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QBW251

Clinical Trial Protocol CQBW251B2202

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A randomized, subjects and investigator blinded, placebo controlled parallel group study to assess the mode of action of QBW251 in patients with Chronic Obstructive Pulmonary Disease (COPD)

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

AE	Adverse Event
ALP	ALkaline Phosphatase
ALT	ALanine aminoTransferase
ANCOVA	ANalysis of COVAriance
AST	ASpartate aminoTransferase
ATS	American Thoracic Society
AUC	Area Under the plasma concentration-time Curve
AUC0-24h	Area Under the plasma concentration Curve over 24 hours
b.i.d.	bis in die (twice a day)
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CASA-Q	Cough and Sputum Assessment Questionnaire
CAT	COPD Assessment Test
CD-ROM	Compact Disc – Read Only Memory
CF	Cystic Fibrosis
CFR	Code of Federal Regulation
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CFU	Colony Forming Unit
CK	Creatinine Kinase
Cmax	Concentration Maximum
Cmin	Concentration Minimum
CMO&PS	Chief Medical Office & Patient Safety
CO	Country Organization
CO_2	Carbon dioxide
COA	Clinical Outcome Assessments
COPD	Chronic Obstructive Pulmonary Disease
COUI	Cough Impact domain
COUS	Cough Symptoms domain
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactiv Protein
CSR	Clinical study report
CV	Coefficient of Variation
CYP1A2	Cytochrome P450 1A2 enzyme
CYP2B6	Cytochrome P450 2B6 enzyme
CYP3A4	Cytochrome P450 3A4 enzyme
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DNA	Desoxyribo-Nucleic Acid

DRF	Dose Range Finding
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
EDD	Expected Data of Delivery
EMA	European Medicines Agency
EQ-5D-3L	Euro Quality of life - 5 Dimensions - 3 Levels
ERS	European Respiratory Society
eSAE	Electronic Serious Adverse Event
EXACT-PRO	EXAcerbations of COPD Tool - Patient Reported Outcome
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GOLD	Global Initiative for Chronic Obstructive Lung Disease
H	hour
HCRU	Health Care Resource Utilization
HRCT	High Resolution Computed Tomography
hs-CRP	high sensitive-C Reactiv Protein
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled CorticoSteroid
IEC	Independent Ethics Committee
IN	Investigator Notification
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra-Uterine Device
IUS	Intra-Uterine System
LABA	Long-Acting Beta-2 Agonist
LAMA	Long Acting Muscarinic receptor Antogonist
LDH	Lactate Dehydrogenase
LFT	Liver function test
LLOQ	Lower Limit Of Quantification
MAR	Missing At Random
MedDRA	Medical dictionary for Regulatory Activities

Mg	milligram(s)
mL	milliliter(s)
MMRM	Mixed-effect linear Model for Repeated Measures
MoA	Mode of Action
NDA	New Drug Application
NYHA	New York Heart Association
OAT3	Organic Anion Transporter 3
OATP1B1	Organic Anion transporter 1B1
OATP1B3	Organic Anion Transporter 1B3
o.d.	Once per day
p.o.	per os
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcomes
PT	Prothrombin Time
PT/INR	Prothrombin Time / International Normalized Ratio
QMS	Quality Management System
QTC	QT interval Corrected
QTcF	QT interval corrected by Fridericia's formula
RBC	Red Blood Cell(s)
SABA	Short Acting Beta-2 receptor Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGRQ	Saint George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SoC	Standard of Care
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
t.i.d	Three times per day
Tmax	Time to reach maximum (peak) plasma concentration following drug administration
UGT	UDP-Glucuronosyltransferase
UGT1A1	Uridine Diphosphate-Glucuronosyltransferase 1A1
UGT2B7	Uridine Diphosphate-Glucuronosyltransferase 2B7
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification
VAS	Visual Analogue Scale
WBC	White Blood Cell(s)
WHO	World Health Organization

WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug/treatment	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Patient	An individual with the condition of interest
Period	The subdivisions of the trial design (e.g.: Screening, Treatment, Follow-Up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.
Personal data	Subject information collected by the investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Start of the study	The start of the study is defined as the signature of the informed consent by the first subject.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

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Protocol summary

Protocol number	CQBW251B2202
Full Title	A randomized, subjects and investigator blinded, placebo controlled parallel group study to assess the mode of action of QBW251 in subjects with Chronic Obstructive Pulmonary Disease (COPD).
Brief title	Study of mode of action of QBW251 in subjects with COPD
Sponsor and Clinical Phase	Novartis , Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	**Purpose** The purpose of this study is to determine whether potentiating the cystic fibrosis transmembrane conductance regulator (CFTR) with QBW251 in adult subjects with COPD will be efficacious with regards to reducing lung and systemic inflammation and bacterial colonization as potential drivers of airway obstruction, airway destruction, remodeling and exacerbations. This will, provide supportive data to investigate the safety of QBW251, the relationship of COPD phenotype and QBW251 response in small airway structure, function, mucus load and spirometry indices as well as in improvement of overall COPD symptoms and quality of life after treatment with QBW251. **Rationale** The study will assess QBW251 as an add-on to background therapy, in adult subjects with COPD associated with chronic bronchitis and history of exacerbations in the 12 months prior to the study. Chronic bronchitis, history of frequent exacerbations are expected to be enrichment factors for subjects who may particularly benefit from improved activity (potentiation) of the CFTR channel. A fibrinogen level of ≥320 mg/dL as well as a sputum sample positive for at least one potentially pathogenic organism at screening are further population enrichment factors.
Primary Objective	**The primary objective** of this study is to assess the effect of QBW251 compared to placebo after 12 weeks of treatment on fibrinogen plasma concentration by testing the hypothesis: (i) there is no reduction in fibrinogen from baseline (H0) and (ii) there is a reduction in fibrinogen from baseline (H1).
Secondary Objectives	**Objective 1**: To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on sputum bacterial load by measuring the total bacteria load of colony forming units (CFU/mL) of potentially pathogenic microorganisms in sputum. **Objective 2**: To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on airway structure and function by measuring with HRCT airway wall and lumen parameters along with extent of global and regional air trapping. **Objective 3:** To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on spirometry by measuring trough FEV1, FVC and FEV1/FVC.

	Objective 4: To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on health status measured by EQ-5D-3L questionnaire. **Objective 5**: To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on clinical symptoms, cough and sputum clinical symptoms with CASA Questionnaire. **Objective 6**: To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on COPD subjects symptom burden changes with CAT questionnaire. **Objective 7**: To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on COPD exacerbations by measuring: • Time to first COPD exacerbation • Proportion of subjects with exacerbation • Annualized rate of exacerbations as defined by EXACT-PRO questionnaire **Objective 8**: To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on changes in health-related quality of life with SGRQ. **Objective 9**: To assess the safety and tolerability of QBW251 in subjects with COPD evaluating ECG intervals, vital signs, standard clinical laboratory and adverse events. **Objective 10**: To assess QBW251 pharmacokinetics (PK) in subjects with COPD, on Day 1, Day 28, Day 56 and Day 84 (trough concentration at pre-dose and Cmax post dose) as well as Cmax and AUC on Day 1 and Day 28 in a subset of subjects.
Study design	This is a randomized, subject and investigator blinded, parallel-group, placebo controlled study investigating the mode of action (MoA) and preliminary efficacy and safety of QBW251 administered orally twice daily (b.i.d.) for 12 weeks in subjects with moderate to severe COPD (GOLD 2-3). Approximately 100 subjects will be randomized in a 1:1 ratio to receive either QBW251 or placebo treatment. Based on the assumption of a 15% drop-out rate (% drop out based on completed proof-of-concept COPD study CQBW251X2201), it is expected to have approximately 84 subjects to complete the study. Commercially Confidential Information The study consists of the following periods: Screening, Baseline / Day 1, Treatment, and End of the Study followed by an additional post-treatment safety phone call. The total duration for each subject in the study is up to approximately 19 weeks.

Population	The study population will consist of approximately 100 male and female subjects, aged 40 years old and above, with moderate to severe COPD (GOLD 2 to 3) with features of chronic bronchitis, a smoking history of at least 10 pack / years, and at least two moderate or one severe exacerbation(s)since January 2019.. All subjects must have a plasma fibrinogen level of ≥ 320 mg/dL, a CAT score of at least 10 and have been on LAMA/LABA or LABA/ICS or LABA/LAMA/ICS therapy at stable dose for at least 3 months prior study start. COPD subjects are allowed to stay on macrolides as background therapy if they have bronchiectasis as a secondary diagnosis and if they have been treated with them for at least 3 months at stable dose before study start. In addition, subjects' sputum must be colonized with at least one potentially pathogenic bacteria).
Key Inclusion criteria	• Male and female adults aged ≥40 years at screening. • Subjects with stable COPD, stages GOLD 2-3, according to the current GOLD strategy (GOLD 2019) at screening. • Subjects with a post-bronchodilator FEV1/FVC < 0.70 at screening. • Subjects with airflow limitation indicated by a post-bronchodilator FEV1 ≥ 30% and FEV1 < 80% of the predicted normal at Screening who must have had at least 2 documented moderate or at least 1 documented severe exacerbation(s) between January 2019 and study screening. • Subjects with sputum positive for at least one strain of potentially pathogenic microorganism at screening (H influenzae, H parainfluenzae, P aeruginosa, S pneumoniae, S aureus, Moraxella catarrhalis, Enterobacteriaceae, Stenotrophomonas maltophilia, Burkholderia species, and Achromobacter species or any potential bacteria measured by dilution/outgrowth. Any organism that is to be included and that is not included in the list of the protocol defined pathogens should be discussed case by case between the Principal Investigator and Novartis Medical Expert) • Subjects who have been treated with a combination of LABA/LAMA or LABA/ICS or LABA/LAMA/ICS at a stable dose for the last 3 months prior to screening. COPD subjects are allowed to stay on macrolides as background therapy if they have bronchiectasis as a secondary diagnosis and if they are treated with them at a stable dose 3 months before screening. • Subjects with plasma fibrinogen level ≥ 320 mg/dL at screening. • A COPD Assessment Test (CAT) score of at least 10 at screening. • Current or ex-smokers who have a smoking history of at least 10 pack years (e.g. 10 pack years = 1 pack/day x 10 years, or 0.5 pack/day x 20 years) at screening.

Key Exclusion criteria	• Subjects with a history of long-QT syndrome or whose QTcF interval at screening (Fridericia method) is prolonged (QTcF >450 ms in males, >460 ms in females). • Subjects who have clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction), neurological, endocrine, immunological, psychiatric, gastrointestinal, or hematological abnormalities, which could interfere with the assessment of the efficacy and safety of the study treatment, or subjects with uncontrolled Type II diabetes. • Subjects with a history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin. Subjects with a history of cancer and 5 years or more disease free survival time may be included in the study by agreement with Novartis Medical Expert on a case-by-case basis. • Subjects who develop a COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization during screening. Re-screening is permitted after a minimum of 2 weeks after the resolution of the COPD exacerbation (i.e. 2 weeks after the stop of SOC therapy for exacerbation). • Subjects who have had a respiratory tract infection within 4 weeks prior to screening. If a respiratory tract infection occurs during screening, subjects can be re-screened after a minimum of 2 weeks after resolution of the respiratory tract infection. • Subjects with history of asthma or any other clinically relevant lung diseases. • Subjects with suspected active pulmonary tuberculosis or currently being treatment for active pulmonary tuberculosis. • Subjects with pulmonary lobectomy, lung volume reduction surgery, bronchoscopic lung volume reductions, or lung transplantation. • Subjects participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the trial. Participation in a maintenance program is permitted. • Subjects who have not achieved an acceptable spirometry result at screening in accordance with American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria for acceptability and repeatability.
Study treatment	The study treatment includes: • Investigational drug: capsules of QBW251 dose of 300 mg b.i.d. • Matching placebo
Efficacy and Pharmacodynamic assessments	• Plasma fibrinogen level • Commercially Confidential Information • Bacterial load in sputum • Airway structure CCI evaluated by High Resolution Computed Tomography (HRCT) • Spirometry • CASA-Q, CAT, SGRQ, EQ-5D-3L and EXACT-PRO questionnaires

Pharmacokinetic assessments	Pharmocokinetic blood sampling will be collected : • In all subjects at pre and post-dose (+3hrs) on Day 1, Day 28, Day 56 and Day 84. • In a subset of subjects (approx 30 to 40 subjects), in addition, a serial sampling up to 8hrs post-dose on Day 1 and Day 28. Due to Covid and inability/difficulty of subjects remaining at a clinic for 8+ hours, this number may be reduced if the effects of the Covid pandemic on site and subject limitations prevents these timepoints • When a subject is experiencing a treatment-emergent SAE.
Key safety assessments	Key safety assessments consist in: • Adverse events monitoring • COPD exacerbations (EXACT-PRO questionnaire) • Physical examination Commercially Confidential Information • ECG • Clinical Outcome Assessments: CAT, CASA-Q, SGRQ, EQ-5D-3L
Other assessments	Commercially Confidential Information
Data analysis	**Primary endpoint** A mixed-effect linear model for repeated measures (MMRM) will be fitted to the changes from baseline in fibrinogen for all time points until Day 84 visit. The null hypothesis of no difference between QBW251 and placebo will be tested at a one-sided significance level of 10% against the alternative hypothesis that a difference exists between QBW251 and placebo in favor of QBW251. **Key secondary pharmacodynamic endpoint**: • Change from baseline in the logarithm of total number of colony forming units (CFU/mL) of potentially pathogenic microorganisms in spontaneous sputum after 12 weeks of treatment will be analyzed similar to the primary analysis. **Secondary pharmacodynamic and efficacy endpoints:** • Change from baseline in airway wall and lumen parameters along with extent of global and regional air trapping as measured by HRCT and change from baseline in FEV1, FVC and FEV1/FVC measured by spirometry after 12 weeks of treatment will be summarized. All spirometry parameters and HRCT parameters including regional and global air trapping changes will be summarized as well. The summaries will be calculated at all time points as specified in the assessment schedule (Table 8-1), and specifically at the primary time point of interest (Day 84) considering placebo as the reference treatment.

