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QBW251

Clinical Trial Protocol CQBW251B2201 / NCT04072887

A 24-week multi-center, double-blind, placebo controlled dose-range finding study to investigate the efficacy and safety of oral QBW251 in COPD patients on triple inhaled therapy (LABA/LAMA/ICS)

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List of abbreviations

AE	adverse event
AIC	Akaike information criterion
Alb	Albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS/ERS	American Thoracic Society (ATS)/European Respiratory Society (ERS)
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration curve over 24 hours
b.i.d.	twice a day
BCRP	Breast Cancer Resistance Protein
BD	bronchodilator
BMI	Body Mass Index
BTPS	body temperature, pressure, saturated with water vapor
BUN	blood urea nitrogen
CASA-Q	Cough and sputum assessment questionnaire
[redacted]	[redacted]
CAT	COPD assessment test
CF	Cystic fibrosis
CFR	Code of Federal Regulation
CFTR	Cystic fibrosis transmembrane conductance regulator
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CMO & PS	Novartis Chief Medical Office and Patient Safety
COPD	Chronic Obstructive Pulmonary Disease
COUI	cough impact domain
COUS	cough symptoms domain
COVID-19	Corona Virus Disease 2019
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Commercial Research Organization
[redacted]	[redacted]
CT	computer-assisted tomography
CTT	Clinical Trial Team
CV	coefficient of variation
CYP1A2	Cytochrome P450 1A2 enzyme
CYP2B6	Cytochrome P450 2B6 enzyme
CYP3A4	Cytochrome P450 3A4 enzyme
DAR	Dose Administration Record
DDE	Direct Data Entry
DMC	Data Monitoring Committee

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DR	Dose response
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED50	efficacious dose in 50% of subjects
EDC	Electronic Data Capture
EDD	expected date of delivery
EMA	European Medicines Agency
E-RS	Evaluating Respiratory Symptoms in COPD
ER	emergency room
ERS	European Respiratory Society
eSAE	Electronic Serious Adverse Event
EU	European Union
EXACT	EXAcerbations of COPD Tool
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
h	Hour
hCG	Human chorionic gonadotropin
HCRU	Health care resource utilization
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
[redacted]	[redacted]
ICS	Inhaled CorticoSteroid
IEC	Independent Ethics Committee
IN	Investigator Notification
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
IVRS/IWRS	interactive voice response system/interactive web-based response system
J2R	jump-to-reference
LABA	Long-Acting β2-Agonist

[redacted]

LAMA	Long-Acting Muscarinic receptor Antagonist
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	Lower limit of quantification
MAR	Missing at random
MCP-Mod	Multiple comparison procedure-modelling
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
mMRC	modified Medical Research Council scale
MMRM	Mixed-effect linear model for repeated measures
MRI	magnetic resonance imaging
mRNA	messenger Ribonucleic Acid
NDA	New Drug Application
ng	nanogram
NOAEL	No Adverse Event Level
NYHA	New York Heart Association
OAT3	Organic Anion Transporter 3
OATP1B1	Organic Anion Transporter 1B1
OATP1B3	Organic Anion Transporter 1B3
PD	pharmacodynamic(s)
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
pMDI	pressurized Metered Dose Inhaler
PRO	patient-reported outcome
PSW	premature subject withdrawal
PT/INR	Prothrombin time international normalized ratio
QMS	Quality Management System
QT	QT interval (measure between Q wave and T wave in the heart's electrical cycle)
QTc	corrected QT interval
QTcF	QT interval with Fridericia's correction
RAS	Randomized analysis set
RoW	rest of world
SABA	short-acting beta2-receptor agonist
SAE	serious adverse event
SAP	Statistical analysis plan
SCS	Systemic corticosteroids
SD	standard deviation
SGRQ	St George's Respiratory Questionnaire
SPUI	sputum impact domain
SPUS	sputum symptoms domain
SUSAR	Suspected Unexpected Serious Adverse Reactions

[redacted]

t.i.d	3 times a day
TBL	total bilirubin
T_{max}	time to reach maximum (peak) plasma concentration following drug administration
ug	microgram
UGT	UDP-glucuronosyltransferase
UGT1A1	Uridine Diphosphate-Glucuronosyltransferase 1A1
UGT2B7	Uridine Diphosphate-Glucuronosyltransferase 2B7
UK	United Kingdom of Great Britain and Northern Ireland
ULN	upper limit of normal
US	United States of America
WHO	World Health Organization

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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.
Cohort	A specific group of subjects fulfilling certain criteria.
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial.
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 (IVRS) 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 study	The end of the clinical study is defined as the last visit of the last subject or at a later point in time as defined in 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	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 number	A unique identifier on the label of each study drug package in studies that dispense study drug 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.
Run-In Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject's intervention or other treatment).
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 the data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.

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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 drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date.
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of informed consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data.

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Protocol summary

Protocol number	CQBW251B2201
Full Title	A 24-week multi-center, double-blind, placebo controlled dose-range finding study to investigate the efficacy and safety of oral QBW251 in COPD patients on triple inhaled therapy (LABA/LAMA/ICS)
Brief title	Dose-range finding efficacy and safety study for QBW251 in COPD patients
Sponsor and Clinical Phase	Novartis Pharma AG Phase IIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to support the dose selection for the future development program of QBW251 by evaluating efficacy and safety of different QBW251 doses in patients with Chronic Obstructive pulmonary disease (COPD) with chronic bronchitis and a history of exacerbations. QBW251 treatment will be added on top of a triple combination therapy of a long-active beta2-agonist (LABA), a long-acting muscarinic receptor-antagonist (LAMA) and an inhaled corticosteroid (ICS). The study has a parallel design with QBW251 doses ranging from 25 to 450 mg administered twice daily (b.i.d.), which is expected to adequately describe the dose-response of QBW251. It is compared to placebo as a control in the absence of an approved COPD drug in this class. The study will standardize the COPD background therapy to a LABA/LAMA/ICS triple combination to limit its confounding potential on the study outcomes. The choice of the medications reflects their global availability, the convenience of once daily dosing, and the recommendation of The Global Initiative for chronic Obstructive Lung Disease (GOLD) strategy (GOLD 2018) for use of triple inhaled therapy for exacerbating and symptomatic patients despite therapy with ICS/LABA or LABA/LAMA. This patient population closely mimics the patient population targeted by this study.
Primary Objective(s)	The primary objective of this study is to characterize the dose-response relationship of QBW251 administered orally over 12 weeks on lung function, compared to placebo, when added to inhaled triple combination therapy (LABA/LAMA/ICS). Trough forced expiratory volume in one second (FEV_1) will be assessed at Week 12 and evaluated as change from baseline after 12 weeks of treatment.
Secondary Objectives	Objective 1: To evaluate symptoms (overall COPD symptoms, cough and sputum) across various dose levels of QBW251 administered orally over 24 weeks, compared to placebo at Weeks 12 and 24. Endpoints are • Change from baseline in the Evaluating Respiratory Symptoms in COPD (E-RS) weekly mean scores (total and subscale scores). • Change from baseline in Patient Global Impression of Severity (PGI-S) score. • Change from baseline in the Cough and Sputum Assessment Questionnaire (CASA-Q) domain scores - cough symptoms, cough impact, sputum symptoms, and sputum impact.

	Objective 2: To evaluate health-related quality of life across various dose levels of QBW251 administered orally over 24 weeks, compared to placebo, at Weeks 12 and 24. The endpoint assessed is the change from baseline in St. George's Respiratory Questionnaire (SGRQ) total and domain scores at Weeks 12 and 24. Objective 3: To evaluate lung function across various dose levels of QBW251 administered orally over 24 weeks, compared to placebo, over 4, 8, 16, 20 and 24 weeks. Trough FEV_1 change from baseline after 4, 8, 16, 20 and 24 weeks of treatment, respectively, will be evaluated. Objective 4: To evaluate safety and tolerability across various dose levels of QBW251, administered orally over 24 weeks, compared to placebo, as assed by ECGs, laboratory tests (hematology and clinical chemistry, urinalysis), vital signs, and adverse events (AEs) per treatment group. Objective 5: To assess the pharmacokinetics (PK) of QBW251 in COPD patients through measurement of trough concentration and minimum concentration (C_{min}) on all visits and around maximum concentration (C_{max}) on Days 1, 15 and 169. The area under the plasma concentration-time curve (AUC) and C_{max} on Days 1 and 15 will be assessed in a sub-group of patients.
Study design	This study uses a 6 treatment arm, parallel-group, randomized, double-blind study design. One treatment arm (450 mg b.i.d.) has been discontinued. The study is placebo-controlled with a standardized COPD background treatment. The treatment period lasts 24 weeks, the total duration of study participation for a patient is 31 weeks.
Population	The study population will consist of approximately 956 male and female patients (≥ 40 years of age) with moderate to severe COPD (GOLD 2 and 3) and a smoking history of at least 10 pack years. It is expected that approximately 1500 patients will be screened globally to achieve the targeted number of randomized patients.
Key Inclusion criteria	• Male and female COPD patients aged ≥ 40 years, who have signed an Informed Consent Form (ICF) prior to initiation of any study-related procedure. • Current or ex-smokers who have a smoking history of at least 10 pack years. • Patients who have been treated with a triple combination of LABA/LAMA/ICS for the last 3 months prior to screening. • A COPD Assessment Test (CAT) score of at least 10 at Run-In 1 visit. • Patients with a post-bronchodilator FEV_1 to forced vital capacity (FVC) ratio (FEV_1/FVC) < 0.70 at Run-In 1 visit. • Patients with airflow limitation indicated by EITHER a post-bronchodilator FEV_1 ≥ 30% and FEV_1 < 50% of the predicted normal at Run-In 1, who must have had at least 1 documented moderate or severe healthcare resource utilization (HCRU) exacerbation in the 12 months prior to study entry (screening), OR a post-bronchodilator FEV_1 ≥ 50% and < 80% of the predicted normal at Run-In 1, who must have had at least 2 documented moderate or at least 1 documented severe HCRU exacerbation(s) in the 12 months prior to study entry (screening)

