you can use a larger number, e.g. 12 or still higher (that's why "Absolute maximum" is marked with a dot "•").

It's very important that you report what you actually experience or feel, not what you think you should report. Be as spontaneous and honest as possible and try to avoid under- or overestimating. Look at the verbal descriptors and then choose a number.

When rating exertion give a number that corresponds to how hard and strenuous you perceive the work to be. The perception of exertion is mainly felt as strain and fatigue in your muscles and as breathlessness or any aches.

0 "Nothing at all", means that you don't feel any exertion whatsoever, no muscle fatigue, no breathlessness or difficulties breathing.

1 "Very weak" means a very light exertion. As taking a shorter walk at your own pace.

3 "Moderate" is somewhat but not especially hard. It feels good and not difficult to go on.

5 "Strong". The work is hard and tiring, but continuing isn't terribly difficult. The effort and exertion is about half as intense as "Maximal".

7 "Very strong" is quite strenuous. You can still go on, but you really have to push yourself and you are very tired.

10 "Extremely strong – Maximal" is an extremely strenuous level. For most people this is the most strenuous exertion they have ever experienced previously in their lives.

● Is "Absolute maximum" for example "12" or even more.

Any questions?

0	Nothing at all	
0.3		
0.5	Extremely weak	Just noticeable
0.7		
1	Very weak	
1.5		
2	Weak	Light
2.5		
3	Moderate	
4		
5	Strong	Heavy
6		
7	Very strong	
8		
9		
10	Extremely strong	"Maximal"
11		
✦		
●	Absolute maximum	Highest possible

Borg CR10 Scale®
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English

Appendix 7
Hearing Handicap Inventory in the Elderly–Screening Questionnaire

Hearing Handicap Inventory in the Elderly – Screening Questionnaire*

Instructions: Answer Yes, No, or Sometimes for each question. Do not skip a question if you avoid a situation because of a hearing problem. If you use a hearing aid, please answer according to the way you hear with the aid.

1. Does a hearing problem cause you to feel embarrassed when you meet new people?
2. Does a hearing problem cause you to feel frustrated when talking to members of your family?
3. Do you have difficulty hearing when someone speaks in a whisper?
4. Do you feel handicapped by a hearing problem?
5. Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbors?
6. Does a hearing problem cause you to attend religious services less often than you would like?
7. Does a hearing problem cause you to have arguments with family members?
8. Does a hearing problem cause you difficulty when listening to TV or radio?
9. Do you feel that any difficulty with your hearing limits or hampers your personal or social life?
10. Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?

Scoring: No = 0; Sometimes = 2; Yes = 4.

Interpretation of Total Score:
0-8 = no handicap; 10-24 = mild to moderate handicap; 26-40 = severe handicap.

** Adapted from: Ventry I, Weinstein B. Identification of elderly people with hearing problems. ASHA. 1983; 25:37-42.*

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