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Key words	COPD, fibrinogen, bacterial load, HRCT

1 Introduction

1.1 Background

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the lung and the third leading cause of death worldwide (GBD 2015 Mortality and Causes of Death 2016). Subjects suffer from persistent respiratory symptoms (dyspnea, cough, sputum production) and poorly reversible airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles/gases, in particular cigarette and biomass smoke exposure. Chronic airflow limitation is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) with most subjects having some characteristics of both.

Chronic bronchitis due to mucus hypersecretion with increased mucus viscosity and dysfunctional mucociliary clearance constitutes a key phenotype in subjects with COPD which is characterized by frequent pulmonary exacerbations, pulmonary and systemic inflammation, airway bacterial colonization, accelerated decline in lung function, impaired health-related quality of life, and possibly increased mortality (Kim et al 2012). However effective treatment options are limited for these subjects.

COPD exacerbations are frequent causes of hospital admissions and important events in the natural history of COPD that drive morbidity and mortality (Donaldson et al 2002). Airway inflammation is a key factor contributing to pulmonary exacerbation. While increased levels of inflammatory markers and cells reflecting systemic and pulmonary inflammation such as fibrinogen, tumor necrosis factor-alpha (TNF-α), interleukins (IL-8, IL-6), leukotriene B4, neutrophils, lymphocytes, and eosinophils are observed during exacerbations (Beasley et al 2012), inhibition of inflammation by inhaled corticosteroids or the PDE-4 inhibitor roflumilast is associated with a reduction of COPD-exacerbation rate.

Furthermore, respiratory infections caused by potentially pathogenic bacterial strains are thought to play a major role in the pathogenesis of both stable COPD and acute exacerbations. Detection rates of bacterial infection in samples collected during exacerbations are high, suggesting that newly acquired bacterial strains may precipitate pulmonary exacerbations (Beasley et al 2012). This is further supported by clinical data demonstrating an increase in rates of sputum colonization from 43-48.3% in stable subjects to 69.6-76% during exacerbations (Hurst et al 2005), and an increase in bacterial infections of protected brush specimens from 29% in stable subjects to 54% during exacerbations (Rosell et al 2005).

In addition to newly acquired bacterial infections, other potential mechanisms triggering exacerbations are an increase in the load of preexisting organisms present in stable COPD subjects as suggested by the data above, or a change in the composition of the airway microbiome. However, data are sparse and partly conflicting (Sethi and Murphy 2008) and further studies are needed to fully elucidate the role of the airway microbiome in the pathogenesis of COPD.

Nonetheless, the concurrence of bacterial colonization, airway inflammation and frequent exacerbation is evident and appears to be relevant in the pathogenesis of COPD in the majority of subjects presenting with a chronic bronchitic phenotype.

Current standard of care in the management of COPD consists of short and long acting bronchodilators (LABA/LAMA) +/- inhaled corticosteroids (ICS) indicated in subjects experiencing symptoms and exacerbations. The COPD guidelines (GOLD 2019) also consider macrolide antibiotics and roflumilast as additional add-on therapy to triple therapy (LABA+LAMA+ICS) in specific subgroups of subjects. However, 30 to 40% of subjects receiving even triple inhaled therapy continue to have moderate or severe (hospitalized) exacerbations (Vestbo et al 2017, Mullerova et al 2017). In addition, long-term macrolide antibiotics are complicated by microbial resistance (Pomares et al 2018) and roflumilast, a non-bronchodilator (PDE4 inhibitor) has poor tolerability (Chong et al 2017). Mucolytics have shown small and inconsistent benefits on exacerbation reduction and the efficacy of mucolytics on top of maximal inhaled treatment has yet to be clearly established (Wedzicha et al 2017). Thus despite currently available treatments almost 70% of subjects remain significantly limited by breathlessness (mMRC $\geq$ 2) and 40% experience $\geq$2 moderate or $\geq$1 severe exacerbation per year (Mullerova et al 2017). With the exception of antibiotics, none of the available treatments target bacterial colonization. Therefore additional novel therapies are urgently needed.

Research indicates that cigarette smoking induces an acquired state of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction in the respiratory tract (Cantin et al 2006; Sloane et al 2012; Dransfield et al 2013), even in the absence of CFTR mutations (i.e., in the wild type CFTR). This is hypothesized to contribute to the pathogenesis of COPD. Furthermore, current and former smokers with COPD have elevated sweat chloride levels compared with normal control subjects, indicating reduced CFTR activity (Raju et al 2013). CFTR dysfunction due to smoke exposure adversely affects mucociliary transport and is associated with symptoms of chronic bronchitis (Sloane et al 2012).

Therefore, the modulation of CFTR function may improve airway hydration, decrease mucus viscosity and thus enhance mucociliary clearance. CFTR also regulates airway surface liquid pH by bicarbonate secretion, which is important in the fight against pathogens (Pezzulo et al 2012). Hence, CFTR potentiation may be effective in subjects with COPD in reducing airway inflammation/infection and obstruction. A small 14 day pilot study with Ivacaftor in COPD subjects with chronic bronchitis showed improvement in sweat chloride as an indication of augmentation of CFTR function, improvement in symptoms, but did not show a difference compared to placebo in lung function, the authors argue the study was most probably too brief to detect definitive changes in lung function. (Solomon et al 2016).

QBW251 is a novel potentiator of the CFTR channel that was safe and well tolerated in the studies conducted in HVs and subjects up to now.

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In addition there was a significant reduction of fibrinogen in blood, a systemic inflammation marker, which is considered to be a prognostic biomarker for subjects at increased risk for all-cause mortality or COPD exacerbation (Mannino et al 2015) and approved as such by FDA.

This study is designed to provide evidence on the mode of action of QBW251 in COPD.
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1.2 Purpose

The purpose of this study is to determine whether potentiating the cystic fibrosis transmembrane conductance regulator (CFTR) with QBW251 in subjects with COPD will be efficacious with regards to reducing lung and systemic inflammation and bacterial colonization as potential drivers of airway obstruction, airway destruction, remodeling and exacerbations.

Furthermore, this study will provide supportive data to investigate the relationship of COPD phenotype and the response in small airway structure, function CCI and spirometry indices as well as in improvement of overall COPD symptoms and quality of life.
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2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on fibrinogen plasma concentration.	• Change from baseline in fibrinogen plasma concentration.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Key secondary objective:** To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on sputum bacterial load.	• Change from baseline in total bacteria load of colony forming units (CFU/mL) of potentially pathogenic microorganisms in sputum.
• **Secondary objectives:** To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on airway structure and function.	• Change from baseline in airway wall and lumen parameters along with extent of global and regional air trapping, as measured by HRCT.
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on COPD subjects symptom burden changes.	• Change from baseline in COPD Assessment Test (CAT) questionnaire.

Objective(s)	Endpoint(s)
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on health status.	• Changes from baseline in the Euro Quality of Life-5 Dimensions-3 Level (EQ-5D-3L) questionnaire.
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on changes in health-related quality of life.	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total and domain scores.
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on COPD exacerbations.	• Time to first COPD exacerbation • Proportion of subjects with exacerbations • Annualized rate of exacerbations as defined by EXACT-PRO questionnaire
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on clinical symptoms, cough and sputum.	• Change from baseline in Cough and Sputum Assessment Questionnaire (CASA-Q) domain scores.
• To assess the safety and tolerability of QBW251 in subjects with COPD.	• ECG intervals • Vital signs • Standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis) • Adverse events
• To assess QBW251 pharmacokinetics (PK) during and after 12 weeks of treatment.	• Assessment of drug exposure (Ctrough collected at pre-dose and Cmax at post-dose) on Day 1, Day 28, Day 56 and Day 84. Cmax and AUC on Day 1 and Day 28 in a subset of the subject population (serial samplings up to 8hr).
• To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on spirometry.	• Change from baseline in trough FEV1, FVC, and FEV1/FVC.
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

Objective(s)	Endpoint(s)

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3 Study design

Figure 3-1 Study design

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This is a randomized, subject and investigator blinded, parallel-group, placebo-controlled study investigating the mode of action (MoA) and preliminary efficacy and safety of QBW251 administered orally twice daily (b.i.d.) for 12 weeks in subjects with moderate to severe COPD (GOLD 2-3). Approximately 100 subjects will be randomized in a 1:1 ratio to either QBW251 or placebo. Based on the assumption of a 15% drop-out rate (% drop out based on completed proof-of-concept COPD study CQBW251X2201), it is expected to have approximately 84 subjects to complete the study.

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The study consists of the following periods: Screening, Baseline / Day 1, Treatment, and End of the Study followed by an additional post-treatment safety phone call. The total duration for each subject in the study is up to approximately 19 weeks.

The study design is summarized in Figure 3-1 above.

3.1 Study Visits

Screening (from D-42 to Day -1)

Informed consent must be obtained prior to implementing any study specific procedure.

Screening assessments can be performed over a 6-week period maximum. Inclusion and exclusion criteria will be checked to confirm subject's eligibility.

This check includes medical history, background therapy (LABA/ICS or LABA/LAMA or LABA/LAMA/ICS or macrolides), physical examinations and other safety and clinical tests in order to determine subjects' initial eligibility. During screening, in addition to a history of exacerbations, results from an analysis of blood and sputum samples must be colonized with at least one strain of potentially pathogenic microorganism (H influenzae, H parainfluenzae, P aeruginosa, S pneumoniae, S aureus, Moraxella catarrhalis, Enterobacteriaceae, Stenotrophomonas maltophilia, Burkholderia species, and Achromobacter species or any potential pathogenic bacteria measured by dilution/outgrowth.) Any organism that is to be included and that is not included in the list of the protocol defined pathogens should be discussed case by case between the site PI and the Novartis Medical Expert.

Sputum collection and analysis as well as fibrinogen collection and analysis are permitted to be repeated once (for a total of two resulted tests, respectively) during the screening period. It is preferred that the subjects provide a morning sample at the clinic during their study visit. It is important to ensure samples are collected at the same time of day throughout the study.

At screening all subjects will be provided with an electronic diary (eDiary) and be trained on how to record information about their study medication intake (from Day 1 onwards), rescue medication (salbutamol/albuterol) and how to complete various scales and questionnaires.

A HRCT must be performed within the screening period to Baseline / Day 1 before randomization, preferably towards the end of the screening period after most other screening assessments have been completed and passed. HRCT data is not required to define subject eligibility.

Baseline / Randomization Day 1

Subjects who meet the eligibility criteria at screening will go under Baseline / Day 1 safety and efficacy evaluations before randomization. During baseline, sputum samples will be collected at the same time of the day (sputum collection procedure and timing will be detailed in the SOM and laboratory manual) Commercially Confidential Information

Once all baseline assessments have been completed and subjects are again confirmed as being eligible for the study, they can be randomized on the same day (baseline/ randomization Day 1).

If sputum sample or other assessments can't be collected at baseline visit for various reasons, the site can't randomize the subject the same day. An unscheduled visit within 3 days needs to be planned to collect sputum before randomization and treatment allocation. Once sputum is collected, the subject can be randomized the same day of the unscheduled visit.

On Day 1, all eligible subjects will be randomized according to their smoking status (current or ex-smokers as a stratification criterion) to ensure that the number of subjects being smokers and ex-smokers are equally distributed in the treatment and placebo groups.

Treatment period (from Day 1 to Day 84)

Once eligibility has been confirmed from Screening and Baseline assessments, subjects will be randomized in 1:1 ratio into one of the two treatment arms: placebo b.i.d. or QBW251 300 mg b.i.d.

The treatment period is 84 days in duration, with dosing twice daily. During this period, subjects will have to return to the site at Day 28, Day 56 and Day 84 for CCI blood/sputum sample collections, PK, safety, efficacy assessments, and eDiary check. At these visits, subjects will return all used and unused study medication and packaging. At Day 14, the site will call the subject to evaluate compliance and to check subject's wellbeing.

Pharmacokinetic blood sampling (pre and post-dose) will be done at Day 1, Day 28, Day 56 and Day 84 visits. Additionally, a subset of approximately 30-40 subjects will undergo pharmacokinetic serial sampling pre and up to 8 hours post-dose on Day 1 and on Day 28.

As a formal thorough QT assessment of QBW251 has not been completed, triplicate ECGs pre- and post-dose at Tmax will be performed at visits on Day 1, Day 28, Day 56 and Day 84 (end of treatment). These assessments will be complemented by PK sampling (trough and Cmax) on the matching time-points, at visits on Day 1, Day 28, Day 56 and Day 84.

A second HRCT will be performed at Day 84 after the morning dose of study medication at site. If the HRCT can't be performed at Day 84 for any reason, the exam needs to be planned within the 3 coming days and subject must continue to take study medication.

Subjects experiencing an exacerbation during the treatment period will continue with the study treatment along with the standard of care (SOC) therapy for a moderate exacerbation (i.e. antibiotic and/or systemic corticosteroids). Prior to the SOC therapy administration, subjects have to visit their study center for sputum sample collection in order to determine if there are changes in pathogen or bacterial load which may have resulted in the exacerbation.

Subjects with a severe exacerbation who need to be treated in the hospital will be discontinued of study treatment during this time with the possibility to restart study treatment 2 weeks after the last SOC therapy intake for the exacerbation.

End of treatment assessments will be performed at Day 84 visit.

End of study (EOS) visit (Day 91)

Approximately one week after completion of the treatment period, subjects will be invited to the center for end of study (EOS) assessments.

Safety follow-up call (Day 114)

A follow-up telephone call for safety assessment will occur upon study visit completion (EOS) 30 days after last study dose administration. The safety follow-up includes adverse events safety monitoring.