	• Patients featuring chronic bronchitis, defined by the presence of cough and bronchial hypersecretion, that occurs for at least 3 consecutive months in each of 2 consecutive years prior to study entry (screening), documented in patient history.
Key Exclusion criteria	• Patients who have a history of long-QT syndrome, or a clinically significant ECG abnormality at Run-In 1 or Run-In 2, or whose corrected QT interval (QTc) measured at Run-In 1 is prolonged. • Patients who have clinically significant renal, cardiovascular, neurological, endocrine, immunological, psychiatric, gastrointestinal, or hematological abnormalities, which could interfere with the assessment of the efficacy and safety of the study treatment, with a clinically significant laboratory abnormality at Run-In 1, or patients with Type I diabetes or uncontrolled Type II diabetes. • Patients who have had a COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization, or a respiratory tract infection in the 4 weeks prior to screening, or between screening and Day 1. • Patients with any documented history of asthma, or with an onset of chronic respiratory symptoms, including a COPD diagnosis, prior to age 40 years. • Patients with a body mass index (BMI) of more than 40 kg/m^2. • Use of other investigational drugs (approved or unapproved) within 30 days or 5 half-lives prior to screening, or until the expected pharmacodynamic (PD) effect has returned to baseline (e.g. biologics), whichever is longer; or longer if required by local regulations. • Pregnant or nursing (lactating) women, and women of childbearing potential not willing to use acceptable effective methods of contraception during study participation.
Study treatment	• Treatment arm 1: QBW251, 450 mg, b.i.d. (discontinued) • Treatment arm 2: QBW251, 300 mg, b.i.d. • Treatment arm 3: QBW251, 150 mg, b.i.d. • Treatment arm 4: QBW251, 75 mg, b.i.d. • Treatment arm 5: QBW251, 25 mg, b.i.d. • Treatment arm 6: Placebo matching QBW251, b.i.d. All patients are receiving standardized background COPD medication consisting of fluticasone furoate, umeclinidium and vilanterol.
Efficacy assessments	• Spirometric assessments (forced spirometry) • Electronic diary/EXACT questionnaire • St. George's Respiratory Questionnaire (SGRQ) • Patient global impression of severity questionnaires • Cough and Sputum Assessment Questionnaire (CASA-Q) • [redacted]
Pharmacokinetic assessments	• Pharmacokinetic blood sampling

[redacted]

Key safety assessments	• Adverse event monitoring • Physical examinations • Vital signs • Electrocardiograms (ECGs) • Monitoring of laboratory markers in blood and urine • Pregnancy monitoring
Other assessments	[redacted] • Baseline characterization of patients through using the COPD Assessment Test (CAT) [redacted]
Data analysis	Primary objective: The MCP-Mod methodology will be used on the primary endpoint of trough FEV1 change from baseline after 12 weeks of treatment to address the primary objective. 1. The adjusted mean responses at each individual dose will be estimated by modeling the primary endpoint using a mixed-effect linear model for repeated measures (MMRM). The null hypothesis of flat dose-response (DR) relationship will be tested at a one-sided significance level of 5% against the alternative hypothesis of a non-constant DR curve using a multiple contrast test, taking model uncertainty into account by considering a wide range of possible DR relationships. 2. Once the DR signal is declared, the final DR curve and the target dose(s) of interest will be estimated by model averaging. Corresponding 90% confidence intervals are obtained using bootstrapping. Secondary objectives: The following secondary endpoints will be analyzed using a MMRM - change from baseline in the E-RS weekly mean total and domain scores, CASA-Q domain scores, SGRQ total and domain scores, and trough FEV1. PGI-S values will be analyzed using a proportional odds model for repeated measures. Treatment-emergent adverse events will be summarized. Summary statistics will be provided by treatment and visit/time for each lab, vital signs, ECG, and pharmacokinetics variable.
Key words	Placebo-controlled dose-range finding study for QBW251 in bronchitic COPD patients in stage GOLD 2 and 3.

[redacted]

1 Introduction

1.1 Background

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms (dyspnea, cough, sputum production) and airflow limitation (diagnosed using spirometry) that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles/gases, in particular cigarette smoke. Chronic airflow limitation is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema).

COPD is a critically important disease, with a prevalence of 10% to 15% in Europe (Blanco et al 2018), approximately 10% in South East Asia and approximately 15% in the Americas (Adeloye et al 2015). COPD affects over 15 million people in the United States of America (US) alone (National Center for Health et al 2017), and is the third leading cause of death worldwide (World Health Organization 2018). COPD is associated with episodic periods of symptom deterioration termed exacerbations. Exacerbations are amongst the most common causes of medical admission to hospital and are also important events in the natural history of COPD that drive lung function decline (Donaldson et al 2002), increased risk of cardiovascular events (Donaldson et al 2010) and are responsible for much of the morbidity and mortality associated with this highly prevalent condition (Soler-Cataluña et al 2005).

COPD is also associated with significant healthcare expenditures with total economic costs in the US estimated at $49.9 billion in 2010, and total direct costs of medical care estimated at $29.5 billion annually. Direct costs associated with hospitalizations for COPD exacerbations in the US exceed $20 billion annually (Guarascio et al 2013). In the European Union, the annual costs of healthcare and lost productivity due to COPD are estimated at €48.4 billion (ERS 2013).

Chronic bronchitis, due to mucous hypersecretion and mucociliary dysfunction characterized by chronic cough and sputum, is a key phenotype amongst COPD patients. Bronchitic patients have higher exacerbation frequency (Seemungal et al 1998) and are more likely to be hospitalized (Vestbo et al 1996, Kim et al 2011). However, effective treatment options are extremely limited in this group. Current standard of care in the management of COPD consists of bronchodilators ± inhaled corticosteroids with triple inhaled therapy (long-acting β2-agonist + long-acting muscarinic receptor antagonist + inhaled corticosteroid = LABA+LAMA+ICS) indicated in patients experiencing exacerbations with dual combination treatments (LAMA+LABA, LABA+ICS). The guidelines also consider macrolide antibiotics and roflumilast as additional add-on therapy to triple therapy in specific sub-groups of patients: in fact 30% to 40% of patients receiving triple inhaled therapy continue to have moderate or severe (hospitalized) exacerbations (Vestbo et al 2017, Mullerova et al 2017). However, long-term macrolide antibiotics are complicated by microbial resistance (Pomares et al 2018) and roflumilast, a non-bronchodilator (PDE4 inhibitor), has modest efficacy and 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 patients remain significantly limited by breathlessness (modified Medical Research Council scale (mMRC) ≥ 2) and 40% experience ≥ 2 moderate or ≥ 1 severe exacerbation per year (Mullerova et al 2017), therefore additional novel therapies are urgently needed.

[redacted]

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), even in the absence of CFTR mutations, and may contribute to the pathogenesis of COPD. CFTR dysfunction due to smoke exposure adversely affects mucociliary transport and is strongly associated with symptoms of chronic bronchitis (Sloane et al 2012). Cigarette smokers and COPD patients exhibit reduced CFTR function by nasal potential difference measurements, accompanied by reduced CFTR mRNA levels (Cantin et al 2006, Sloane et al 2012, Dransfield et al 2013). 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).

Modulation of CFTR function should improve airway hydration, decreasing mucus viscosity and so enhancing mucociliary clearance. CFTR also regulates bicarbonate secretion, whose effect on airway surface liquid pH is important in the fight against pathogens (Pezzulo et al 2012). This mechanism would support a reduction of the airway inflammation/infections and obstruction leading to clinical benefits such as improvement of respiratory function, symptoms of COPD, and a decrease in the rates of exacerbations and respiratory tract infections.

CFTR potentiators increase the activity of the CFTR channel that is present in the cell membrane of the lungs epithelium: this can include wild type CFTR. QBW251 is a novel potentiator of the CFTR channel that is safe and well-tolerated. In study CQBW251X2201, a 28-day randomized, placebo-controlled trial, QBW251 in GOLD 2-3 COPD patients with chronic bronchitis and with various background inhaled therapies demonstrated improvement in lung function (FEV_1) and sweat chloride over placebo, in addition to reducing systemic inflammation (measured by fibrinogen). Furthermore, exploratory sputum analyses have suggested a trend for decreased bacterial colonization with QBW251.

Therefore, QBW251 will be a first-in-class oral CFTR potentiator, with the capacity to reduce COPD exacerbations and improve symptoms, quality of life and lung function when added to inhaled therapies.

1.2 Purpose

The purpose of this Phase 2b study is to support the dose selection for future studies by evaluating efficacy and safety of different QBW251 doses in COPD patients with chronic bronchitis and a history of exacerbations, compared to placebo, when added to a triple combination therapy of LABA/LAMA/ICS. Lung function improvement will be the primary endpoint: trough FEV_1 change from baseline after 12 weeks of treatment.