Spontaneous sputum collection

On scheduled sputum collection visits, at least two spontaneous sputum specimens should be collected in the morning at pre-dose timepoint and before breakfast. In case subjects can't produce enough sputum on the individual scheduled visits, they can come back to the site up to 3 days after the scheduled visit to try to produce a sputum sample. If two spontaneous sputum collection attempts are still not satisfactory, investigator may take decision to collect sputum sample after induction by the inhalation of saline (induction process will be described in the SOM).

The site staff will check the sputum appearance directly after expectoration to determine whether they see significant saliva amount. Once the sputum quality has been evaluated and considered as acceptable by the site, sputum can be processed and sent to the central laboratory for analysis. If sample is determined to be sub-optimal, a new sputum collection will be requested by the site's staff. Sputum quality assessment and processing will be described in the SOM and laboratory manual.

If spontaneous sputum collection is not possible at Day 84, the site will need to reschedule the visit up to 3 days after Day 84 and subject will have to continue to take study medication. Other Day 84 assessments don't need to be repeated.

Furthermore, all subjects with signs of an exacerbation will have to come to the study center where an additional sputum sample along with a blood sample for fibrinogen and hsCRP will be collected. The analysis of the sputum sample would help to determine whether the bacterial load or colonization may change with an exacerbation.

In case of exacerbation, the subject has to come back to the site 14 days after last antibiotics intake for another sputum/blood sample collection.

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For a full list of assessments and timepoints please refer to the Assessment Schedule (Table 8-1).

4 Rationale

4.1 Rationale for study design

This randomized, double-blind, parallel-group, and placebo-controlled design supports the assessment of efficacy as well as safety.

The study will assess QBW251 as an add-on to background therapy, in adult subjects with COPD associated with chronic bronchitis and history of exacerbations in the 12 months prior to the study. Chronic bronchitis, history of frequent exacerbations are expected to be enrichment factors for subjects who may particularly benefit from improved activity (potentiation) of the

CFTR channel. A fibrinogen level of ≥ 320 mg/dL as well as a sputum sample that is positive for potentially pathogenic bacteria at screening are further population enrichment factors.

This study is designed to assess the effect of QBW251 on reduction of systemic and lung inflammatory biomarkers, potentially pathogenic microorganisms and other secondary endpoints compared to placebo.

Rationale for key aspects of this design are as follows:

- Study duration includes screening (up to 6 weeks), baseline (1 day), treatment (12 weeks) and an end of the study visit approximately 1 week after the last study drug administration. A study duration up to 19 weeks is of adequate time in order to confirm subject's eligibility and stability before randomization, as well as, to provide data for study objective(s) and to ensure subjects safety during study conduct. In addition, the study employs a safety follow up call approximately 30 days after the last study dose intake.
- The primary objective, fibrinogen, an inflammation marker in plasma, is considered a prognostic biomarker by FDA and EMA for subjects at increased risk for all-cause mortality or a COPD exacerbation (Mannino et al 2015). Systemic inflammation is associated with worse clinical outcomes in COPD.

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- The key secondary endpoint assesses a reduction from baseline in colony forming units of potentially pathogenic bacteria and microorganisms in spontaneous sputum. The reduction by one $\log_{10}$ unit is associated with a significant reduction in risk of exacerbation by approximately 20% in subjects with bronchiectasis, which is considered to be clinically relevant in COPD as well (Chalmers et al 2012). Also, a study with Azithromycin maintenance treatment in COPD with the frequent exacerbater phenotype showed a significantly decreased exacerbation rate (Uzun et al 2014).

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4.1.1 Rationale for choice of background therapy

The selected background therapy will consist of subject individual inhaled combinations (LABA/LAMA or LABA/ICS or LABA/LAMA/ICS) that was taken at a stable dose for 3 months before study start either as a fixed combination or a free combination given once or twice daily. Subjects will continue taking this background medication during the trial. GOLD strategy (GOLD 2019) suggests the decision to use the background therapy should be guided

by the level of symptoms (e.g. CAT score of at least 10) and exacerbation frequency. In addition, subjects are allowed to stay on macrolides at a stable dose if they were treated within 3 months before study start and/or if they have bronchiectasis as a secondary diagnosis. Many COPD subjects, especially with a secondary diagnosis of bronchiectasis, are on a maintenance macrolides therapy if they suffer from frequent exacerbations.

Depending on the severity of COPD disease it is expected that 20-40% of COPD subjects in this trial may have bronchiectasis as a secondary diagnosis (Martinez-Garcia et al 2011).

4.2 Rationale for dose/regimen and duration of treatment

QBW251 is a small molecule intended for oral administration. The half-life of QBW251 following a single dose ranges from 10 to 16 hours. The twice daily dosing regimen was chosen based on the half-life and the intent to have a sustained effect on the ion channel. Additionally, a twice daily regimen is expected to provide a reduced Cmax/trough fluctuation compared to once daily dosing. A twice daily regimen was also tested in the proof of concept study (CQBW251X2201) and was shown to be effective in COPD subjects at 300 mg b.i.d. The 300 mg b.i.d. is also selected in alignment with Dose Range Finding study (CQBW251B2201) with doses up to 300 mg b.i.d. as the highest dose based on a recommendation of the data monitoring committee to ensure that subjects' systemic exposures are generally consistent with an exposure threshold AUC0-24≥ 91'700 ng*h/mL, which was established based on animal data. The 300 mg b.i.d. regimen was well tolerated in an earlier study in cystic fibrosis (CF) subjects (study CQBW251X2101) as well.

12 weeks of treatment should be sufficient to detect fibrinogen plasma level changes and changes in bacterial load and colonization reflective of the target profile of QBW251. In the PoC study (CQBW251X2201) reduction in fibrinogen in plasma and bacterial colonisation were detected after 4 weeks. A positive signal across these endpoints at this time point would support early decision making for a transition into confirmatory phase III studies. In addition, 12 weeks treatment, as compared to the 4 weeks treatment in the completed proof of concept study (CQBW251X2201), enables a longitudinal assessment. The proposed exposure will also increase the robustness of the safety and tolerability assessment and may provide exploratory insights relative to the effect.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

There is currently no approved CTFR potentiator for treatment of COPD on top of inhaled therapy of LABA/LAMA or LABA/ICS or LABA/LAMA/ICS or macrolides that could serve as a comparator. Therefore, QBW251 is tested against placebo on top of background therapy, which is also in accordance with the robust method for the evaluation of an investigational agent, to standards meeting both regulatory requirements and accepted scientific principles. This includes optimizing the study design for high levels of confidence in the rigor and validity of the resulting data, and minimizing the risk of inconclusive results.

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

Risks

The risks to subjects in this trial will be minimized through compliance with the eligibility criteria, study procedures, safety evaluations, PK data, as well as close clinical monitoring.

Potential risks of QBW251

Potential risks of QBW251 are the adverse events observed with increased exposure of QBW251 as noted in previous studies, comprising (refer to Investigator Brochure):

- Gastrointestinal events (nausea, diarrhea, vomiting)
- Nervous system disorders (headache, fatigue and dizziness)
- Hypersensitivity reactions to QBW251 cannot be excluded, but have not been observed in the previous studies with QBW251.

Risks associated with SoC (double or triple inhaled therapy or macrolides)

Adverse events associated with inhaled COPD background therapy include:

Nasopharyngitis, hypertension, back pain and oropharyngeal pain, dyspepsia, gastroenteritis, chest pain, fatigue, peripheral edema, angioedema, rash/pruritus, insomnia, dizziness, bladder obstruction/urinary retention, atrial fibrillation, palpitations, tachycardia, upper and lower respiratory tract infection, pneumonia, diarrhea, headache, gastroesophageal reflux disease, hyperglycemia, rhinitis (approved information for Ultibro Breezhaler®).

The most common adverse effects associated with triple COPD background therapy are headache, back pain, dysgeusia, diarrhea, cough, oropharyngeal pain, nasopharyngitis, upper respiratory tract infection, arthralgia, gastroenteritis, and oral candidiasis (approved information for Trelegy Ellipta®, Breo Ellipta® -EU name Relvar Ellipta®- and Incruse Ellipta ®).

The most common adverse effects associated with macrolide antibiotics (e.g. erythromycin products) are gastrointestinal. They include nausea, vomiting, abdominal pain, diarrhea and anorexia. Reversible hearing loss associated with doses of erythromycin usually greater than 4g per day has been reported (Erythromycin UK SmPC).

Procedural risks

Procedural risks may include:

- Local reactions to venipuncture, including pain, hematomas, fainting, swelling, infections, and erythema.
- Spirometry may be associated with cough, shortness of breath and headache.
- HRCT involves exposure to radiation. The total amount of radiation for acquisition at screening and Week 12 HRCT scans will be optimized to be within the annual limits of exposure defined in both US and EU guidelines.
- Hypertonic saline solution for sputum induction might cause bronchospasm

Risk mitigation

Based on the above risk considerations, clinical monitoring includes the use of an electronic diary with the EXACT-PRO questionnaire to enable daily symptoms assessment, as well as safety assessments during visit days at the investigational site. These include a careful assessment of adverse events, as well as triplicate ECGs, hematologic and clinical chemistry laboratory assessments, urinalysis and vital signs measurements. As a formal thorough QT assessment of QBW251 has not been completed, triplicate ECGs pre- and post-dose (at the time to reach maximum (Cmax) plasma concentration following drug administration (Tmax)) will be performed at Day 1, at Day 28 (when subjects are expected to have reached steady state concentration of the investigational drug), and at Day 84 (end of treatment). These assessments will be complemented by the corresponding PK sampling (Ctrough and Cmax). The PK sampling is also part of a more granular PK monitoring, which has been put in place to ensure that subject exposures are in general consistent with an exposure threshold (area under the plasma concentration curve over 24 hours (AUC0-24h) = 91 700 ng×h/mL) that was established based on animal (monkey) data. As this threshold represents an average of the exposures observed in those animals after 39 weeks of treatment with QBW251, this limit is not absolute, this is a mean value and few subjects are expected to exceed it. In prior QBW251 studies, subjects with exposures above this threshold reported either no adverse events or mild to moderate ones.

In addition to the sampling described above, the PK monitoring plan will generate Cthrough data at all visits and additional PK samples are requested to be taken in case of treatment-emergent serious adverse events. Study drug discontinuation and study stopping rules related to exposure are described in Section 9.1.4.1.

Finally a sub-group of approximately 30 to 40 subjects will undergo serial PK assessments to further characterize the PK profile of QBW251 in COPD subjects.

Investigators and subjects will be instructed on how to react to worsening of COPD symptoms and exacerbations (Section 8.4.4). For the worsening of COPD symptoms, a short-acting beta-2 agonist (SABA) is provided as rescue medication. With respect to the treatment of exacerbations, a suggested therapy consists of 5 days of oral prednisolone (or equivalent) 40 mg/day and/or an oral 7 day course of amoxicillin 500 mg three times per day (t.i.d.) (alternatively amoxicillin clavulanate 625 mg t.i.d. or clarithromycin 500 mg b.i.d.), though investigators are free to treat COPD exacerbations according to the medical needs of the subjects. The diary will also trigger alerts to both subjects and investigators when an algorithm detects a deterioration of symptoms compatible with an exacerbation. The investigator will provide the subject with written instructions to contact them if symptoms of COPD worsen.

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study. Based on a reproductive toxicity study, women of childbearing potential are allowed to enter the study as long as they are using an acceptable effective method of contraception (see also exclusion criteria). This group of subjects is relevant for the targeted disease and their inclusion is aligned with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) M3 (R2) guidance. However, in a hormonal contraception study, it was demonstrated that QBW251 may enhance cytochrome P450 mediated degradation of contraceptive hormones with the consequence that hormonal contraception is not an acceptable method of contraception in the study.

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However, efficacy of the inhaled therapies (such as LABA/LAMA, LABA/ICS, LABA/LAMA/ICS) is not expected to be impacted due to the delivery directly to the lungs. In addition to the inhaled therapies, as a perpetrator, QBW251 is not expected to have impact on the PK exposure of the macrolides (such as Erythromycin and Clarithromycin) as they are no substrates of metabolite enzymes of CYP1A2, 3A4 or UGTs.

Please refer to the respective labels of the background therapy for additional information on drug interactions. Any concomitant medications should be noted in the eCRF. As additional information becomes available when clinical drug interaction studies are conducted during the QBW251 development program, this information will be further updated and reflected in the QBW251 Investigator Brochure.

Benefits

With respect to clinical benefits, a proof of concept study showed a statistically significant and clinically relevant decrease in systemic inflammation (fibrinogen; based on expert opinion), an improvement of pulmonary function (FEV1) and a reduction of the bacterial load of selected pathogens after 4 weeks of treatment with QBW251 in COPD subjects.

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Finally, an independent Data Monitoring Committee will oversee the developing clinical database to support ensuring subjects' well-being throughout the study.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation (approximatively 150 mL) is planned to be collected during Screening, Baseline, during the 12 weeks of the treatment period and at the end of the study , from each subject. For subset of subjects participating to serial PK sampling, approximatively 30 mL will be collected in addition.

Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the assessment schedule (Table 8-1).

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and Central laboratory manual.

See Section 8.5.3.1 on the potential use of residual samples.

5 Population

The study population will consist of approximately 100 male and female subjects, aged 40 years old and above, with moderate to severe COPD (GOLD 2 to 3) with features of chronic bronchitis, a smoking history of at least 10 pack / years, and at least two moderate or one severe exacerbation(s)between January 2019 and their screening visit. All subjects must have a plasma fibrinogen level of ≥ 320 mg/dL, a CAT score of at least 10, and have been on LAMA/LABA or LABA/ICS or LABA/LAMA/ICS therapy at stable dose for at least 3 months prior study start. COPD subjects are allowed to stay on macrolides as background therapy if they have bronchiectasis as a secondary diagnosis and if they have been treated with them for at least 3 months at stable dose before study start. In addition, subjects' sputum must be colonized with potentially pathogenic bacteria (>0 CFU) at screening.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Patients who have signed an Informed Consent Form prior to initiation of any study-related procedure.
2. Male and female adults aged ≥40 years at screening.
3. Patients with stable COPD, stages GOLD 2-3, according to the current GOLD strategy (GOLD 2019) at screening.

   Patients with a post-bronchodilator FEV1/FVC < 0.70 at screening
4. Superseded as of amendment V01

   4a. Patients with airflow limitation indicated by a post-bronchodilator FEV1 ≥ 30% and FEV1 < 80% of the predicted normal at Screening who must have had at least 2 documented moderate or at least 1 documented severe exacerbation(s) between January 2019 to study screening

   Notes:

- Post-bronchodilator refers to 15 to 30 min after inhalation of 400 µg salbutamol/360 µg albuterol (or equivalent dose).
- Exacerbations are defined as moderate if leading to treatment with systemic glucocorticosteroids and/or antibiotics, and as severe if leading to hospital admission or emergency room visit lasting > 24 h in addition to treatment with systemic glucocorticosteroids and/or antibiotics.
- Patients not meeting the FEV1 criteria may be re-screened once.

5. 5 and 5a: Superseded as of amendment V02

   5b. Patients with sputum positive (>0 CFU) for at least one strain of potentially pathogenic microorganism at screening (H influenzae, H parainfluenzae, P aeruginosa, S pneumoniae, S aureus, Moraxella catarrhalis, Enterobacteriaceae, Stenotrophomonas maltophilia, Burkholderia species, and Achromobacter species or any potential pathogenic bacteria measured by dilution/outgrowth. Any organism that is to be included and that is not included in the list of the protocol defined pathogens will be discussed case by case). Sputum samples may be re-collected and re-tested once during the screening period.
6. Patients who have been treated with a combination of LABA/LAMA or LABA/ICS or LABA/LAMA/ICS at a stable dose for the last 3 months prior to screening.
   COPD patients are allowed to stay on macrolides as background therapy if they have bronchiectasis as a secondary diagnosis and if they are treated with them at a stable dose 3 months before screening.
   Note: Fixed or free combinations are acceptable.
7. Superseded as of amendment V01

   7a. Patients with plasma fibrinogen level ≥ 320 mg/dL at screening. Fibrinogen may be re-tested once during the screening period.
8. A COPD Assessment Test (CAT) score of at least 10 at screening.
9. Current or ex-smokers who have a smoking history of at least 10 pack years (e.g. 10 pack years = 1 pack/day x 10 years, or 0.5 pack/day x 20 years) at screening.
   Note: A pack of cigarettes is equal to 20 cigarettes. Bidi or other similar non-filtered cigarette may be considered applicable to smoking history. They should be counted in the same way as standard cigarettes. Occasional smoking of cigars, pipes, e-cigarettes, or inhaled nicotine products are not relevant to smoking history.
   Note: An ex-smoker is defined as a subject who has not smoked for≥ 6 months at screening or at the time of assessment.
10. Patients featuring chronic bronchitis, defined as productive cough that occurs on most days (defined as >50% of days) during at least 3 consecutive months in the year prior to screening, as assessed by documentation of patient recollection (anamnesis) or documented in patients' records.
11. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Patients with a history of long-QT syndrome or whose QTcF interval at screening (Fridericia method) is prolonged (QTcF >450 ms in males, >460 ms in females).
2. Superseded as of amendment V01

   2a. Patients who have a clinically significant* ECG abnormality before randomization.

   Note: Clinically significant abnormalities may include but are not limited to the following: left bundle branch block, Wolff-Parkinson-White syndrome, clinically significant arrhythmias (e.g., atrial fibrillation, ventricular tachycardia).
3. Clinical laboratory values abnormalities (including Gamma GT, AST, ALT, total bilirubin or creatinine) considered as clinically significant* in the opinion of the Investigator at screening. For additional guidance on hepatic parameters see exclusion criterion #5.
4. Patients who have clinically significant* renal, cardiovascular (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction), neurological, endocrine, immunological, psychiatric, gastrointestinal, or hematological abnormalities, which could interfere with the assessment of the efficacy and safety of the study treatment, or patients with uncontrolled Type II diabetes.

   ** Note: Clinically significant is defined as any disease that, in the opinion of the investigator, would put the safety of the patient at risk through participating, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study, or would compromise patient compliance or preclude completion of the study.*
5. Superseded as of amendment V01

   5a. Patients with a history or current treatment for hepatic disease including but not limited to acute hepatitis, cirrhosis or hepatic failure.
   - Patients with stable chronic hepatitis may be included in the study by agreement with Novartis Medical Expert on a case-by-case basis.
   - A history of resolved Hepatitis A is not exclusionary.
   - Patients with prothrombin time international normalized ratio (PT/INR) of more than 1.5xULN at screening. Patients excluded for the PT/INR of more than 1.5xULN can be re-screened when the values have returned to normal.
6. Patients with a history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin. Patients with a history of cancer and 5 years or more disease free survival time may be included in the study by agreement with Novartis Medical Expert on a case-by-case basis.
7. Patients who develop a COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization during screening. Re-screening is permitted after a minimum of 2 weeks after the resolution of the COPD exacerbation (i.e. 2 weeks after the stop of SOC therapy for exacerbation).
8. Patients who have had a respiratory tract infection within 4 weeks prior to screening. If a respiratory tract infection occurs during screening, patients can be re-screened after a minimum of 2 weeks after resolution of the respiratory tract infection.
9. Patients with history of asthma or any other clinically relevant lung diseases.
10. Patients with suspected active pulmonary tuberculosis or currently being treatment for active pulmonary tuberculosis.

Note: Patients with a history of pulmonary tuberculosis can be enrolled if they meet the following requirements: history of appropriate drug treatment followed by negative imaging results within 12 months prior to screening suggesting low probability of recurrent active tuberculosis.

11. Patients with pulmonary lobectomy, lung volume reduction surgery, bronchoscopic lung volume reductions, or lung transplantation.
12. Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the trial. Participation in a maintenance program is permitted. Note: the supervised pulmonary rehabilitation program as a maintenance program has to be ongoing for at least 3 months at the time of enrollment.
13. Patients with a body mass index (BMI) of more than 40 kg/m^2.
14. Patients receiving any medications in the classes listed in Table 6-5.
15. Patients receiving any COPD related medications in the classes specified in Table 6-6, unless they undergo the required washout period prior to screening and follow the adjustment to treatment program.
16. Patients receiving medications in the classes listed in Table 6-2 should be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met.
17. Use of other investigational drugs (approved or unapproved) within 30 days or 5 half-lives prior to screening, or until the expected pharmacodynamic effect has returned to baseline (e.g., biologics), whichever is longer; or longer if required by local regulations.
18. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using acceptable effective methods of contraception during study participation. Acceptable effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps). For the United Kingdom of Great Britain and Northern Island (UK); with spermicidal foam/gel/film/cream/ vaginal suppository.
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    - Note that systemic hormonal contraception (e.g. oral contraception or hormone vaginal ring) is not an acceptable means of contraception due to potential influence of

QBW251 in decreasing the systemic levels of these hormones and therefore making them ineffective (see Section 6.2.1.2)

- If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

20. Patients who have not achieved an acceptable spirometry result at screening in accordance with American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria for acceptability and repeatability (refer to the SOM and vendor manual for Spirometry Guidance).

    Note: one re-test may be performed in patients that do not meet the ATS/ERS criteria. Patients who have failed the test and re-test during screening period may be re-screened only once.

6 Treatment

6.1 Study treatment

The study treatment includes:

- Investigational drug QBW251 dose of 300 mg b.i.d.
- Matching placebo

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing, and taking study treatment are outlined in the SOM.

Refer to the Section 6.2.4.1 for details of dosing and food intake.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drugs

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply type	Sponsor (global or local)
QBW251 300 mg b.i.d	Capsule[1]	Oral use	Double-blind supply; bottles	Novartis Pharma AG
QBW251 Placebo b.i.d.	Capsule[1]	Oral use	Double-blind supply; bottles	Novartis Pharma AG

All capsules are of identical appearance to ensure blinding
[1] QBW251 final pharmaceutical dosage form is a Hard Gelatin Capsule Tab content to maintain double-blind

6.1.2 Additional study treatments

Background therapy

In order to be eligible for this trial, all subjects will be required to have been on a stable background therapy regimen (LABA/LAMA or LABA/ICS or LABA/LAMA/ICS) and/or macrolides for at least 3 months prior to screening. From screening onwards, subjects will continue with their background therapy until end of study visit.

Background therapy will be taken in the morning approximately between 7 and 10 am for once daily drugs and, in addition to the morning use, approximately 12 hours later in the evening in case of twice daily drugs.

Refer to Table 6-6 regarding background therapy prior to spirometry assessments on visit days.

Rescue medication

All subjects will be provided with a short-acting beta agonist (salbutamol 100 µg or albuterol 90 µg or equivalent dose). Subjects will be instructed to use it throughout the study on an as needed basis. No other rescue medication is permitted during the study. Rescue medication will be sourced locally. (See Section 6.2.3 for rescue medication further information.)

Sites will be instructed to record the background therapy information and rescue medications in the corresponding eCRF pages.

6.1.3 Treatment arms/group

On Day 1, subjects will be randomized to one of the following 2 treatment arms in a ratio of 1:1

- QBW251 300 mg b.i.d.
- Matching placebo to QBW251 b.i.d.

All subjects will receive their respective QBW251 or placebo capsules for 12 weeks (from Day 1 through Day 84).

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies administered after the subject was enrolled into the study must be recorded in the concomitant medications/significant non-drug therapies or procedures eCRF page.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. Please note that the lists provided below may not be exhaustive. If in doubt, the investigator should contact the Novartis Medical Expert before randomizing a subject or

allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Table 6-2 provides an overview of medications permitted under certain conditions, including bronchodilator medications which need to be withheld for certain timeframes prior to spirometry assessments on visit days, and an overview regarding actions to be taken for antibiotics.

Table 6-2 Medications permitted under certain conditions

Rationale/Group	Medication	Prohibition Period	Action Taken
COPD maintenance background therapy	e.g.Vilanterol, Umeclidinium, Indacaterol Glycopyrronium	Hold treatment for 24 hours (+/-2 hours) prior to each FEV_1/ spirometry measurement on visit days for once daily inhaled background therapy and 12 hours (+/-2 hours) for twice daily inhaled background therapy	In case the washout criterion is not fulfilled, reschedule spirometry accordingly. Trough spirometry (-45 min and -15 min assessments) should be done within 24 hours for once daily inhaled background therapy such as LABA/LAMA or LABA/ICS or LABA/LAMA/ICS from dosing on the previous morning and approximately 12 hours for twice daily LABA/LAMA or LABA/ICS or LABA/LAMA/ICS from dosing on the previous evening. Otherwise, postpone visit to the next day where washout criteria can be fulfilled
Rescue medication only	Short-Acting Beta-2 Agonists (SABA)	Hold treatment at least 6 hours prior to each FEV_1/spirometry measurement	If possible, postpone spirometry measurement on the same day until the washout criterion is fulfilled. Trough spirometry (-45 min and -15 min assessments) should be done within 6 hours after last rescue medication intake
Antibiotics for treatment of exacerbations and macrolides as background medication	Antibiotics, e.g. amoxicillin Macrolides, e.g. erythromycin	Systemic and/or inhaled antibiotics are allowed for treatment of acute infections, or are allowed for the treatment of acute exacerbations.	All data will be set to missing during the exacerbation time(time of SoC intake) and for 14 days thereafter with the exception of macrolides for those

Rationale/Group	Medication	Prohibition Period	Action Taken
		Permanent prophylactic treatment for other indications are not allowed - with the exception of macrolides for COPD subjects with secondary diagnosis of bronchiectasis if those subjects are on stable doses of macrolides at least 3 months before screening and throughout the study. Topical treatment (e.g. use of intraocular, intraconjunctival antibiotic treatments, topical use of creams, etc.) is permitted.	COPD subjects with a secondary diagnosis of bronchiectasis and on stable dose of macrolides for three months before screening.

QBW251 may inhibit the metabolic clearance of co-medications metabolized by CYP1A2. In addition, QBW251 is a time-dependent inhibitor and inducer of CYP3A4/5. Drugs that are sensitive substrates of CYP1A2 have potential for an increase in exposure with QBW251 due to inhibition of CYP1A2. The net effect of QBW251 on CYP3A4 is anticipated to be induction based on results of an oral contraceptive study resulting in a decrease in exposure.

Weak *in vitro* inhibition of BCRP, OAT1/3, OATP1B1, OATP1B3, UGT1A1 and UGT2B7 was also observed. QBW251 may increase the exposure of drugs which are substrates of the mentioned pathways.

These drugs are listed in Table 6-3 and can be used when indicated and no alternative treatment is available. Safety and efficacy of drug should be monitored accordingly.

The following lists are not considered exhaustive and labels for individual drugs should be referred to.

Table 6-3 Medications which may be co-administered with QBW251 (if no alternative treatment is available)

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6.2.1.2 Systemic contraceptives

Systemic contraceptives such as those listed in Table 6-4 are not an acceptable means of contraception (refer also to definition of acceptable effective contraception in Section 5.2), since these drugs may be ineffective due to decreased exposure in combination with QBW251 and result in contraceptive failure. These drugs may be taken for other indications (e.g., osteoporosis prophylaxis); the efficacy of the treatment may be impaired by low systemic availability, though, and should be monitored.

Table 6-4 Examples of contraceptives not recommended for systemic use as acceptable means of contraception as efficacy may be compromised by QBW251 administration.