The study will also provide information on longitudinal spirometry assessments over 24 weeks, patient reported outcome (PRO) tools and safety.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**

Objective(s)	Endpoint(s)
• Characterize the dose-response relationship of QBW251 administered orally over 12 weeks on lung function, compared to placebo when added to inhaled triple combination therapy (long-acting β2-agonist/long-acting muscarinic receptor antagonist/inhaled corticosteroid; LABA/LAMA/ICS).	• Trough FEV_1 change from baseline after 12 weeks of treatment.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Evaluate symptoms (overall COPD symptoms, cough and sputum) across various dose levels of QBW251 administered orally over 24 weeks, compared to placebo at Weeks 12 and 24.	• Change from baseline in the Evaluating Respiratory Symptoms in COPD (E-RS) weekly mean scores (total and subscale scores). • Change from baseline in Patient Global Impression of Severity (PGI-S) score. • Change from baseline in the Cough and Sputum Assessment Questionnaire (CASA-Q) domain scores - cough symptoms, cough impact, sputum symptoms, and sputum impact.
• Evaluate health-related quality of life across various dose levels of QBW251 administered orally over 24 weeks, compared to placebo, at Weeks 12 and 24.	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total and domain scores at Weeks 12 and 24.
• Evaluate lung function across various dose levels of QBW251 administered orally over 24 weeks, compared to placebo, over 4, 8, 16, 20 and 24 weeks.	• Trough FEV_1 change from baseline after 4, 8, 16, 20 and 24 weeks of treatment, respectively.
• Evaluate safety and tolerability across various dose levels of QBW251, administered orally over 24 weeks, compared to placebo.	• Assessment of ECGs, laboratory tests, vital signs, and adverse events per treatment group.
• Assess the pharmacokinetics of QBW251 in COPD patients. Additionally this information may be used to understand the relation between drug exposure and efficacy and/or safety.	• Assessment of drug exposure (trough concentration; C_{min}) on all visits and around C_{max} on Days 1, 15 and 169. AUC and C_{max} on Days 1 and 15 in a sub-group of patients.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

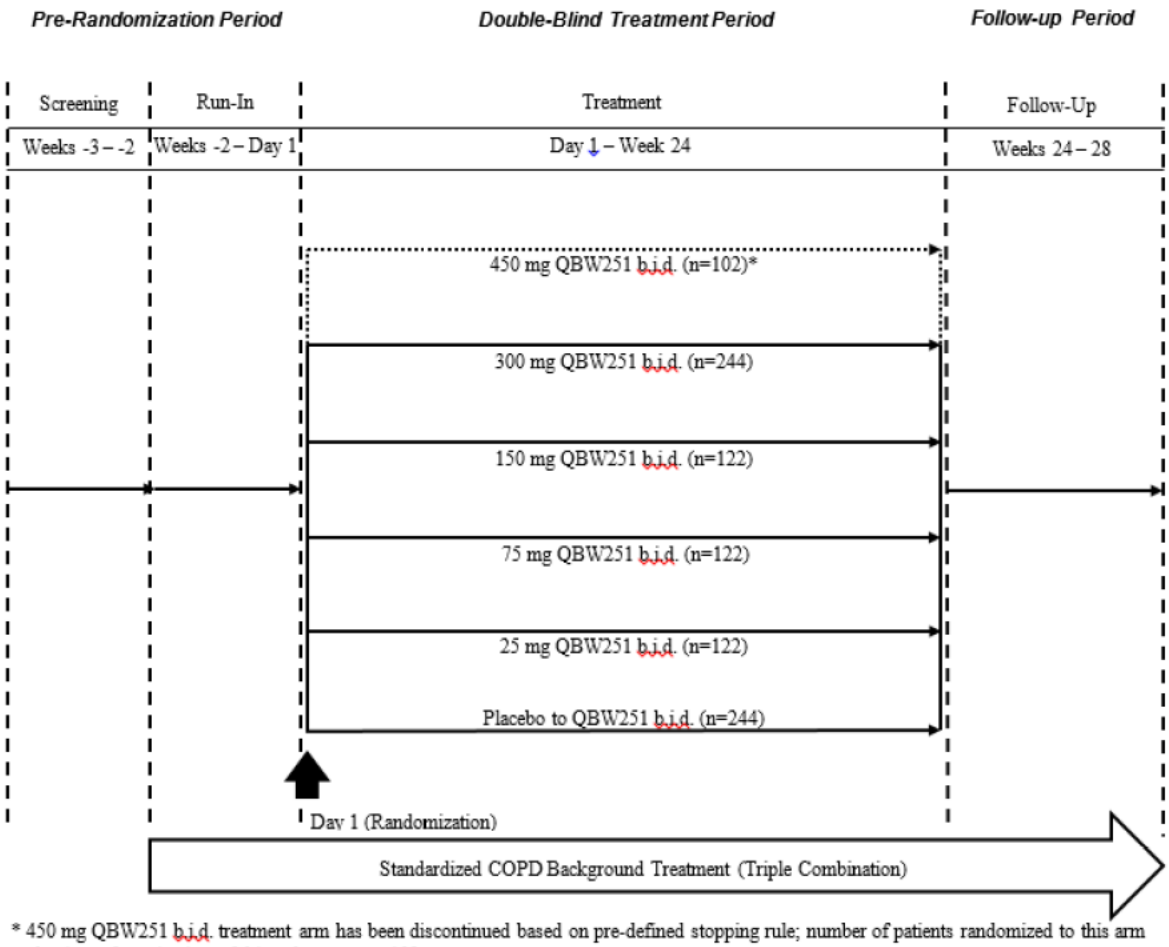
Objective(s)	Endpoint(s)
[redacted]	[redacted]

3 Study design

This study uses a 6 treatment arm, parallel-group, randomized, double-blind study design. One treatment arm (450 mg b.i.d.) was discontinued after reaching a pre-defined stopping criterion (see Section 9.1.4.1 and Section 12.7.1) at the first DMC interim analysis. Approximately 956 male and female COPD patients are randomized into the trial and initially undergo a screening period of 1 week. This screening period (Weeks -3 to -2) serves to assess eligibility and to taper patients off disallowed medications. Subsequently, patients enter the run-in period (2 weeks; Days -14 to 1) to establish baseline values for symptom assessments, to standardize the COPD background therapy (triple combination LABA/LAMA/ICS), and to complete eligibility assessments. At visit Run-In 2 final eligibility will be assessed. Eligible patients will move into the Day 1 visit where they are stratified according to their smoking status (current or ex-smoker) and severity of airflow limitation (FEV1 $\geq$ 30% to $<$ 50% and $\geq$ 50% to $<$ 80%) and then randomized into 1 of 6 treatment arms with a randomization ratio of 2:2:1:1:1:2 (450 mg b.i.d., 300 mg b.i.d., 150 mg b.i.d., 75 mg b.i.d., 25 mg b.i.d., placebo - see also Figure 3-1). After reaching the pre-defined exposure-based stopping criterion, patients were no longer randomized to the 450 mg b.i.d. treatment, resulting effectively in a 2:1:1:1:2 randomization ratio (300 mg b.i.d.:150 mg b.i.d.: 75 mg b.i.d.: 25 mg b.i.d.: placebo) from the day of 450 mg b.i.d. discontinuation (20-Apr-2020) onward. Day 1 also generates additional baseline data and study treatment is initiated. The treatment period consists of 24 weeks, during which the patient returns to the site for regular visits (Day 1 – Week 24). Upon completion of the treatment period, patients are followed up for safety assessments during the Follow-Up period (Weeks 25 – 28).

[redacted]

Figure 3-1 Study design



* 450 mg QBW251 b.i.d. treatment arm has been discontinued based on pre-defined stopping rule; number of patients randomized to this arm at the time of termination of this cohort was n=102.

4 Rationale

4.1 Rationale for study design

The randomized, double-blind, parallel-group, and placebo-controlled design supports the assessment of efficacy as well as safety by minimizing bias. The selected 5 doses will support the description of the dose-response relationship that will enable dose selection for the confirmatory Phase 3.

The study will assess QBW251 as an add-on to triple therapy (LABA/LAMA/ICS), in adult patients with chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis and a history of exacerbations in the 12 months prior to the study. Chronic bronchitis is expected to be an enrichment factor for patients who may particularly benefit from improved activity (potentiation) of the CFTR channel. [redacted]

4.1.1 Rationale for choice of background therapy

The study will standardize the COPD background therapy to limit its confounding potential on the study outcomes. The selected standard background therapy will consist of a triple inhaled combination (LABA/LAMA/ICS): either a fixed combination of fluticasone furoate, vilanterol and umeclidinium, or, where not accessible, a free combination of fluticasone furoate/vilanterol and umeclidinium. The choice of these medications reflects their global availability and the convenience of once daily dosing. GOLD strategy (GOLD 2018) suggests the use of triple inhaled therapy for exacerbating and symptomatic patients despite therapy with ICS/LABA or LABA/LAMA. This patient population closely mimics the patient population targeted by this study.

4.2 Rationale for dose/regimen and duration of treatment

QBW251 is a small molecule intended for oral administration. Half-life of QBW251 following single dose ranges from 10 to16 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 would provide a reduced C_{max}/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 patients at 300 mg b.i.d.

The study covers a dose range from 25 to 450 mg b.i.d., which is expected to adequately describe the dose-response of QBW251. While the COPD proof of concept study CQBW251X2201 has provided evidence of efficacy with a 300 mg b.i.d. regimen, there is no indication that this regimen may have reached the plateau of the dose-response. Therefore, the 450 mg b.i.d. was also proposed. The 450 mg b.i.d. regimen was well tolerated in an earlier study in cystic fibrosis (CF) patients (CQBW251X2101). The respective treatment arm in this study has been stopped and patients on the 450 mg b.i.d. regimen have been prematurely discontinued from treatment after the Data Monitoring Committee (DMC) had found that the criterion for the pre-defined pharmacokinetic-based cohort stopping rule (Section 9.1.4.1) had been fulfilled. The DMC confirmed that the regimen was also well tolerated in this patient population and the stop was not based on adverse reactions to the 450 mg b.i.d. regimen. The lowest dose (25 mg b.i.d.) is intended to capture the location of the increasing part of the dose-response curve (e.g. around the efficacious dose in 50% of subjects (ED50)) to ensure that the efficacy dose-response curve and the therapeutic margin of QBW251 are well characterized. Due to the limited available data, ED50 as low as 25 mg b.i.d. cannot be excluded, hence the selection of this dose. The 75 and 150 mg b.i.d. regimens have been selected to achieve uniform coverage of the exposure range between the lowest dose and the higher doses described above to enable a sufficiently granular description of the dose-response curve.