Medication	Period during which contraceptive effect may be compromised	Action taken
Drospirenone Ethinyl estradiol Etonogestrel Levonorgestrel Medroxyprogesterone acetate Norelgestromin Norethindrone Norgestimate Norgestrel	Use of these drugs is not prohibited, but in combination with QBW251 these may no longer constitute means of contraception, and thus their use does not fulfill the requirements of contraception stipulated in the exclusion criteria (risk of contraceptive failure). subject is at risk to experience a pregnancy due to the interaction between systemic contraceptive and QBW251.	Avoid concurrent administration; for alternative methods of contraception refer to Section 5.2

6.2.2 Prohibited medication

Use of the treatments displayed in the below table is NOT allowed after the onset of the prohibition period as indicated in Table 6-5 and Table 6-6. Should administration of one of these drugs during the course of the treatment epoch be required, study treatment should be discontinued.

Table 6-5 Prohibited medication

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Table 6-6 Prohibited COPD-related medications and washout period prior to Day 1

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6.2.3 Rescue medication

At screening and whenever needed thereafter, subjects will be provided with a short-acting beta agonist (salbutamol 100 µg or albuterol 90 µg) inhaler to use as rescue medication on an as needed basis throughout the study. No other rescue medication is permitted.

The rescue medication salbutamol/albuterol which is provided at screening for use during the stud will be recorded once in the eCRF at the beginning of the study. The rescue medications intake should not be recorded on the concomitant page of the eCRF, rescue medication intake being registered in the eDiary.

For the use of rescue medication or for the worsening of COPD symptoms and exacerbations, the subject will be instructed to complete the rescue medication information in the eDiary twice daily at the same time in the morning and evening, approximately 12 hours apart (number of puffs taken in the previous 12 hours). This will be completed prior to taking the study drug. For the worsening of COPD symptoms please refer to Section 6.6.2.

The eDiary will also trigger alerts to both the subject and the investigator, when an algorithm (please refer to Section 8.4.4) detects a deterioration of symptoms compatible with an exacerbation. The investigator will provide the subject with written instructions on how to contact the center if symptoms of COPD worsen.

The rescue medication will be provided by the study center and reimbursed by Novartis.

6.2.4 Restriction for study subjects

For the duration of the study, subjects should be informed and reminded of the restrictions outlined in this section.

6.2.4.1 Dietary restrictions and smoking

Dietary restrictions

The following are the instructions for the investigational drug (QBW251/placebo):

- it is recommended not to take the investigational drug together with high-fat meals (refer to the SOM for details). The definition of high-fat meals follow the definition suggested

by FDA in the draft guidance on Assessing the Effects of Food on Drugs in INDs and NDAs (FDA 2019): a meal containing at least 1000 kcal (4184 kJ), and at least 50% of that energy content from fat.

An example of a high fat meal would be for a total nutritional energy value of 1000 kcal:

- of which from proteins: 150 kcal
- of which from carbohydrates: 250 kcal
- of which from fats: 600 kcal.

- Subjects can drink water as needed.
- Subjects should be instructed not to take grapefruit, Seville oranges or their juice for 14 days prior to dosing, during treatment and until 7 days following the last dose as these products are considered inhibitors of CYP3A.

Smoking

Subjects will be stratify by their smoking status (current or ex-smokers).

6.2.4.2 Other restrictions

Not applicable.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see the 'Subject numbering' section in the SOM

6.3.2 Treatment assignment, randomization

Upon signing the informed consent form, the subject will be assigned the next sequential number by the investigator. The investigator or his/her staff will contact IRT and provide the requested identifying information for the subject to register them into the Interactive Response Technology (IRT).

At Day 1, all eligible subjects will be randomized via IRT to one of the treatment arms. Randomization will be stratified by smoking status (current or ex-smoker).

The investigator or his/her delegate will contact IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the subject. The randomization number will not be communicated to the site personnel, but will be used by the IRT system. The subject will retain the subject number throughout the study as their unique identifier. If the subject fails to be treated for any reason, the IRT should be notified within 2 days that the subject was not treated, and the reason will be entered into the eCRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

Subjects, investigator staff, and site personnel performing the assessments, will remain blinded to the treatment from the time of randomization until database lock, using the following methods:

(1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: statistician and programmer supporting the CQBW251B2202 study and upon request by the DMC for study to unblind all the DMC members.

(2) the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

The sponsor will remain blinded until study completion except trial statistician and programmer who will be responsible for interim analyses at any time for efficacy and safety. However, an independent statistician and independent programmer will be unblinded to support all DMC requirements (see Section 10.2.3).

Unblinding this study to the sponsor will only happen in the case of subject emergencies that will be deemed necessary by the DMC to evaluate the safety outcome to safeguard all subjects.

The randomization codes associated with subjects from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until database lock.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site.

Table 6-7 Blinding Levels

Role	Time or Event			
	Randomization list generated	Treatment allocation and dosing	Safety event (single subject unblinded)	Interim Analysis & DMC purposes
Subjects	B	B	UI	B
Site staff	B	B	UI	B

Drug Supply and Randomization Office	UI	UI	UI	U
Unblinded sponsor staff (see text for details)	B	UI	UI	U
Statistician / Statistical Programmer / Data Analysts	B	B	UI	U
Independent Committee used for assessing interim results	B	B	UI	B*
All other sponsor staff not identified above	B	B	UI	B

B Remains blinded
B* Remains blinded unless safety and/or exposure concerns
UI Allowed to be unblinded on individual subject level
U Remains unblinded

6.5 Dose escalation and dose modification

Investigational treatment dose adjustments are permitted under specific circumstances described in Section 6.5.1 and Section 6.5.1.2. Temporary dose interruptions are permitted under specific circumstances described in Section 6.5.1.

6.5.1 Dose interruptions

Study drug interruptions are not permitted unless the investigator considers a temporary interruption is necessary for the treatment of an adverse event. If the adverse event grade is severe and suspected to be related to the investigational study drug the investigational study drug should be permanently discontinued as described in Section 9.1.1.

Any interruption of study medication during the treatment of an AE for more than 5 consecutive days during the treatment period should be discussed with the local Novartis Medical Expert to review the subject's eligibility to continue in the trial.

The study drug dose interruptions must be recorded in the Dosage Administration Record eCRF.

6.5.1.1 Dose modifications

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6.5.1.2 QTcF prolongation

In case of QTcF > 500 msec (or QTcF prolongation > 60 msec from baseline/Day 1):

- Assess the quality of the ECG recording and the QT value and repeat, if needed
- Interrupt study investigational treatment
- Determine the serum electrolyte levels (in particular for hypokalemia, hypomagnesemia). If abnormal, correct abnormalities.
- Consider collecting a time-matched PK sample on that visit (if not already scheduled per Table 8-1) and record time and date of last study treatment intake.
- If QTcF confirmed by the Central Reading > 500 msec:

- Permanently discontinue the study treatment (see Section 9.1).
- Take a blood sample for PK analysis. Timepoint should be as close as possible to the ECG recording in question
- Consult with a cardiologist (or qualified specialist)
- Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 msec
- Review concomitant medication use for other causes for QT prolongation (refer to http://www.qtdrugs.org for known QT prolonging drugs), and for drugs with the potential to increase the risk of drug exposure related QT prolongation
- Check the dosing schedule and treatment compliance

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Study drug compliance should be assessed by the investigator and/or center personnel at all visits by verifying subjects' eDiary. The Investigator or designee will collect from the subject the used / unused investigational study drug and packaging at each visit and at the End of Treatment (Day 84). Study drug compliance will be assessed from the capsule count (unused medication) and from information provided by the subject and/or caregiver in the eDiary. The total number of doses of investigational treatment administered should be captured in the source documentation, and the start and end date of investigational study drug, and any missed doses, derived from eDiary, will be recorded on the eCRF.

The number of puffs of rescue medication inhaled will be recorded twice daily by the subject in the eDiary. At screening, subjects will be provided with the eDiary and the use of rescue medication will be discussed. The use of study medication and rescue medication will be reviewed at each visit and data from the eDiary downloaded at each visit. Where necessary, the Investigator will discuss compliance/documentation issues regarding study drug and other medications use with the subject.

The COPD maintenance background therapy compliance will also be monitored at all visits and information captured in the source documents at site. Information on the start date, end date and interruptions of more than three days must be captured in the eCRF. Any compliance issues must be discussed with the subject.

The investigator must promote compliance by instructing the subject to take the study treatment as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

6.6.2 Recommended treatment of adverse events

Subjects in the study may develop symptoms that normally appear in COPD, however an increase in frequency and severity of these symptoms is not expected. If during the study symptoms occur that are severe enough to interfere with the activities of daily living of the subjects, they should be treated according to current clinical practice. For the worsening of COPD symptoms, a short-acting beta-2 agonist (SABA) is provided as rescue medication. With respect to the treatment of exacerbations, a suggested therapy consists of 5 days of oral

prednisolone (or equivalent) 40 mg/day and/or an oral 7 day course of amoxicillin 500 mg t.i.d. (alternatively amoxicillin clavulanate 625 mg t.i.d. or clarithromycin 500 mg b.i.d.), though investigators are free to treat COPD exacerbations according to the medical needs of the subjects.

Medication used to treat adverse events (AEs) must be recorded in the eCRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- site number
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

After emergency unblinding, the subject will be permanently discontinued from the study investigational treatment as described in Section 9.1.1

6.7 Preparation and dispensation

Each study site will be supplied with investigational study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label). Immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

Investigational study drug consists of oral capsules and no preparation prior to dispensation is required.

QBW251 or placebo will be taken orally by the subject at home with the exception of the following visits: Day 1, Day 28, Day 56 and Day 84 when morning dose drug intake will occur at the study site.

On the day of site visits with spirometry assessments, investigators should instruct subjects to have site visits always at approximately the same time (no more than two hours different to the baseline visit).

See the Site Operations Manual for further details.

6.7.1 Instruction of prescribing and taking study medication

The following are the instructions for the investigational drug (QBW251/placebo):

- QBW251/ placebo is an oral capsule.
- One capsule should be taken twice a day at approximately the same time each day, with about 12 hours between each dose administration (approximately in the morning between 7 and 10 a.m. and in the evening between 8 and 11 p.m.)
- Refer to Section 6.2.4.1 Dietary restrictions linked to QBW251 intake.
- If vomiting occurs during the course of treatment, subjects should be instructed not to take the study drug again before the next scheduled dose.
- Subjects should be instructed not to make up for missed doses.
- Subjects should be instructed to swallow whole capsules and not to chew or open them.
- Instructions for the maintenance treatment and rescue medication should be according to the respective product label.
- On study visit days, subjects should be reminded not to take either the investigational drug (QBW251/placebo) or the maintenance therapy doses prior to the site visit to ensure compliance with the pre-dose PK sampling procedure and spirometry pre-dose measurements. The morning dose on the visit days should be taken after the pre-dose PK sampling and spirometry assessments have been completed, within 15 min approximately.

Of note, spirometry on visit days shall be conducted

- 10-14 hours after the last intake of investigational drug on the evening before for b.i.d. drugs, and
- 22-26 hours after the last inhalation of daily maintenance background medication on the morning before o.d. drugs (see also Section 8.3.1).

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation) IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements. Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

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A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final EOS visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

Table 8-1 Assessment Schedule

Period	Screening	Screening	Treatment							
Visit Name	Screening	Baseline	Week 1							
Visit Numbers[1]	1	20	100							
Days	-42 to -1	1 -3 +1	1							
Time (post-dose)	-	-	pre-dose	dose	1h	2h	3h	4h	6h	8h
Informed consent	X									
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Inclusion / Exclusion criteria	X	X	X							
Demography	X									
Physical Examination	S	S	S							
Body Height	X									
Body Weight	X									
Vital Signs	X	X	X				X			X[2]
Medical history/current medical conditions	X									
COPD exacerbation history	X									

Period	Screening	Screening	Treatment							
Visit Name	Screening	Baseline	Week 1							
Visit Numbers[1]	1	20	100							
Days	-42 to -1	1 -3 +1	1							
Time (post-dose)	-	-	pre-dose	dose	1h	2h	3h	4h	6h	8h
Concomitant medications	X	X	X							
Spirometry	X		X[3]							
Smoking status	X	X	X							
Electrocardiogram (ECG)	X		X				X			

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Fibrinogen blood collection[7]	X		X							

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Pregnancy test[9]	X		X							
Hematology	X		X							
Clinical Chemistry[10,7]	X		X							
Urinalysis[11]	S		S							

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High Resolution CT of Chest	X[13]									
Cough And Sputum Assessment Questionnaire (CASA-Q)			X							
St. George's Respiratory Questionnaire (SGRQ)			X							
EQ-5D-3L			X							
COPD Assessment Test (CAT)	X									
EXACT-PRO Questionnaire[14]			X							

Period	Screening	Screening	Treatment							
Visit Name	Screening	Baseline	Week 1							
Visit Numbers[1]	1	20	100							
Days	-42 to -1	1 -3 +1	1							
Time (post-dose)	-	-	pre-dose	dose	1h	2h	3h	4h	6h	8h
Dispensation of study drug			X							
Study drug intake at site				X						

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e-Diary [16]	X	X	X							
PK blood collection			X		X[17]	X[17]	X	X[17]	X[17]	X[17]
Adverse Events	X[18]	X								
Serious Adverse Events	X									
Telephone follow-up										
Safety Follow up Call										

Period	Treatment									
Visit Name	Week 2	Week 4								Week 8
Visit Numbers[1]	110	120								130
Days	14 ±2	28 ±3								56 ±3
Time (post-dose)	-	pre-dose	dose	1h	2h	3h	4h	6h	8h	pre-dose
Informed consent										
Commercially Confidential Information										
Inclusion / Exclusion criteria										
Demography										
Physical Examination										
Body Height										
Body Weight										
Vital Signs		X				X			X[19]	X
Medical history/current medical conditions										
COPD exacerbation history										
Concomitant medications		X								X
Spirometry[23]		X[3]								X[3]
Smoking status		X								X
Electrocardiogram (ECG)		X				X				X
Commercially Confidential Information										
Fibrinogen blood collection[7]		X								X
Commercially Confidential Information										
Pregnancy test[9]		X								X

Period	Treatment									
Visit Name	Week 2	Week 4								Week 8
Visit Numbers[1]	110	120								130
Days	14 ±2	28 ±3								56 ±3
Time (post-dose)	-	pre-dose	dose	1h	2h	3h	4h	6h	8h	pre-dose
Hematology		X								X
Clinical Chemistry[10]		X								X
Urinalysis[11]		S								S
Commercially Confidential Information										
High Resolution CT of Chest										
Cough And Sputum Assessment Questionnaire (CASA-Q)		X								X
St. George's Respiratory Questionnaire (SGRQ)		X								X
EQ-5D-3L										
COPD Assessment Test (CAT)										
EXACT-PRO Questionnaire[14]		X								X
Dispensation of study drug		X								X
Study drug intake at site			X							
Commercially Confidential Information										
e-Diary [16]		X								X
PK blood collection		X		X[17]	X[17]	X	X[17]	X[17]	X[17]	X
Adverse Events	X									
Serious Adverse Events	X									
Telephone follow-up	X									
Safety Follow up Call										

Period	Treatment					Treatment Completion Follow-Up	Treatment Completion Follow-Up	Unscheduled
Visit Name	Week 8		Week 12			EOS/Early Termination	Safety Follow Up call	Unscheduled[21]
Visit Numbers[1]	130		140			1999	150	160
Days	56 ±3		84 ±3			91 ±3	114 ±3	-
Time (post-dose)	dose	3h	pre-dose	dose	3h	-	-	-
Informed consent								
Informed consent DNA								
Inclusion / Exclusion criteria								
Demography								
Physical Examination						S		S
Body Height								
Body Weight						X		
Vital Signs		X	X		X	X		X
Medical history/current medical conditions								
COPD exacerbation history								
Concomitant medications			X			X		X
Spirometry[23]			X					X[24]
Smoking status			X			X		
Electrocardiogram (ECG)		X	X		X	X		X

Period	Treatment					Treatment Completion Follow-Up	Treatment Completion Follow-Up	Unscheduled
Visit Name	Week 8		Week 12			EOS/Early Termination	Safety Follow Up call	Unscheduled[21]
Visit Numbers[1]	130		140			1999	150	160
Days	56 ±3		84 ±3			91 ±3	114 ±3	-
Time (post-dose)	dose	3h	pre-dose	dose	3h	-	-	-

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Fibrinogen blood collection[7]			X					

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Pregnancy test[9]			X			X		X
Hematology			X			X		X
Clinical Chemistry[10]			X			X		X
Urinalysis[11]			S			S		S

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High Resolution CT of Chest			X					
Cough And Sputum Assessment Questionnaire (CASA-Q)			X					X
St. George's Respiratory Questionnaire (SGRQ)			X					X
EQ-5D-3L			X					
COPD Assessment Test (CAT)			X					
EXACT-PRO Questionnaire[14]								X

Period	Treatment					Treatment Completion Follow-Up	Treatment Completion Follow-Up	Unscheduled
Visit Name	Week 8		Week 12			EOS/Early Termination	Safety Follow Up call	Unscheduled[21]
Visit Numbers[1]	130		140			1999	150	160
Days	56 ±3		84 ±3			91 ±3	114 ±3	-
Time (post-dose)	dose	3h	pre-dose	dose	3h	-	-	-
Dispensation of study drug								
Study drug intake at site	X			X				
Rescue medication use and record	X							X
e-Diary [16]			X			X		X
PK blood collection		X	X		X			X[22]
Adverse Events	X						X	X
Serious Adverse Events	X							X
Telephone follow-up								
Safety Follow up Call							S	

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] Only for serial PK subjects
[3] trough FEV1
[4] In case the first two attempts were not satisfactory to obtain sputum, the Investigator may proceed with sputum induction.
[5] Sampling can be done at BL or Day 1 morning. Results do not need to be available prior to randomization as bacterial colonization was confirmed during screening.
[6] In case of sign of exacerbation and 14 days after last SoC (antibiotics) intake, subject would need to come back to site for an additional sputum sample collection. See Section 8.4.4 for complete details.
[7] In case of sign of exacerbation and 14 days after last SoC intake, subject would need to come back to site for an additional blood sample collection. See Section 8.4.4 for complete details.

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[9] Only for women assessed as being of childbearing potential. At screening, serum pregnancy test (central lab). Other visits: urine pregnancy test (local). In case of positive test in urine, this would need to be confirmed by a test in serum.

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[11] Dipstick test conducted on site. If dipstick reveals abnormal readings, a urine sample is to be submitted to the central laboratory for analysis.
[12] Optional DNA collection requires a separate consent. DNA sample can be collected prior or after randomization or any subsequent visits.
[13] To be performed, if possible, after subject has passed all other screening criteria.
[14] It is to be completed by the subject at the end of every day at bedtime.

[16] eDiary will record a) background therapy and rescue medication (salbutamol/albuterol) captured twice daily before taking study medication; b) subjects self-assessments questionnaire(s) and c) QBW251 medication intake. The e-Diary is to be reviewed at each clinic visit until study completion.
[17] only in subset of subjects
[18] During screening period, exacerbation(s) will be reported in Adverse Events eCRF page. No other adverse events will be collected during screening period.
[19] Only for serial PK subjects
[20] In case subjects can't produce enough sputum on scheduled visits, they can come back up to 3 days after the scheduled visits to try to produce sputum sample.
[21] An unscheduled visit can be planned at any time based on medical needs with vital signs, physical examination, hematology, biochemistry, urine pregnancy test, urinalysis and ECG as minimum to be assessed. In case of SAE, PK sampling needs to be added. Other assessments are at investigator's discretion based on the purpose of the unscheduled visit.
[22] A PK assessment is only expected in case the unscheduled visit occurs due to a SAEs, unless a planned visit for this subject is occurring within a week time of the reported SAE (scheduled PK sample).

[23] Bronchodilator challenge will only be performed during screening spirometry.

[24] Spirometry should not be performed if the unscheduled visit is for an exacerbation

8.1 Screening

If a subject fails to meet the eligibility criteria, re-screening is allowed in the cases described in Section 5. Re-screening should occur after a subject has failed screening. A new subject number will be assigned and the site must record the re-screening information in the corresponding eCRF and in IRT.

In the case where the subject meets all inclusion/exclusion criteria but does not meet sputum positivity for pathogenic bacteria, or the sputum sample volume is inadequate (<5mL), a second sputum collection on a separate day during screening is permitted to be performed prior to randomization for further assessment of qualification. Results must be received before randomization.

In the case where the subject meets all inclusion/exclusion criteria but does not meet serum fibrinogen requirement a second serum fibrinogen collection on a separate day is permitted to be performed prior to randomization for further assessment of qualification. Results must be received before randomization.

In the case where a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study and considered as screened failed.

If a subject re-screens for the study, then the subject must sign a new ICF and be issued a new subject number prior to any screening assessment being conducted. The investigator/qualified site staff will record if the subject was re-screened on the re-screening eCRF along with the screening number the subject was issued prior to the current screening number. Subjects who have previously screen failed once or twice due to sputum CFU level being too low under the original protocol with or without fibrinogen being too low, but who had sputum positive for at least one potentially pathogenic organism, may be re-screened for the study once using the updated inclusion/exclusion criteria from the protocol amendment v02 (inclusive of version 01 changes). If this screen fail subject had a HRCT as part of original screening activities, a repeat HRCT is not required unless more than 12 months have passed since the prior HRCT.

The date of the new informed consent signature must be entered on the informed consent eCRF corresponding to the new screening subject number. For re-screening, all screening assessments must be performed per protocol.

Information on what data must be collected for screening failures and further information on re-screening is outlined in the Site Operations Manual.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent but fail to continue into the Baseline/Day 1 visit for any reason will be considered a screen failure. The reason for the screening failure will be entered on the screening disposition page. If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

Information on what data must be collected for screening failures and further information on re-screening is outlined in the Site Operations Manual.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data are to be collected on all subjects. Relevant medical history/current medical condition present before signing the informed consent will be recorded. Investigators will have the discretion to record abnormal test findings on the appropriate eCRF whenever, in their judgment, the test abnormality occurred prior to the informed consent signature.

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

Details are outlined in the Site Operations Manual.

8.3 Efficacy / Pharmacodynamics

The efficacy assessments selected are standard for this indication/subject population.

Blood and sputum samples will be collected and evaluated in all subjects at the timepoints defined in the Assessment Schedule (Table 8-1). Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing, and shipment. Number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

For all completed scales/questionnaire described below, the Investigator will be required to review and examine responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the scale but also for any unsolicited comments written by the subject. If the occurrence of AEs or SAEs is confirmed, the investigator / physician should record the events as per instructions given in Section 9.

8.3.1 Spirometry

Spirometry testing will be performed according to the ATS/ERS guidelines (Miller et al 2005a; Miller et al 2005b) at screening to assess subject eligibility for the study and at the visits detailed in the assessment schedule in Table 8-1.

The spirometry evaluation should be performed at the site prior to the morning investigational drug intake and the daily COPD maintenance background therapy, as pre and post-bronchodilator. Refer to instructions for medication washouts in Table 8-1.

Bronchodilator challenge will only be performed during the screening visit to establish data to meet inclusion/exclusion criteria related to asthma. Spirometry without bronchodilator challenge will be performed at all other visits.

The spirometry equipment used during the trial will be provided to all study sites by a Central Spirometry vendor. The equipment must meet or exceed the minimal ATS/ERS recommendations for diagnostic spirometry equipment as defined in the guideline provided by the vendor. Calibration of the spirometry equipment is mandatory on all visit days and must be performed before the first subject spirometry test is assessed. All calibration reports and subject spirometry reports should be stored as source data.

The same spirometry equipment should be used for all assessments performed by a subject. A limited number of qualified staff, as designated by the investigator, will evaluate all subjects

at all visits throughout the entire trial at each site. Where possible the same technician should perform all maneuvers for an individual subject. All staff conducting the spirometry tests must have received appropriate training which must be documented.

A Spirometry Manual will be provided to all sites as separate document.

All spirometry assessments will be undergoing review by a central overreader. Acceptability of a spirometric assessment attempt depends on the overreader's judgement for compliance with and acceptability according to the ATS/ERS criteria.

8.3.2 High Resolution Computed Tomography (HRCT)

High Resolution Computed Tomography (HRCT) will be performed at Screening and at Day 84. The HRCT performed during screening should be performed toward the end of the screening period after most or all other screening assessments have been confirmed. By conducting the HRCT close to last in screening procedures, those subjects who fail screening will not be exposed to unnecessary radiation as HRCT would no longer be needed. The acquisition will include inspiratory and expiratory image sets at both assessment time points. Protocol specific requirements of the HRCT and machine settings will be provided to all sites as part of a separate Imaging Manual. Additionally, the imaging vendor will provide centralized review of the HRCT scans. Screening HRCT data are not required to define subject eligibility.

In summary, evaluation of the HRCT scans will be used to assess extent of:

- airway structure and function for evaluation of change from Screening / Baseline compared to Day 84
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Note: The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

8.3.3 Appropriateness of efficacy assessments

Not applicable.

8.3.4 Fibrinogen

Fibrinogen is a glycoprotein, which is the most abundant clotting factor in plasma. Elevated levels of fibrinogen among subjects with COPD were found to be associated with more frequent/more severe outcomes commonly used as endpoints in investigations of COPD (Mannino et al 2015). For details on the collection, handling and storage/shipment of samples, refer to the Laboratory Manual. Samples will be collected at the time points defined in the Assessment Schedule (Table 8-1).

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8.3.6 Bacterial load

Sputum samples will be collected for analysis of pathogenic bacterial colonization (CFU/mL)(H influenzae, H parainfluenzae, P aeruginosa, S pneumoniae, S aureus, Moraxella

catarrhalis, Enterobacteriaceae, Stenotrophomonas maltophilia, Burkholderia species, and

Achromobacter species or any potential pathogenic bacteria measured by dilution/outgrowth. Any organism that is to be included and that is not included in the list of the protocol defined pathogens should be discussed on a case by case basis with the Novartis Medical Expert.

Depending on different laboratories, the unit of bacterial load CFU/mL is considered equal to CFU/g.

In addition, 16S sRNA based analysis will be performed to provide microbial profiling. The analysis will be performed on remaining sputum samples collected for microbiology assessment.

Spontaneous sputum collection: on scheduled sputum collection visits, including Screening and Baseline at least one sputum specimen should be collected in the morning before breakfast and at pre-dose time-point during the treatment period. In case subjects can't produce enough sputum on the individual scheduled visits, they can come back up to 3 days after the scheduled visits to try to produce sputum sample. If two spontaneous sputum collection attempts are still not satisfactory, an investigator may take decision to collect sputum sample after induction by the inhalation of saline (please refer to the Lab Manual

Treatment emerging pathogens will be determined at all visits.

Microbiological analyses, including bacterial colonization and bacterial load profiling, will be performed centrally at a qualified microbiology laboratory.

Finally, all sputum samples must be of good quality, according to the quality criterion as specified in Laboratory Sputum Collection Manual. If the sample is determined to be a sub-optimal, the site's staff should be contacted immediately and a request should be made for a new sample. Details on the collection and shipment of samples, generation of data and reporting of results by the microbiology laboratory are provided in the Sputum Collection Manual.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to the AE section (Section 10.1.1).

The methods, assessment, specification, and recording for each assessment will be detailed in the SOM.

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be done at all visits starting from Day 1 except where a complete physical examination is required (see above). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include BP and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Section 16.1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the Laboratory Manual. Laboratory assessments will be performed in the visits specified in Table 8-1.