Twelve weeks of treatment are sufficient to detect a spirometric signal (FEV_1) and are aligned with a symptomatic benefit reflective of the target profile of QBW251. A positive signal across these endpoints at this timepoint would enable an early decision making for a transition into confirmatory Phase 3.

The 24-week treatment enables a longer longitudinal assessment, which is more aligned with the intended chronic use of QBW251. The proposed exposure will also increase the robustness of the safety and tolerability assessment and may provide exploratory insights relative to the effect.

[redacted]

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 triple inhaled therapy of LABA/LAMA/ICS that could serve as a comparator. Therefore, QBW251 is tested against placebo on top of triple inhaled 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

4.4.1 Safety

In addition to monitoring safety data, an independent external safety data monitoring committee (DMC) will evaluate the results of pre-specified interim PK to ensure that patients' exposures are generally consistent with an exposure threshold, see Section 9.1.4.1 and Section 12.7.1. Based on their review, the DMC can make recommendations regarding the conduct of the trial. Recommendations from the DMC could trigger alteration of the current protocol, such as termination of a treatment arm. The communication flow process of the outcome of their reviews and any other recommendations by the DMC Chairman, on behalf of the members, will be outlined in the DMC charter. The planned interim analyses will be performed when the predefined amount of data are available; details are included in the DMC charter.

4.4.2 Efficacy

Up to 2 interim analyses (IAs) may be conducted on efficacy data. The purpose of the IA(s) is to have an early assessment of the efficacy data for planning future studies in the QBW251B program. The first IA will be triggered when approximately the first 645 to 680 randomized patients have either discontinued or completed 12 weeks of treatment. If the first IA does not lead to a clear decision for the planning of the QBW251B program, a second IA may be performed when all randomized patients have either discontinued or completed 12 weeks of treatment. The efficacy IA results will not trigger any design adaptations.

4.5 Risks and benefits

The risks to subjects in this trial will be minimized by compliance with all of the eligibility criteria and by close clinical monitoring which will include PK monitoring as well.

The inclusion and exclusion criteria are selected to enroll patients with COPD that are most likely to benefit from QBW251 while participating in the study: symptomatic patients at higher risk of exacerbations defined by the CAT score, presence of chronic bronchitis, and with a history of exacerbations in the 12 month prior to study entry. The study requires all patients to be on a triple combination (LABA/LAMA/ICS). The standardization of the concomitant COPD treatment aims at limiting the variability from this potential confounding source and ensures treatment of all patients, including those randomized to placebo. Accordingly, patients remain on the triple COPD background therapy throughout the study.

[redacted]

Potential risks of QBW251 are the common adverse events of QBW251 as noted in previous studies, comprising of gastrointestinal events (nausea, diarrhea, vomiting) and nervous system disorders (headache, fatigue and dizziness). There is also the possibility of hypersensitivity reactions against QBW251.

The most common adverse effects associated with the standardized triple COPD background therapy are headache, back pain, dysgeusia, diarrhea, cough, oropharyngeal pain, nasopharyngitis, upper respiratory tract infection, arthralgia, gastroenteritis, and oral candidiasis (approved labels for Trelegy Ellipta, Breo Ellipta (EU name Relvar Ellipta) and Incruse Ellipta). Recent data also suggests a potential increase of the risk of pneumonia (including fatal cases) related to the use of the inhaled corticosteroid (update to approved label for Trelegy Ellipta in September 2017).

Clinical monitoring includes the use of an electronic diary with the EXACT 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 (peak) plasma concentration following drug administration (T_{max})) will be performed at Day 1, at Day 15 (when all patients have reached steady state concentration of the investigational drug), and at Day 169 (end of treatment). These assessments will be complemented by the corresponding PK sampling (trough and C_{max}). The PK sampling is also part of a more granular PK monitoring (detailed in schedule of assessment Table 8-1), which has been put in place to ensure that patient exposures are in general consistent with a threshold (area under the plasma concentration curve over 24 hours ($AUC_{0\text{-}24h}$) = 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 and few patients are expected to exceed it. In prior QBW251 studies, patients 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 C_{min} 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 cohort stopping rules related to exposure have been introduced into the protocol as well (see Section 9.1.4.1)

Finally a sub-group of approximately 48 patients will undergo serial PK assessments to further characterize the PK profile of QBW251 before transitioning into the confirmatory Phase 3.

Investigators and patients will be instructed how to react to worsening of COPD symptoms and exacerbations. 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 patients. The diary will also trigger alerts to both patients and investigators when an algorithm detects a deterioration of symptoms compatible with an exacerbation. The investigator will provide the patient with written instructions to contact them if symptoms of COPD worsen.

[redacted]

Procedural risks in this clinical trial are local reactions to venipuncture, including pain, hematomas, fainting, swelling, infections, and erythema. Forced spirometry testing on visit days may furthermore induce cough, dyspnea and dizziness.

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 for the duration of their study participation. If withdrawing from the study prematurely, contraception as stipulated should be continued for at least 7 days following the last administration of investigational medicinal product. If there is any question that the subject will not reliably comply, she 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 patients 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 enhances cytochrome pathways that lead to accelerated degradation of hormone levels; systemic hormones are therefore not approved as an acceptable effective method of contraception in this study.

Reflecting the currently limited characterization of QBW251 potential for clinical drug-drug interactions, the protocol uses cautionary language for drugs that may potentially interact with QBW251 based on available *in vitro* data. These drugs are sensitive substrates of CYP1A2, CYP2B6, CYP3A4, OAT3, BCRP, OATP1B1, OATP1B3, UGT1A1, and UGT2B7 (see List of abbreviations for full protein names). These drugs are not prohibited but their substitution with alternative agents is advised: when not possible closer monitoring is recommended. Additionally use of sensitive substrates of CYP1A2 with a narrow therapeutic range is prohibited. Due to the involvement of multiple metabolic pathways in QBW251 metabolism, it is anticipated that the use of QBW251 with concomitant drugs will likely have no significant clinical impact on QBW251 exposure. However, as Uridine Diphosphate-Glucuronosyltransferase (UGT) mediated glucuronidation is likely a significant elimination pathway, use of certain UGT inhibitors is prohibited.

QBW251 may also impact the systemic exposure of the individual components of inhaled triple therapy LABA/LAMA/ICS, whose most common adverse effects have been described above. However, efficacy of the triple therapy is not expected to be impacted due to the delivery directly to the lungs. Please refer to the respective labels of LABA/LAMA/ICS for additional information on drug interactions. Any concomitant medications should be noted in the electronic Case Report Form (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's Brochure (IB).

With respect to clinical benefits, a proof of concept study showed an improvement of pulmonary function (FEV_1) and provided additional observations that could be associated with a restoration of the mucociliary clearance (decrease in systemic fibrinogen and reduction of the bacterial load of selected pathogens). Nevertheless, the exploratory nature of the latter observations will require further assessment to confirm them.

[redacted]

Finally, an independent Data Monitoring Committee will oversee the developing clinical database and ensure the well-being of the patients throughout the study.

5 Population

The study population will consist of approximately 956 male and female patients (≥ 40 years of age) with moderate to severe COPD (GOLD 2 and 3) and a smoking history of at least 10 pack years. Assuming a screen-failure rate of 40%, it is expected that approximately 1500 patients will be screened globally to achieve the targeted number of randomized patients.

5.1 Inclusion criteria

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

All patients in the study

The following criteria apply to all patients in the QBW251B2201 study.

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.
3. Patients with stable COPD according to the current GOLD strategy (GOLD 2018) at Screening visit.
4. Patients who have been treated with a triple combination of LABA/LAMA/ICS for the last 3 months prior to screening. Fixed or free combinations are acceptable, but will be exchanged for standard combinations at Run-In 1.

   At the Run-In 1 visit, the background treatment will be switched to a fixed combination of fluticasone furoate, vilanterol and umeclidinium, or, where not accessible, to a free combination of fluticasone furoate/vilanterol and umeclidinium.
5. A COPD Assessment Test (CAT) score of at least 10 at Run-In 1.
6. Patients with a post-bronchodilator $FEV_1/FVC < 0.70$ at Run-In 1.
7. Patients with airflow limitation indicated by
   EITHER
   a post-bronchodilator $FEV_1 \geq 30\%$ and $FEV_1 < 50\%$ of the predicted normal at Run-In 1, who must have had at least 1 documented moderate or severe healthcare resource utilization (HCRU) exacerbation in the 12 months prior to study entry (screening),
   OR
   a post-bronchodilator $FEV_1 \geq 50\%$ and $< 80\%$ of the predicted normal at Run-In 1, who must have had at least 2 documented moderate or at least 1 documented severe HCRU exacerbation(s) in the 12 months prior to study entry (screening).
   Notes:
   - Post-bronchodilator refers to 30 to 60 min after inhalation of 400 µg salbutamol/360 µg albuterol (or equivalent dose).
   - 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.

[redacted]

- Patients not meeting the FEV_1 criteria may be re-screened once.

Figure 5-1 Illustration of inclusion criteria 6. and 7.

FEV_1/FVC	Post-BD FEV_1 % predicted	Number of documented exacerbations (HCRU)*
< 0.70	<80 % ≥ 50 %	2 moderate OR 1 severe
	< 50 % ≥ 30 %	1 moderate or severe

*see text above in criterion 7. for definition of moderate and severe exacerbations.

8. 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).
   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 cigarette.
   The habitual inhalation of vapors from heated e-Liquids ("vaping"), regardless of the composition of the liquid, regardless whether with or without nicotine, and regardless of the device used for vaporizing (e.g. e-cigarettes, vaporizers, Juul), are to be reported as smoking history, separately from tobacco smoking.
   Occasional smoking of cigars, pipes, e-cigarettes, or inhaled nicotine products are not relevant to smoking history (Behera et al 1991, Dinakar and O'Connor, 2016).
   An ex-smoker may be defined as a subject who has not smoked for ≥ 6 months at screening or at the time of assessment.
9. Patients featuring chronic bronchitis, defined by the presence of cough and bronchial hypersecretion, that occurs for at least 3 consecutive months in each of 2 consecutive years prior to study entry (screening), documented in patient history.