Clinically significant abnormalities must be recorded as either medical history or adverse events as appropriate. All subjects with laboratory tests containing clinically significant abnormalities should be followed regularly until the values return to within the normal ranges or until a valid reason other than drug-related adverse experiences is identified, even after the medication has discontinued. Clinically notable laboratory findings are defined in Section 16.1.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Table 8-2 Laboratory evaluations

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), high-sensitivity C-reactive Protein (hs-CRP), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting)
Urinalysis	Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals only if abnormalities on the macroscopic panel (dipstick) are detected) Macroscopic Panel (Dipstick) (Blood, pH, Protein, Specific Gravity)
Coagulation	Prothrombin time (PT) / International normalized ratio [INR]), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)
Pregnancy Test	Serum / Urine pregnancy test (refer to 'Pregnancy and assessments of fertility' Section 8.4.3)

8.4.2 12-lead Electrocardiogram (ECG)

Triplicate 12-lead ECG will be collected at the time points indicated in Table 8-1.

PR interval, QRS duration, heart rate, RR interval, QT interval, QTcF will be assessed.

Where clinical decisions are based on the QT interval, the length of the QT interval is to be calculated according to the Fridericia QT correction formula (QTcF).

As applicable, QTcF may be calculated at the clinical site, unless auto-calculated by the ECG machine.

Clinically significant abnormalities must be reported as adverse events.

Additional details pertaining to ECG collection and reporting are included in the SOM.

The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. A minimum 3 minutes rest period from the beginning of ECG assessments to the start of spirometry maneuvers must be observed at all times.

For each ECG performed, original traces and identical duplicate traces should be printed. Each ECG will be sent electronically for central review directly from the ECG machine. Two identical duplicate print-outs will be generated and kept at the investigator site as source documentation and as back up for submission to the central laboratory in case of problems with the electronic transmission. Each print-out will be kept at the investigator site and will be dated and signed. The subject's number, the date, actual time of the tracing and study code must appear on each page of the tracing. Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.3 Pregnancy and assessments of fertility

See the Assessment schedule Table 8-1 for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

Refer to Section 10.1.4 for details on Pregnancy reporting.

8.4.4 COPD Exacerbation

Symptom-defined COPD exacerbations identified by the EXACT-PRO instrument (EXACT-PRO-defined exacerbations) are defined as a persistent increase from baseline in total EXACT-PRO score of ≥9 points for 3 days or ≥12 points for 2 days. Whenever the EXACT-PRO diary data suggest that the subject symptoms are worsening according to the above definitions, the diary will trigger an alert advising the subject to contact the site.

A healthcare resource utilization (HCRU)-defined exacerbation is defined as an acute worsening of respiratory symptoms (consisting of at least two of the following symptoms: dyspnea, cough, sputum volume, sputum purulence, chest tightness or wheeze) that requires a change in treatment. HCRU exacerbations are defined as moderate if leading to treatment with systemic glucocorticosteroids and/or antibiotics, and as severe if leading to hospital admission or emergency room (ER) visit lasting >24 h in addition to treatment with systemic glucocorticosteroids and/or antibiotics. Mild HCRU exacerbations are events that can be managed with an increase in usual medication and without the addition of systemic therapy.

Exacerbation therapy is at the discretion of investigators. Suggested therapy includes 5 days of oral prednisolone (or equivalent) 40 mg/day and/or an oral 7 day course of amoxicillin 500 mg t.i.d. (alternatively amoxicillin/clavulanic acid 625 mg t.i.d. or clarithromycin 500 mg b.i.d.) (GOLD 2018).

Subjects who develop a COPD exacerbation between screening and prior to treatment will be screen failed but will be permitted to be re-screened after a minimum of 2 weeks after exacerbation SOC therapy has been stopped. (see Section 5). Scheduled spirometry should not be performed during an exacerbation until it has completely resolved, therefore any scheduled visits that include spirometric assessment should be postponed until the subject has recovered. Visits that do not include spirometric assessment can go ahead as planned. Of note, budesonide and fluticasone are sensitive substrates of CYP3A. Where administered systemically for a COPD exacerbation, efficacy and safety of these drugs should be carefully monitored (see also Section 6.2 for further details).

In case of exacerbation alerts, subjects will need to visit the Site as soon as reasonably possible and be assessed to confirm the exacerbation. This visit will be considered as an unscheduled visit.

Subjects experiencing a moderate exacerbation during the treatment period will continue with their study treatment along with the standard of care (SOC) therapy for exacerbation (i.e. antibiotics and/or systemic corticosteroids). In case subjects are treated with antibiotics for their moderate exacerbation, subjects will have to come back to the site for another unscheduled visit approximately 2 weeks after last intake of their antibiotics, as a follow-up visit to provide sputum and blood samples. If the follow-up visit occurs within approximately 1 week from the next study visit, subjects can come back directly to the planned visit as per Assessment schedule and proceed with the respective procedures as per protocol for this study visit day.

Subjects experiencing a severe exacerbation who need to be treated in the hospital will be discontinued of study treatment during this time, with the possibility to restart study treatment approximately 2 weeks after the last day of their antibiotics intake for their exacerbation. Those subjects who took antibiotics should also provide sputum and blood samples before restart with study treatment. Subjects who were not treated with antibiotics during their hospital stay can restart with study drug directly after hospital stay.

Exacerbation start time is considered as the day the subject is provided with antibiotics or systemic corticosteroids. Exacerbation end date is considered as the day after the last intake of antibiotics or systemic corticosteroids. In case of intake of both antibiotics and systemic corticosteroids, start and end date of the exacerbation refers to the start and end date of the antibiotics intake.

Finally, if an exacerbation happens after EOS visit, subjects will be treated at the discretion of the subject's physician.

Following treatment for the exacerbation, the subject will be expected to continue in the study provided the investigator considers that the subject can safely return to their pre-exacerbation medications.

All HCRU-defined exacerbation events and given therapy should be recorded on relevant eCRF pages.

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

The impact of COPD on a subject's health status will be assessed by the following subject-reported outcomes questionnaires (PROs):

- The COPD assessment test (CAT) assesses globally the impact of COPD (cough, sputum, dysnea, chest tighteness) (Jones et al 2009)
- Cough And Sputum Assessment Questionnaire (CASA-Q) measures cough and sputum production (Crawford et al 2008)

- The St. George Respiratory Questionnaire (SGRQ) (Jones el al 1992) provides health status measurements
- EXACT-PRO Questionnaire evaluates frequency, severity, and duration of exacerbations.
- The European Quality of Life-5 Dimension-3 Levels (EQ-5D-3L) evaluates global health status of subjects.

A subject's refusal to complete all or any part of a PRO measure should be documented in the study EDC system and will not be considered a protocol deviation.

Subject questionnaires will be completed in the language most familiar to the subject.

The site personnel should check PRO measures for completeness and ask the subject to complete any missing responses. The responses stored electronically on the eDiary will be considered the source file.

Completed measures and any unsolicited comments written by the subject should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in the subject's source records. If AEs or SAEs are confirmed, the study investigator should not encourage the subject to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 10 (e.g. reference "Adverse Events" section) of the study protocol.

The appropriate language version of the questionnaires will be used in each participating country. The same language should be used by a particular subject throughout the study. The site personnel administering the questionnaire should be familiar with the measures and the associated user guides and training materials provided. The subject should complete the questionnaires in a quiet area and be allowed to ask questions; however site personnel should take care not to influence the subject's responses. The subject will be instructed to provide the truest and best response for them.

8.5.1.1 The COPD assessment test (CAT)

The COPD assessment test (CAT) is a short instrument used to quantify the symptom burden of COPD and will be used to assess the health status of subjects in this study (Jones et al 2009). The assessment will be completed by the subject at the beginning of the visit prior to any other assessment taking place, to avoid influencing subject responses. The CAT will be completed electronically by the subject at the investigator's site at the visit schedule indicated in Table 8-1.

The assessment consists of eight items, each presented as a semantic 6-point differential scale, providing a total score out of 40. A higher score indicates a worse health status. The result is immediately available without the need for any calculation, apart from summing the scores on individual items. Scores of 0 - 10 (mild), 11 - 20 (moderate), 21 - 30 (severe) and 31 - 40 (very severe) represents the clinical impact of COPD upon the subject.

8.5.1.2 St. George's Respiratory Questionnaire (SGRQ)

The St. George Respiratory Questionnaire (SGRQ) will be used to provide the health status measurements in this study (Jones el al 1992). The SGRQ will be electronically completed by the subject at the investigator's site at the visits indicated in the Assessment schedule.

The SGRQ questionnaire should always be completed before any other assessments (including any other questionnaires) are made to avoid influencing the responses. A detailed guide relating to the administrative procedures of the questionnaire is given in SOM.

Instrument scoring and handling of missing item data will be conducted in accordance with the user guide for the SGRQ.

The SGRQ contains 50 items divided into two parts covering three aspects of health related to COPD: Part I covers "Symptoms" and is concerned with respiratory symptoms, their frequency and severity; Part II covers "Activity" and is concerned with activities that cause or are limited to breathlessness; Part II is also concerned with "Impacts", which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease. A score will be calculated for each of these three subscales and a "Total" score will also be calculated. In each case the lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of health status.

8.5.1.3 Cough And Sputum Assessment Questionnaire (CASA-Q)

The CASA-Q is a validated questionnaire instrument used to measure cough and sputum production, and their impact in subjects with chronic obstructive pulmonary disease (COPD) and/or chronic bronchitis (Crawford et al 2008). The assessment will be completed by the subject at the beginning of the visit prior to any other assessment taking place. The CASA-Q contains a total of 20 items on a 5-step scale distributed in four domains: Cough symptoms (COUS; 3 items), Cough impact (COUI; 8 items), Sputum symptoms (SPUS; 3 items) and Sputum impact (SPUI; 6 items).

There are only domain scores and no overall score. The score in each domain ranges from 0 to 100, with lower score indicating more severe symptoms or a higher impact.

The CASA-Q will be completed electronically by the subject at the investigator's site at the visit schedule indicated in Table 8-1.

8.5.1.4 EXACT-PRO Questionnaire

The EXACT-PRO is a validated 14-item electronic questionnaire designed to detect the frequency, severity, and duration of exacerbations in subjects with COPD (Leidy et al 2011; Leidy et al 2014a, Leidy et al 2014b). It is to be completed by the subject at the end of every day at bedtime in order to measure the underlying day to day variability of COPD, and detect worsening indicative of an exacerbation.

Within the 14-item EXACT-PRO tool, the Evaluating Respiratory Symptoms (E-RS™) scale is based on the 11 respiratory symptom items. These 11 items generate a total score, quantifying respiratory symptom severity overall, and 3 subscale scores assessing breathlessness, cough and sputum, and chest symptoms.

The single questionnaire will be used for two functions: quantification of respiratory symptoms in using E-RS total and subscale scores, and the assessment of acute exacerbations using the entire EXACT-PRO instrument.

8.5.1.5 Electronic Diary (eDiary)

At Screening all subjects will be provided with an electronic diary (eDiary).

eDiary will record CCI background therapy and study drug medications intake (dose) after randomisation, as well as the study questionnaires (EXACT-PRO (daily), CAT, CASA-Q , SGRQ and EQ-5D-3L) at prespecified timepoints. Refer to SOM for details in different registration starting time-points (for background therapy, CCI questionnaires, study drug intake).

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Starting from Day 1, subjects will be required to complete the EXACT-PRO questionnaire daily as well (see Section 8.5.1.4 for EXACT-PRO questionnaire). The eDiary is to be reviewed at each clinic visit until study completion.

Sites and subjects will receive appropriate training and guidance on the use of the eDiary device.

A list of eDiary questions is provided in SOM.

8.5.1.6 EQ-5D-3L

The European Quality of Life–5 Dimensions–3 Level (EQ-5D-3L) developed by the EuroQol Group provides a standardized self-reported measure of health status. It is a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). The EQ-5D-3L consists of two pages – the descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with three levels: no problems, some problems, and extreme problems. The subject is asked to indicate his/her present health state according to the most appropriate statement for each of the five dimensions. The EQ VAS records the subjects' self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. There is no recall period and subject responds to the present health status.

The EQ-5D-3L will be used for the purpose of the computation of utilities that can be used in health economic studies.

8.5.2 Pharmacokinetics

Blood samples will be obtained from all subjects as per visits and timepoints indicated in Table 8-1.

Pharmacokinetic blood sampling (pre- and post-dose) will be done and evaluated in all subjects at Day 1, Day 28, Day 56 and Day 84 visit. Additionally, a subset of approximately 30 to 40 subjects will undergo pharmacokinetic serial sampling up to 8 hours post-dose at the beginning of the treatment on Day 1 and Day 28 as per Table 8-1, to examine the time-concentration profiles of QBW251 after single dose and multiple doses in COPD subjects.

Furthermore, additional PK samples will be collected, where possible, from subjects experiencing a treatment-emergent SAE, unless a scheduled PK sampling occurs within 7 days of the start date of the SAE.

While PK sampling occurs also in subjects receiving placebo, plasma PK samples will be evaluated only in subjects who have been administered QBW251. QBW251 will be analyzed by a validated LC-MS/MS method with an anticipated lower limit of quantification (LLOQ) of 1 ng/mL of QBW251. Concentration below the LLOQ will be reported as zero and missing data will be labeled as such in the bioanalytical report.

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): Cmax, Tmax, AUClast, AUC0-8h, T1/2 from the plasma concentration-time data.

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8.5.3 Biomarkers

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8.5.4 Other Assessments

Not applicable.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be permanently discontinued for a subject under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment Section 6.2.2
- Any situation in which study participation might result in a safety risk to the subject (e.g. hospitalization)
- Following emergency unblinding

- Emergence of AE reported as severe and suspected to be related to investigational drug or an SAE reported and suspected to be related to investigational drug
- Emergence of an SAE not suspected to be related to investigational drug in a subject with a verified exposure above the threshold AUC0-24h≥91,700 ng*h/ml. The investigator must permanently discontinue the investigational study drug as soon as possible upon receipt of the PK results.
- A subject with a verified exposure above the upper range of the individual animal (monkey) model exposure (AUC0-24h≥159,000 ng*h/ml). The investigator must stop study drug as soon as possible upon receipt of the PK results.
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study
- Any liver event requiring immediate discontinuation of study treatment, as specified in Table 16-2
- Individual serum creatinine increase ≥ 50% compared to baseline (must be confirmed). Confirmation of the assessment should be made as quickly as possible after an abnormal result is received. A renal event leading to subject discontinuation should be followed up until event resolution (Serum Cr within 10% of baseline), or event stabilization (Serum Creatinine level within ±10% variability over last 6 months)
- Study drug can be temporarily interrupted as a response to the occurrence of adverse events that do not fulfill the requirements above described for permanent discontinuation (refer to Section 6.5.1).

As a consequence, investigational study drug must be permanently discontinued in a subject exhibiting

- an estimated AUC0-24h > 91,700 ng*hr/ml in association with a reported SAE

or

- an estimated AUC0-24h > 159,000 ng*hr/ml even in the absence of any SAE (please see more details regarding this topic on Section 6.5.1.1) .

If a female subject of childbearing potential withdraws from the study prematurely, the investigator should recommend her to maintain contraceptive measures for at least 3 days after the last dose of the study drug.

If permanent discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code Section 6.6.3.

Subjects who have their study treatment permanently discontinued should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section). **Where possible, they should return for the assessments indicated in the**

assessment schedule in Table 8-1**.** If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule. If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule and at a minimum information on new/ concomitant treatments and adverse events /serious adverse events should be obtained.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table (Table 8-1).

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For EU and US: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 Study stopping rules

9.1.4.1 Dose Reduction

Commercially Confidential Information

9.1.4.3 Overall study stopping rules

Enrollment in the study will be placed on hold if the Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justify putting the study on hold. Related criteria are defined in the DMC charter.

The study may resume following the full safety review, if the Principal Investigator and Sponsor agree it is safe to proceed. Any restart following a temporary hold due to stopping rules being met will require the Competent Authorities and Ethic Committees to approve the study to proceed, as required per country regulations.

In case of significant exposure scenarios, study may be stopped after DMC review. Related criteria are defined in the DMC charter. See also Section 6.5.1.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Exposure driven decision rules are described below in Section 9.1.4.1. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible. The Investigator should ensure contact is made as quickly as possible by telephone and/or e-mail and/or letter. If the study is stopped for a change in the benefit/risk assessment or for medical reasons, subjects may be instructed to stop taking the investigational drug QBW251 immediately. Else, subjects may be instructed to continue QBW251 intake until they can return to the site for a final assessment. Background medication LABA/LAMA, LABA/ICS or LABA/LAMA/ICS or macrolides should be continued until the final visit. The subject should be treated as a prematurely withdrawn subject and undergo all assessments of the premature withdrawal visit. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their end of study (EOS) completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision (e.g. each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

Upon completion of a subject's participation in the study, he/she should be treated according to his/her individual needs. It is not planned to provide QBW251 to study participants after the study is completed due to the early stage of development. Since this study is a Phase 2 study, the safety profile of the drug has not yet been established to the extent considered adequate for a provision of QBW251 with less stringent safety monitoring.

Randomized and/or treated subjects will have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3 and in the SOM. Documentation of attempts to contact the subject should be recorded in the source documentation.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying AEs.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the subject at each visit during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

AEs must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade:
2. mild: usually transient in nature and generally not interfering with normal activities
3. moderate: sufficiently discomforting to interfere with normal activities
4. severe: prevents normal activities
5. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of

underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject

6. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
7. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
8. Action taken regarding with study treatment

All AEs must be treated appropriately. Treatment may include one or more of the following:

- Dose not change
- Drug interrupted/withdrawn
- its outcome (i.e. recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values that are considered to be non-typical in subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are referenced in Section 16.1.

Follow the instructions found in the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires insubject hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outsubject basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Screen Failures: If a subject fails screening (e.g. a subject who is screened but is not treated or randomized), SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Randomized Subjects who discontinue prematurely: SAEs collected between the time a subject signs the ICF until 30 days after the subject discontinued or stopped study treatment, or had their last study visit, which ever is later should be reported to Novartis/sponsor safety within 24 hours of learning of its occurrence.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, and under no circumstances later than 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis Chief Medical Office and subject Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. **Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.**

10.1.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and subject Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational study drug any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Follow up of pregnancies should be conducted as described below:

- At expected date of delivery (EDD) +1 month: Mandatory to all pregnancy cases; pregnancy outcome, and other clinically relevant pregnancy data or changes in data, should be collected.

- At EDD +2 months: Mandatory if no answer is obtained after request at EDD+1 month; same information as at EDD+1 month should be collected.
- At EDD+3 months: Mandatory for all cases of live birth/unknown outcome; status of the baby 3 months after delivery, any development issue or abnormality that would not be seen at birth
- EDD+12 months: Mandatory for all cases of live birth/unknown outcome; infant health status and development

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections (AE Section 10.1.1, SAE definition Section 10.1.2 and SAE reporting Section 10.1.3).

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 16-1 in Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information, and the procedures performed must be recorded as appropriate in the eCRF. Refer to the SOM for additional details.

10.2.2 Renal safety monitoring

Renal safety monitoring for the investigational drug will be performed in the study. This includes baseline measurements of serum creatinine, calcium, potassium and urine dipstick and at subsequent visits as indicated in the Schedule of Assessments Table 8-1.

10.2.3 Data Monitoring Committee

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded and entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and

adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

For the HRCT scans, a dedicated imaging CRO will collect all HRCT data from the sites The analysis results will be generated by the imaging CRO and transformed into a Novartis format defined by a data transfer specification. The transformed output will then be sent to Novartis data management for incorporation into the CSR. The imaging CRO will be responsible for all image data clarification forms and missing data at all sites.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA organization. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according

to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The baseline value is defined as the last assessment prior to first dose administration. In case the scheduled baseline assessment value is missing, the screening value if available will be used instead.

No multiplicity adjustments will be considered due to the non-confirmatory nature of this study.

Screen failure subject's data will not be reported unless an SAE occurs during screening. For SAEs in screening, all subject data will be reported

12.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study treatment.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects with PD data at both baseline and at least one post-baseline assessment which are not affected by any protocol deviations.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the safety analysis set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The duration of exposure to study treatment will be summarized by means of descriptive statistics using the Safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis of the primary endpoint(s)

The primary objective of the study is to assess the change from baseline on fibrinogen plasma concentration levels after 12 weeks of treatment with QBW251 compared to placebo.

12.4.1 Definition of primary estimand

The primary estimand, defined below, quantifies a hypothetical effect of 12 weeks treatment that would have been observed if all subjects remained on their treatment for 12 weeks:

- **Target population**: subjects with moderate to severe COPD with features of chronic bronchitis and a history of exacerbations and treated with any of the combinations of LABA, LAMA, or ICS along with or without macrolides as background therapy
- **Variables of interest**: change from baseline in fibrinogen after 12 weeks of treatment.
- **Intercurrent events of interest:**
    1. Discontinuation of study treatment or study participation before 12 weeks of treatment
    2. Intake of rescue medications or intake of antibiotics before 12 weeks of treatment
- **Summary measure:** mean difference between treatment groups (QBW251 compared with placebo).

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will include all available data from subjects in the PD analysis set.

The fibrinogen samples taken within 2 weeks after exacerbation or during or after last dose of antibiotics other than macrolide would be set to missing if a valid unscheduled assessment did not happen at that time point for the primary analysis.

The primary analysis will be performed using a one-sided test at alpha=0.1 (two-sided 80% confidence intervals) and estimated treatment difference (QBW251-Placebo) at week 12 will be reported along with associated 80% confidence intervals.

The comparison of QBW251 to placebo will be evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_1):

H_0: There is no reduction in fibrinogen from baseline after 12 weeks of treatment in QBW251 compared to placebo

H_1: There is a reduction in fibrinogen from baseline after 12 weeks of treatment in favor of QBW251 compared to placebo.

The change from baseline in fibrinogen is assumed normally distributed. A MMRM will be fitted to the changes from baseline in fibrinogen for all time points until Day 84 visit including the fixed factors and covariates but are not limited to the following:

- treatment group
- visit/time

- treatment group by visit/time interaction
- smoking status
- baseline fibrinogen value by visit/time interaction.

If normality assumptions are not met, then the fibrinogen data may be log transformed.

12.4.3 Handling of missing values/censoring/discontinuations

Estimates of the missing values due to intake of rescue medications or antibiotics will be derived by the model under the missing at random (MAR) assumption. Alternative assumptions may be explored to investigate the robustness of the results under plausible non-missing at random situations.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

Subjects whose bacterial load or fibrinogen levels collected at the planned visits regardless of the intake of antibiotics other than macrolide or exacerbated during QBW251 treatment period will be included and analysed using repeated measures model similar to primary analyses. This would allow to assess the robustness of the QBW251 treatment effect on fibrinogen and bacterial load drop with and without prohibited antibiotics/exacerbation that would be deemed to affect the outcome of interest.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Key secondary pharmacodynamic endpoint:

- Change from baseline in the logarithm of total number of colony forming units (CFU/mL) of potentially pathogenic microorganisms in spontaneous sputum after 12 weeks of treatment.

The bacterial load will include all available data from subjects in the PD analysis set and will be analyzed similar to the primary analysis. The bacterial load samples taken within 2 weeks after exacerbation or during or after last dose of antibiotics would be set to missing if a valid unscheduled assessment did not happen at that time point for the primary analysis.

Secondary pharmacodynamic and efficacy endpoints are as follows:

- Change from baseline in airway wall and lumen parameters along with extent of global and regional air trapping as measured by HRCT.
- Change from baseline in FEV1, FVC and FEV1/FVC measured by spirometry after 12 weeks of treatment.

In order to be included in the sputum analysis, a subject must provide a sufficient sputum sample at screening, and/or at baseline and at least one post-baseline visit. The change from baseline in the logarithm of the total number of colony forming units including all different micro-organisms (CFU) and change from baseline in the secondary efficacy including global air trapping and spirometry parameter will be analyzed using the same model as for the primary

variable of interest. Contrasts for treatment differences will be provided together with two-sided 80% Confidence Intervals.

All spirometry parameters and HRCT parameters including regional and global air trapping changes will be summarised.

These will be calculated at all time points as specified in the assessment schedule (Table 8-1), and specifically at the primary time point of interest (Day 84) considering placebo as the reference treatment.

Any correlations between changes in air trapping and the lung function parameters measured by spirometry would be explored.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 1 week after the last actual administration of any study treatment.

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation. A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, subject and visit/time, and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

12-lead ECG

All ECG data will be listed by treatment group, subject and visit/time, and abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time, and if normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

12.5.3 Pharmacokinetics

Descriptive statistics of QBW251 plasma concentration data will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the lower limit of quantification (LLOQ). Summary statistics of QBW251 plasma concentration data and PK parameters will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax, where median, minimum, and maximum will be presented.

Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

12.5.4 Patient Reported Outcomes and Exacerbations

Subject reported outcomes

Cough and Sputum Assessment Questionnaire (CASA-Q) and St. George's Respiratory Questionnaire (SGRQ) domain scores, COPD assessment test (CAT), EQ-5D-3L and EXACT-PRO questionnaire data will be summarized by treatment and visit. Prespecified sub-groups and correlation analysis are provided in the SAPCOPD exacerbations based on EXACT PRO Questionnaire.

The following analyses will be performed to explore any differences in the exacerbation events that occur in QBW251 vs placebo:

1) Time to first exacerbation

The time-to-event analyses will be carried out only upon sufficient number of exacerbation events occur during the study to estimate the median in either of the treatment groups.

The time to the first on-treatment exacerbation (event) is defined as the start date of first exacerbation minus the date of randomization +1. Subjects who do not experience an exacerbation or discontinued earlier without an exacerbation will be censored for analyses purposes.

The hazard ratios for QBW251 compared with placebo and their corresponding 80% confidence intervals will be computed using Kaplan-Meier method. The stratification factor may include number of exacerbations.

The Kaplan-Meier estimates of the survival functions for each treatment will be plotted.

2) Annualized rate of COPD exacerbations

The total frequency of COPD exacerbations over the 12 week treatment period will be analyzed using a generalized linear model assuming a negative binomial distribution. The time at risk for a subject is defined as the length of time the subject is on treatment and the log (length of time) will be used as the offset variable in the model. The model will include treatment, antibiotic use, and the number of exacerbations in the past 12 months prior to screening as categorical variables. An estimate of the rate ratio together with 80% confidence intervals and corresponding p-value will be presented.

3) The percentage of subjects experiencing at least a COPD exacerbation

The proportion of subjects with at least one COPD exacerbation will be analyzed using logistic regression. The model will include treatment, antibiotic use, and the number of exacerbations in the past 12 months prior to screening as categorical variables. The estimated odds ratios will be displayed along with the associated 80% confidence intervals.

12.6 Analysis of exploratory endpoints

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12.7 Interim analyses

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Commercially Confidential Information

12.8 Sample size calculation

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13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis

monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory reports. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate eCRF.

Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

See Section 16.2 for specific liver event and laboratory test trigger definitions and follow-up requirements.

For ECGs, a notable QTc value is defined as a QTcF (Fridericia) interval of $\geq$ 450 msec for males or $\geq$ 460 msec for females – all such ECGs will be flagged by the Central ECG reading and require assessment for clinical relevance and continuance of the subject by the Investigator.

16.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN · 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

Table 16-2 Follow up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
Jaundice	• Discontinue the study treatment immediately • Hospitalize the subject • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Appendix 3: Specific renal alert criteria, Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase 50 % + **OR if <18 years old, eGFR 35 mL/min/1.73 m^2**	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider subject hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	• Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

+ Corresponds to KDIGO criteria for Acute Kidney Injury

Additional specialized assessments are available to assess renal function or renal pathology.

(Note: In exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by the RSG to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output

- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

Table 16-4 Renal Event Follow Up

FOLLOW-UP OF RENAL EVENTS
• Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF
• Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. • Analysis of urine markers in samples collected over the course of the DIN event