[redacted]

5.2 Exclusion criteria

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

[redacted]

All patients in the study

The following criteria apply to all patients in the QBW251B2201 study.

1. Patients with a history of long-QT syndrome or whose QTc measured at Run-In 1 is prolonged (QTc > 450 ms in males, > 460 ms in females; Fridericia method), confirmed by the central overreader.
2. Patients who have a clinically significant ECG abnormality at the start of Run-In 1 or at the end of run-in (Run-In 2).

   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).

   Note: These patients must not be re-screened.
3. Patients who have a clinically significant laboratory abnormality at Run-In 1. 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, New York Heart Association (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 Type I diabetes or 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. Patients with a history or current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or prothrombin time international normalized ratio (PT/INR) of more than 1.5x upper limit of normal range (ULN) at Run-In 1. A history of resolved hepatitis A is not exclusionary.

   Patients excluded for the PT/INR of more than 1.5x ULN can be re-screened when the values have returned to normal.
6. Patients contraindicated for treatment with, or having a history of reactions/hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof:
   - Muscarinic antagonist agents,
   - Long- and short-acting β2-agonists,
   - Sympathomimetic amines,
   - Inhaled corticosteroids
   - Inhaled lactose or any of the other excipients of the trial medication, including any background or rescue medication.
7. 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 Monitor on a case-by-case basis.

[redacted]

8. Patients who have not achieved an acceptable spirometry result at Run-In 1 in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for acceptability and repeatability (refer to Section 16.3 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 at Run-In 1 may be re-screened maximally twice.
9. Patients who have had a COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization in the 4 weeks prior to screening. Patients can be re-screened after a minimum of 4 weeks after the resolution of the COPD exacerbation.
10. Patients who develop a COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization between screening and prior to treatment Day 1 will not be eligible, but will be permitted to be re-screened after a minimum of 4 weeks after the resolution of the COPD exacerbation.
11. Patients who have had a respiratory tract infection within 4 weeks prior to screening. Patients can be re-screened after a minimum of 4 weeks after resolution of the respiratory tract infection.
12. Patients who develop a respiratory tract infection between screening and prior to treatment Day 1 will not be eligible, but will be permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection.
13. Patients requiring long term oxygen therapy prescribed for > 12 hours per day.
14. Patients with any documented history of asthma.
    Note: Documented history refers to patient history recorded at screening, documented in source notes, pharmacy records, hospital records, chart records, referral records, or any other medical records of the patient.
15. Patients with an onset of chronic respiratory symptoms, including a COPD diagnosis, prior to age 40 years.
16. Patients with concomitant pulmonary disease (e.g. clinically significant bronchiectasis, lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, α-1 anti-trypsin deficiency) or patients known to have CFTR mutation(s).
17. Patients with suspected active pulmonary tuberculosis or currently being treated 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.
18. Patients with pulmonary lobectomy, lung volume reduction surgery, bronchoscopic lung volume reductions, or lung transplantation.
19. 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.
20. Patients with a body mass index (BMI) of more than 40 kg/m^2.
21. Patients receiving any medications in the classes listed in Table 6-5.

[redacted]

22. 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.
23. 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.
24. 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.
25. Patients unable or unwilling to comply with study-related visits or procedures, including use of an electronic patient diary and EXACT pro diary.
26. Patients unable to use a dry powder inhaler device, metered dose inhaler, or a pressurized MDI (rescue medication) or comply with the study drug regimen.
27. 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.
28. Women of childbearing 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, post-ovulation 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 Ireland (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 the 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 childbearing 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 bilateral tubal

[redacted]

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 childbearing potential.

[redacted]

6 Treatment

6.1 Study treatment

The study treatment consists of:

- Investigational drug QBW251 (doses of 450 mg, 300 mg, 150 mg, 75 mg or 25 mg) or matching placebo (450 mg b.i.d. treatment has been discontinued),
- COPD maintenance background therapy consisting of a combination of fluticasone furoate, vilanterol, and umeclidinium, and
- Rescue medication consisting of a short acting beta agonist (salbutamol /albuterol).

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
QBW251 450 mg b.i.d. *	Capsule	Oral use	Double-blind supply; bottles	Sponsor global
QBW251 300 mg b.i.d.	Capsule	Oral use	Double-blind supply; bottles	Sponsor global
QBW251 150 mg b.i.d.	Capsule	Oral use	Double-blind supply; bottles	Sponsor global
QBW251 75 mg b.i.d.	Capsule	Oral use	Double-blind supply; bottles	Sponsor global

[redacted]

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
QBW251 25 mg b.i.d.	Capsule	Oral use	Double-blind supply; bottles	Sponsor global
QBW251 Placebo b.i.d.	Capsule	Oral use	Double-blind supply; bottles	Sponsor global

All capsules are of identical appearance to ensure blinding. *Following discontinuation of the QBW251 450 mg b.i.d. arm, this dose strength is not supplied to patients any more.

6.1.2 Additional study treatments

All patients will be required to have been on a triple therapy regimen (LABA/LAMA/ICS) for at least 3 months prior to screening. Patients will then be switched at the Run-In 1 visit to a standard background triple therapy:

- Either a once daily fixed triple combination of fluticasone furoate[1], vilanterol, and umeclidinium (100 µg/25 µg/62.5 µg, respectively) using a dry powder inhaler or
- A once daily dual fixed combination of fluticasone furoate[1]/vilanterol (100 µg/25 µg, respectively) with once daily umeclidinium (62.5 µg), both using dry powder inhalers.

The selection of the standard background triple therapy will be determined by the availability in the country of the triple therapy option at study start. Either standard background triple therapy will be taken in the morning approximately between 7 and 10 a.m. Patients will be instructed not to take the triple therapy (LABA/LAMA/ICS) within 24 hours prior to any spirometric assessment visit. If a patient has to use triple therapy (LABA/LAMA/ICS) within 24 hours prior to any spirometric assessment, the visit may need to be rescheduled.

The triple therapy will be supplied to the investigator sites locally by Novartis or provided by the study center and reimbursed by Novartis.

Sites will be instructed to record the triple therapy information in the corresponding COPD eCRF page.

In addition, patients are provided with a short acting beta agonist (salbutamol 100 µg or albuterol 90 µg) to use as rescue medication as needed (see Section 6.2.3 for rescue medication further information).

[1] Fluticasone is a substrate of CYP3A and therefore systemic levels of fluticasone could be influenced by QBW251 administration. However, the efficacy of inhaled fluticasone is not expected to be impacted due to the delivery directly to the lungs.

6.1.3 Treatment arms/group

Subjects will be assigned at Day 1 to 1 of the following 6 treatment arms in a ratio of 2:2:1:1:1:2:

- QBW251 450 mg b.i.d. (discontinued)
- QBW251 300 mg b.i.d.
- QBW251 150 mg b.i.d.
- QBW251 75 mg b.i.d.

[redacted]

- QBW251 25 mg b.i.d.
- Matching placebo to QBW251 b.i.d.

Following discontinuation of the 450 mg b.i.d. treatment arm, subjects will no longer be randomized to this arm, resulting effectively in a 2:1:1:1:2 randomization ratio (300 mg b.i.d. : 150 mg b.i.d. : 75 mg b.i.d. : 25 mg b.i.d. : placebo).

6.1.4 Treatment duration

The planned duration of treatment in the study with QBW251 or matching placebo is 24 weeks (Day 1 to Week 24). Subjects may be discontinued from treatment earlier at the discretion of the investigator if patient safety and well-being are compromised, if unacceptable side-effects occur, or if the subject withdraws informed consent (refer to Section 9.1.1 and Section 6.5.1 for more information).

Patients will be switched to a standardized COPD maintenance background therapy (LABA/LAMA/ICS) at the Run-In 1 visit and will continue throughout the study until the Follow-Up visit.

Patients will receive rescue medication SABA at Screening, which will be used as needed until the Follow-Up visit.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) 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 Monitor 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.

[redacted]

Table 6-2 Medications permitted under certain conditions

Rationale/Group	Medication	Prohibition period / Washout period	Action taken
Study-supplied COPD maintenance background therapy	Vilanterol, Umeclidinium, Fluticasone furoate	Hold treatment for 24 hours (± 2 hours) prior to each FEV_1/spirometry measurement on visit days.	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 10 to 14 hours from dosing on the previous evening. Otherwise, postpone visit to the next day where washout criteria can be fulfilled.
Study-supplied 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 10 to 14 hours from dosing of investigational drug on the previous evening. Otherwise, postpone visit to the next day where washout criteria can be fulfilled.
Systemic antibiotics	Antibiotics	Systemic antibiotics are allowed for short-term (up to 14 days) treatment of acute infections, or are allowed for the treatment of acute exacerbations (but not as permanent prophylactic treatment).	Discontinue study drug if permanent systemic antibiotic treatment cannot be discontinued.

[redacted]

Rationale/Group	Medication	Prohibition period / Washout period	Action taken
		Topical treatment (e.g. use of intraocular, intraconjunctival antibiotic treatments, topical use of creams, etc.) is permitted.	

QBW251 may inhibit the metabolic clearance of co-medications metabolized by CYP1A2 and induce CYP2B6. 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 and decrease in exposure due to induction of CYP2B6. 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 drugs should be monitored accordingly.

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

Table 6-3 Medications the exposure of which may be modified by co-administration with QBW251

Medications that may have decreased exposure due to co-administration with QBW251	
Sensitive Substrates of CYP2B6	bupropion, efavirenz.
Narrow therapeutic index substrates of CYP3A	alfentanil[1], astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus[1], tacrolimus[1], terfenadine[1].
Sensitive substrates of CYP3A	alpha-dihydroergocryptine, alfentanil, almorexant, alisoporivir, aplaviroc, aprepitant, atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, buspirone, capravirine, casopitant, cobimetinib, conivaptan, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, elvitegravir, eplerenone, everolimus, felodipine, grazoprevir, ibrutinib, indinavir, isavuconazole, ivabradine, ivacaftor, levomethadyl, lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, naloxegol, neratinib, nisoldipine, paritaprevir, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, sirolimus, tacrolimus, terfenadine, ticagrelor, tilidine,tipranavir, tolvaptan, triazolam, ulipristal, vardenafil, venetoclax, vicriviroc, voclosporin.

[redacted]

Medications that may have increased exposure due to co-administration with QBW251

Sensitive Substrates of CYP1A2	alosetron, caffeine, duloxetine, melatonin, pirfenidone, ramelteon, selegiline, tacrine, tasimelteon.
BCRP substrates	atorvastatin daunorubicin, doxorubicin, ethinyl estradiol, hematoporphyrin, imatinib, methotrexate[1], mitoxantrone, pitavastatin[1], rosuvastatin[1], SN-38 (irinotecan), simvastatin, sulfasalazine, sofosbuvir[1], sulfasalazine[1], tenofovir[1], topotecan[1].
OAT Substrates	acyclovir, adefovir, anagliptin, beta-lactam antibiotics, bumetanide, captopril, cefonicid, cefaclor, cephradine, cimetidine, chlorothiazide, cidofovir, dapagliflozin, famotidine, furosemide, ganciclovir, ibuprofen, methotrexate, olmesartan, pemetrexed, pravastatin, pitavastatin, quinaprilat, ranitidine, rosuvastatin, tenofovir, tetracycline, topotecan-hydroxyl acid, valsartan, zidovudine, zonampanel.
OATP substrates	aliskiren, ambrisentan, anacetrapib, asunaprevir, atenolol, atrasentan, atorvastatin, bosentan, bromociptine, caspofungin, cerivastatin, celiprolol, danoprevir, digoxin, docetaxel, eliglustat, empagliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, maraviroc, methotrexate, montelukast, olmesartan, paclitaxel, pirataprevir, pitavastatin, pravastatin, repaglinide, rifampin, rosuvastatin, saquinavir, simvastatin acid, simvastatin, SN-38 (irinotecan), telmisartan, ticlopidine, thyroxine, valsartan.
UGT1A1 Substrates	abacavir, acetaminophen, atorvastatin, axitinib, belinostat,buprenorphine, carvediol, diclofenac, dolutegravir, desvenlafaxine succinate, eltrombopag, elvitegravir, estradiol, etoposide, ezetimibe, ezogabine, febuxostat, flurbiprofen, fluvastatin, furosemide gemfibrozil, indacaterol, indomethacin, irinotecan, ketoconazole, levothyroxine, losartan, lovastatin, morphine, muraglitazar, mycophenolate mofetil, mycophenolic acid, naltrexone, naproxen, paracetamol, raloxifene, raltegravir, rosuvastatin, simvastatin, irinotencan, suprofen, telmisartan.

[redacted]

UGT2B7 Substrates	almokalan, ambrisentan, atorvastatin, buprenorphine, canagliflozin, carabamazepine, carvediolol, chloramphenicol, clofibric acid, codeine, cyclosporine, dabigatran etexilate, dapagliflozin, diclofenac, empagliflozin, entacapone, epirubicin, etodolac, ezetimibe, febuxostat, fenofibrate, fenoprofen, flurbiprofen, fluvastatin, furosemide, gemfibrozil, hydromorphone, ibuprofen, indomethacin, ketoprofen, lamotrigine, lorazepam, lorazepam, losartan, lovastatin, methadone, midazolam, mitiglinide, morphine, mycophenolate mofetil, mycophenolic acid, nalorphine, naloxone, naltrexone, naproxen, oxazepam, pitavastatin, sertraline, silodosin, simvastatin, suprofen, tacrolimus, tapentadol, temazepam, zaltoprofen, zidovudine.

Medications in this table were identified as substrates based on either *in vivo* or *in vitro* data.
[1] Also considered sensitive CYP3A substrates. Budesonide and fluticasone are also sensitive substrates of CYP3A, but have not been listed here since these are prohibited medications (except for study-supplied COPD background medication containing fluticasone, as specified in Section 6.1.2, or as systemic corticosteroids for the treatment of COPD exacerbations, as specified in Section 8.3.9). Furthermore, patients 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, due to an ingredient that is an inhibitor sensitive substrate of CYP3A.

6.2.1.2 Systemic contraceptives

Systemic contraceptives such as listed in Table 6-4 are not an acceptable means of contraception (refer also to definition of acceptable effective contraception methods 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 (not acceptable as means of contraception as efficacy may be compromised by QBW251 administration)

Medication	Period during which contraceptive effect may be compromised	Action taken

[redacted]

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). Patient 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 exclusion criterion #28.

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 period be required, study treatment should be discontinued as described in the "Action to be taken" column.

Table 6-5 Prohibited medication

Rationale/Group	Medication[1]	Prohibition period	Action to be taken
Medications with a narrow therapeutic range and potential for increased exposure with QBW251 due to inhibition of CYP1A2:	Theophylline[2] Tizanidine	Discontinue treatment at least 1 week prior to Day 1	Discontinue study treatment.
Medications lacking information on metabolizing enzymes:	Pirbuterol	Discontinue treatment at least 1 week prior to Day 1	Discontinue study treatment.
Strong uridine diphosphate glucuronosyl transferase (UGT) inhibitors, which will potentially increase systemic concentrations of QBW251	Mefenamic acid Probenecid Valproic acid	Discontinue treatment at least 1 week prior to Day 1	Concurrent administration must be avoided; discontinue study treatment.
Mucolytics	Acetylcysteine Ambroxol Bromohexine Erdosteine	Discontinue treatment prior to or on Run-In 1.	Concurrent administration must be avoided to ensure reliable assessment of symptoms.
Antibiotics (long-term maintenance)[3]	Azithromycin Erythromycin Doxycyline	Discontinue treatment at least 30 days prior to Run-In 1.	Discontinue study treatment.

[redacted]

[1] The medications listed here are prominent examples of the group of medications fulfilling the rationale, but all drugs fulfilling the rationale for exclusion are not allowed (e.g. any mucolytic drug).

[2] Note that theophylline has to be terminated 7 days prior to Run-In 1 due to stipulations for prohibited COPD medications (Table 6-6) and is listed here for completeness of information only.

[3] Most frequently used antibiotics are listed only. However, all long-term systemic antibiotic treatment is excluded, regardless of the drug. For use of short term antibiotics for COPD exacerbations: prior to the study refer to the exclusion criteria 9 and 10, during the study, refer to Table 6-2. Any other use of short term antibiotics prior to the study does not require a wash-out.

Table 6-6 Prohibited COPD-related medications

Class of medication[1]	Minimum washout period prior to Run In 1
Long-acting muscarinic antagonists (LAMA) (other than as ingredient of study background therapy)	12 hours for twice-daily LAMAs 24 hours for once-daily LAMAs
Short-acting muscarinic antagonists (SAMA)	6 hours
Fixed combinations of long-acting β_2 agonists and inhaled corticosteroids (LABA/ICS)(other than as ingredient of study background therapy)	12 hours for twice-daily combinations 24 hours for once-daily combinations
Long-acting β_2 agonists (LABA)(other than as ingredient of study background therapy)	12 hours for twice-daily LABAs 24 hours for once-daily LABAs
Short-acting β_2 agonists (SABA) (other than trial rescue medication)	6 hours
Oral phosphodiesterase-IV inhibitor	7 days
Xanthines (any formulation)	7 days
Systemic corticosteroids	30 days
Inhaled corticosteroids (other than as ingredient of study-supplied background therapy)	12 hours
Intra-muscular depot corticosteroids	3 months

[1] This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria. These medications are also prohibited if administered for other indications. This should be taken in the context of COPD severity as well as planned comparator arms. All these medication listed under Table 6-6 may be permitted for the treatment of a COPD exacerbation during the study except intra-muscular depot corticosteroids If intra-muscular depot corticosteroid treatment is required, the patient should be withdrawn from the study treatment. Medications under Table 6-5 are not permitted and should follow the action as listed in the table.

6.2.3 Rescue medication

At Screening and whenever needed thereafter, patients 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. Nebulized salbutamol/albuterol is not allowed as rescue medication throughout the trial. No other rescue medication is permitted.

The use of rescue medication (number of puffs taken in the previous 12 hours) will be recorded (once in the morning and once in the evening) by the patient, in the electronic patient diary. The rescue salbutamol/albuterol provided at Screening for use during the study should not be recorded on the COPD related prior concomitant page of the eCRF.

The rescue medication will be supplied to the investigator sites locally by Novartis or provided by the study center and reimbursed by Novartis.

[redacted]

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

At Day 1, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT supplier using a validated system that automates the random assignment of patient 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 using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by smoking status (current or ex-smoker) and severity of airflow limitation ($FEV_1 \geq 30\%$ to $< 50\%$ and $\geq 50\%$ to $< 80\%$), as assessed at Run-In 1.

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

6.4 Treatment blinding

Subjects, investigator staff, persons performing the assessments, and Clinical Trail Team (CTT) will remain blind to the identity of 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: PK analyst, independent statistician and programmer supporting the DMC and, if deemed necessary by the DMC, 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.

[redacted]

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 data base lock.

Unblinding will occur in the case of subject emergencies, in case of a DMC request as an outcome of their evaluation and at the conclusion of the study.

Unblinding of predetermined CTT members will occur at the time of the efficacy interim analysis. The study will then continue under the management of a separate blinded team. In order to maintain the integrity of the study data, separate blinded team members will not have access to any unblinded data. The detailed procedures will be described in a separate charter. The remainder of members including clinical study team, subjects, investigator staff, persons performing the assessments will remain blinded until the final database lock.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments are not permitted. Dose temporary interruptions are permitted under specific circumstances described in Section 6.5.1.

6.5.1 Dose modifications

Study drug dose temporary 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 should be permanently discontinued as described in Section 9.1.1).

Any interruption of study medication for more than 5 consecutive days during the treatment period should be discussed with the local Novartis Medical Monitor to review the patient'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 adjustments for QTcF prolongation

In case of QTcF > 500 msec, (or QTcF prolongation > 60 msec from baseline)

- Assess the quality of the ECG recording and the QT value and repeat, if needed.
- Interrupt investigational treatment.
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities.
- If possible, collect a time-matched PK sample on that visit (if not already scheduled/taken 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 investigational treatment.
  - 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.

[redacted]

6.5.2 Follow-up for toxicities

Not applicable

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. The Investigator or designee will collect, from the patient, the used/unused investigational study drug and packaging at all dispensing visits. Study drug compliance will be assessed from the capsule count (unused medication) and from information provided by the patient and/or caregiver. This information should be captured in the source documentation. The total number of doses of investigational treatment administered since the last dispensing visit should be captured in the source documentation, and the start and end date of investigational study drug and any interruptions of investigational treatment of more than 5 days or any interruption of investigational treatment due to an Adverse Event will be recorded on the eCRF. Patient will also be instructed to report any missing doses of investigational study drug in the eDiary.

The number of puffs of rescue medication inhaled will be recorded twice daily by the patient in the eDiary. The patient will be instructed accordingly at Screening (when he/she is provided with the eDiary and the use of rescue medication is discussed). The use of 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 rescue medication use with the patient.

The COPD maintenance background therapy compliance will also be monitored at all dispensing visits and information captured in the source documents at site. Information on the start date, end date and interruptions of more than 3 days or due to an Adverse Event must be captured in the eCRF. Any compliance issues must be discussed with the patient.

The investigator must promote compliance by instructing the subject to take the study treatment exactly 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 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.

[redacted]

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

- protocol 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 unblinding can be performed at any time.

Following 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 dispensation capsules and no preparation prior to dispensation is required.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Investigational study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all investigational study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the clinical trial or at the time of discontinuation of study treatment.

[redacted]

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational study treatment, packaging, drug labels and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Additional study treatment (COPD maintenance background therapy and rescue medication) must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the additional study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol.

The investigator must maintain a record of the shipment and dispensing of the additional study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to bring all unused study treatment to the site at all visits including the time of discontinuation of study treatment to allow for medication use review.

6.7.2 Instruction for prescribing and taking study treatment

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.).
- It is recommended not to take the investigational drug in together with high-fat meals. The definition of high-fat meals follows the definition suggested by the 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:
  - Total nutritional energy value: 1000 kcal
    - of which from proteins: 150 kcal
    - of which from carbohydrates: 250 kcal
    - of which from fats: 600 kcal.
- Patients can drink water as needed.
- Patients 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.
- If vomiting occurs during the course of treatment, patients should be instructed not to take the study drug again before the next scheduled dose.
- Patients should be instructed not to make up missed doses.
- Subjects should be instructed to swallow whole capsules and not to chew or open them.

[redacted]

Instructions for the COPD maintenance background therapy and rescue medication should be according to the respective product label.

On study visit days, patients should be reminded not to take either the investigational drug (QBW251/placebo) or the COPD maintenance background 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, and
- 22-26 hours after the last inhalation of COPD background medication on the morning before (see also Section 8.3.2).

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee (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 Good Clinical Practice (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 (IN) 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 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. They shall be informed that contraception should be continued for at least 7 days following the last intake of QBW251/placebo. Patients completing the study as planned are required to exercise acceptable

effective contraception during their entire study participation; thus, the above period is covered by the follow-up period.

The study includes optional assessments such as the additional pharmacokinetic sampling timepoints at Day 1 and Day 15 [redacted]. As previously described, each additional data collection activity may not be conducted in all countries, depending on regulatory acceptability, logistic considerations, and need of participants for the respective activity. Any additional data collections require a separate signature, if the subject agrees to participate. It is required as part of this protocol that the Investigator presents the available options to the subjects, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in 1 or more of these optional assessments ([redacted] additional pharmacokinetic sampling) will in no way affect the subject's ability to participate in the main research study.

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

Subjects might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience (see Section 8.5.4).

8 Visit schedule and assessments

The assessment schedule table (Table 8-1) lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule 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 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.

Below Table 8-2 will describe the order and timepoints for all the timed assessments in all the visits scheduled. If the subject is participating in the additional PK timepoints at Day 1 and Day 15, refer to the Table 8-3 for these visits.

[redacted]

Table 8-1 Assessment Schedule

Period	Screening	Run-In		Treatment									Follow-Up	Unscheduled
Visit Name	Screening	Run-In 1	Run-In 2	Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	PSW[1]	Follow-Up	Unscheduled
Days	-21	-14	1	1	15	29	57	85	113	141	169	-	197	-
Informed consent	X													
Demography	X													
Physical Examination	X										X	X		
Body Height	X													
Body Weight	X										X	X		
Vital Signs	X	X	X	(X)[5]	X	X	X	X	X	X	X	X	X	
Medical history/current medical conditions[2]	X													
COPD exacerbation history	X													
Smoking history	X													
Smoking status	(X)[3]										X	X		
Inclusion/Exclusion criteria	X	X	X											
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispensation of rescue medication	X	X		X		X	X	X	X	X	X			
Dispensation of standard background triple therapy		X		X		X	X	X	X	X	X			
Dispensation of study drug				X		X	X	X	X	X				
Spirometry		X		X		X	X	X	X	X	X	X	X	
Spirometry Reversibility Test		X												

[redacted]

Period	Screening	Run-In		Treatment									Follow-Up	Unscheduled
Visit Name	Screening	Run-In 1	Run-In 2	Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	PSW[1]	Follow-Up	Unscheduled
Days	-21	-14	1	1	15	29	57	85	113	141	169	-	197	-
Electrocardiogram (ECG)[4]		X	X	X[5]	X[6]	X	X	X	X	X	X[6]	X	X	
COPD Assessment Test (CAT)[7]		X												
St. George's Respiratory Questionnaire[7]			X					X			X	X		
Patients Global Impression of Severity Scale (PGI-S general question)[7]			X					X			X	X		
Patients Global Impression of Severity Scale (PGI-S specific question)[7]			X					X			X	X		
Cough And Sputum Assessment Questionnaire (CASA-Q)[7]			X					X			X	X		
[redacted]														
e-Diary - rescue medication use	from Day -21	X	X	X	X	X	X	X	X	X	until Day 169	until PSW		
e-Diary - EXACT Questionnaire[8]		from Day -14	X	X	X	X	X	X	X	X	until Day 169	until PSW		

[redacted]

Period	Screening	Run-In		Treatment									Follow-Up	Unscheduled
Visit Name	Screening	Run-In 1	Run-In 2	Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	PSW[1]	Follow-Up	Unscheduled
Days	-21	-14	1	1	15	29	57	85	113	141	169	-	197	-
[redacted]														
Assessment of childbearing potential	S													
Pregnancy Test (serum)[10]		X												
Pregnancy Test (urine)[10]	X		X			X	X	X	X	X	X	X	X	
Hematology		X		X		X	X	X	X	X	X	X	X	
Clinical Chemistry[11]		X		X		X	X	X	X	X	X	X	X	
Urinalysis[12]		X	X			X	X	X	X	X	X	X	X	
PK blood collection				X[13]	X[13]	X	X	X	X	X	X[13]	X		X[14]
PK Sub-group (serial PK sampling)				X[15]	X[15]									
[redacted]														
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	
Surgeries & procedures review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Contact IVRS/IWRS	X	X	X[16]	X	X	X	X	X	X	X	X	X	X	
Study Disposition Page	X[17]		X[18]								X[19]	X[19]	X[20]	
Study completion information												X[21]	X	
[redacted]														

[redacted]

Period	Screening	Run-In		Treatment									Follow-Up	Unscheduled
Visit Name	Screening	Run-In 1	Run-In 2	Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	PSW[1]	Follow-Up	Unscheduled
Days	-21	-14	1	1	15	29	57	85	113	141	169	-	197	-

[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] Premature Subject Withdrawal.
[2] Including protocol-solicited events.
[3] Smoking status at Screening is part of the smoking history eCRF page.
[4] Triplicate ECG measurement.
[5] ECG at Day 1 is to be conducted as a triplicate measurement 3 hours after dosing. If for any reason Run-In 2 and Day 1 occur on separate days, the pre-dose triplicate ECG and vital signs assessments (Run In 2) need to be repeated at Day 1.
[6] Triplicate ECG measurement with pre-dose and post-dose (3-4 hours) measurements.
[7] Questionnaires are to be completed prior to any objective assessments on the respective visit days.
[8] EXACT is completed by patients daily between Day -14 and Day 169 or whenever the patient prematurely withdraws from the study (not only on study visit days).
[redacted]
[10] Only for women assessed as being of childbearing potential.
[redacted]
[12] Dipstick test conducted on site. If dipstick reveals abnormal readings, a urine sample is to be submitted to the central laboratory for analysis.
[13] Two PK samples of approximately 2.5 mL each are drawn on Days 1, 15, and 169: one pre-dose (trough assessment), and one after the triplicate post-dose ECG (3-4 h after administration of the QBW251 dose). In case a patient prematurely discontinued treatment but continued participation in the study, the first visit after the discontinuation should have a PK trough assessment and thereafter subsequent PK sampling should be suspended.
[14] A PK assessment is only expected in case the unscheduled visit (UV) occurs due to a SAEs. For any SAE, an additional PK sample should be taken, if possible, unless a planned visit for this patient is occurring within a week time of the reported SAE (scheduled PK sample).
[15] For patients participating in the PK sub-group, blood samples will be drawn on Days 1 and 15 at 1 hour pre-dose and at 1, 2, 4, 6, and 8 h post-dose (in lieu of collection timepoints for all other patients; see also timed assessments in Table 8-3).
[16] Only if not randomized on Day 1 (run-in failure).
[17] Screening Study Disposition Page.
[18] Run-In Study Disposition Page.
[19] Treatment Study Disposition Page.
[20] Follow-Up Study Disposition Page.
[21] In case of premature subject withdrawal (PSW) only.
[redacted]

[redacted]

Table 8-2 Timed assessments for all visits

	Time Point[1]	PROs at site	Urine Sample	ECG	Vital Signs[3]	Hemato-logy/ Blood Chemis-try	Spiro-metry[4]	PK Blood Samp-ling
Day 1	Prior to -45 min	X						
			X	X[2]	X			
	Prior to -45 min	Randomization						
	-45 min						X	
	-45 to -20 min approxi mately					X		X
	-15 min						X	
	0	Study drug administered in clinic						
	3 h			X[2]				X
Week 2	Prior to Study drug			X[2]	X			
	Prior to Study drug							X
	0	Study drug administered in clinic						
	3 h			X[2]				X
Week 4	Prior to -45 min			X[2]	X			
	-45 min						X	
	-45 to -20 min approxi mately					X		X
	-15 min						X	
	0	Study drug administered in clinic						
Week 8	Prior to -45 min			X[2]	X			
	-45 min						X	
	-45 to -20 min approxi mately					X		X
	-15 min						X	
	0	Study drug administered in clinic						

[redacted]

	Time Point[1]	PROs at site	Urine Sample	ECG	Vital Signs[3]	Hemato-logy/ Blood Chemis-try	Spiro-metry[4]	PK Blood Samp-ling
Week 12	Prior to -45 min	X						
	Prior to -45 min			X[2]	X			
	-45 min						X	
	-45 to -20 min approxi mately					X		X
	-15 min						X	
	0	Study drug administered in clinic						
Week 16	Prior to -45 min			X[2]	X			
	-45 min						X	
	-45 to -20 min approxi mately					X		X
	-15 min						X	
	0	Study drug administered in clinic						
Week 20	Prior to -45 min			X[2]	X			
	-45 min						X	
	-45 to -20 min approxi mately					X		X
	-15 min						X	
	0	Study drug administered in clinic						
Week 24	Prior to -45 min	X						
			X	X[2]	X			
	-45 min						X	
	-45 to -20 min approxi mately					X		X
	-15 min						X	
	0	Study drug administered in clinic						
	3 h			X[2]				X
PSW	Prior to -45 min	X						
			X	X[2]	X			

[redacted]

	Time Point[1]	PROs at site	Urine Sample	ECG	Vital Signs[3]	Hemato-logy/ Blood Chemis-try	Spiro-metry[4]	PK Blood Samp-ling
	-45 min						X	
	-45 to -20 min approxi mately					X		X
	-15 min						X	
	0	Theoretical study drug timepoint						
	3 h							

[1] Time relates to the dose given from spirometry device at visit unless otherwise specified.
[2] Triplicate ECG measurements required.
[3] Systolic/diastolic blood pressure and heart rate.
[4] A minimum 3 minutes rest period from the beginning of ECG assessments to the start of spirometry maneuvers must be observed at all times.

Table 8-3 Timed assessments for Day 1 and Day 15 for subjects participating in the additional PK sampling sub-group (additional PK timepoints)

	Time Point[1]	PROs at site	Urine Sample	ECG	Vital Signs[3]	Hemato-logy/ Blood Chemis-try	Spiro-metry[4]	PK Blood Samp-ling
Day 1	Prior to -45 min	X						
			X	X[2]	X			
	Prior to -45 min	Randomization						
	-45 min						X	
	-45 to -20 min approxi mately					X		X
	-15 min						X	
	0	Study drug administered in clinic						
	1 h							X
	2 h							X
	4 h			X[2]				X
	6 h							X
	8 h							X
Week 2	Prior to Study drug			X[2]	X			

[redacted]

	Time Point[1]	PROs at site	Urine Sample	ECG	Vital Signs[3]	Hemato-logy/ Blood Chemis-try	Spiro-metry[4]	PK Blood Samp-ling
	Prior to Study drug							X
	0	Study drug administered in clinic						
	1 h							X
	2 h							X
	4 h			X[2]				X
	6 h							X
	8 h							X

[1] Time relates to the dose given from spirometry device at visit unless otherwise specified
[2] Triplicate ECG measurements required.
[3] Systolic/diastolic blood pressure and heart rate
[4] A minimum 3 minutes rest period from the beginning of ECG assessments to the start of spirometry maneuvers must be observed at all times

8.1 Screening

Re-Screening

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

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent but fail to continue into the Run-In period for any reason will be considered a screen failure. The reason for the screening failure will be entered on the screening phase disposition page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a serious adverse event (SAE) during the screening phase (see SAE reporting details in Section 10.1.3). If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

8.2 Subject demographics/other baseline characteristics

Patient demographic and other baseline characteristic data to be collected on all subjects include:

- Year of birth and age
- Gender
- Race

[redacted]

- Ethnicity
- Body height, weight and BMI (calculated)
- Relevant medical history/current medical conditions present before signing informed consent where possible
- Date of COPD diagnosis
- Smoking history and smoking status
- Prior and concomitant medications (COPD and non-COPD related)
- Pre- and post-bronchodilator spirometry (screening spirometry and reversibility testing)
- ECG
- Laboratory assessments
- Vital signs
- Baseline physical examination (not databased other than in the context of relevant medical history)
- COPD Assessment Test (CAT) score
- [redacted]

Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

8.3.1 Appropriateness of efficacy assessments

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

8.3.2 Spirometry

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

The spirometry evaluation will be performed at the site prior to the morning investigational drug intake and the daily COPD maintenance background therapy. Refer to instructions for medication washouts in Table 6-2. In particular, spirometry on visit days shall be conducted 10-14 hours after the last intake of investigational drug on the evening before, and 22-26 hours after the last inhalation of COPD background medication on the prior morning. For the spirometry assessments at the Follow-Up visit, medication washouts for COPD background medication and rescue medication shall be observed, and two assessments shall be conducted approximately 30 minutes apart from each other and approximately at the same time as for the assessments at previous 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 (Appendix 16.3, item "Equipment requirements"). Calibration of the spirometry equipment is mandatory

[redacted]

on all visit days and must be performed before the first patient 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 patients at all visits throughout the entire trial. 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.

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.

For further details, refer to the Spirometry guidelines in Section 16.3.

8.3.3 e-Diary

At Screening all patients will be provided with an electronic diary to record rescue medication (salbutamol/albuterol) use. The patients will be instructed to routinely complete the rescue medication information in the e-Diary twice daily at the same time in the morning and evening (before taking the study drug), approximately 12 hours apart. Starting from Run-In 1, patients will be required to complete the EXACT questionnaire daily as well (see Section 8.3.4 for the EXACT questionnaire).

The e-Diary is to be reviewed at each clinic visit until study completion.

Sites and patients will receive appropriate training and guidance on the use of the e-Diary device.

A list of e-Diary questions is provided in Section 16.6 (EXACT questionnaire) and Section 16.11 (rescue medication).

8.3.4 EXACT questionnaire

The EXACT is a validated 14-item electronic questionnaire designed to detect the frequency, severity, and duration of exacerbations in patients with COPD (Leidy et al 2011, Leidy et al 2014a, Leidy et al 2014b). It is to be completed by the patient 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 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.

[redacted]

An example of the EXACT questionnaire is provided in Section 16.6.

[redacted]

8.3.5 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 patient at the investigator's site at the visits indicated in Table 8-1.

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 are given in Section 16.12.

Instrument scoring and handling of missing item data will be conducted in accordance with the user guide for the SGRQ (Section 16.12).

The SGRQ contains 50 items divided into 2 parts covering 3 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 3 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.

8.3.6 Patient global impression of severity (PGI-S: general and specific)

The PGI-S questionnaire will rate the severity of the respiratory symptoms (general questionnaire) and of the cough and mucus (specific questionnaire) in the last 7 days and will be used to anchor the E-RS total score, E-RS cough and sputum subdomain and CASA-Q.

The PGI-S (a general and a specific question) will be completed electronically by the patient at the investigator's site at the visit schedule indicated in Table 8-1.

An example of the PGI-S is provided in Section 16.8.

8.3.7 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 patients with chronic obstructive pulmonary disease (COPD) and/or chronic bronchitis (Crawford et al 2008). It contains a total of 20 items on a 5-step scale distributed in 4 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 patient at the investigator's site at the visit schedule indicated in Table 8-1.

An example of the CASA-Q is provided in Section 16.4.

Below are instructions for all the questionnaires administered at site, including the CASA-Q:

The appropriate language version of the questionnaires will be used in each participating country. The same language should be used by a particular patient throughout the study. The site personnel administering the questionnaire should be familiar with the measures and the

[redacted]

associated user guides and training materials provided. The patient should complete the questionnaires in a quiet area and be allowed to ask questions; however site personnel should take care not to influence the patient's responses. The patient will be instructed to provide the truest and best response for them.

[redacted]

8.3.9 COPD Exacerbations

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

A healthcare resource utilization (HCRU)-defined exacerbation is defined as an acute worsening of respiratory symptoms (consisting of at least 2 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 augmentin 625 mg (corresponding to 500 mg amoxicillin + 125 mg clavulanic acid) t.i.d. or clarithromycin 500 mg b.i.d.) (GOLD 2018).

All HCRU-defined exacerbations should be recorded on the COPD exacerbation eCRF.

Patients who develop a COPD exacerbation between screening and prior to treatment Day 1 will be discontinued but will be permitted to be re-enrolled after a minimum of 4 weeks and after the resolution of the COPD exacerbation (see exclusion criterion # 10). If systemic corticosteroids (SCS) are taken for a COPD exacerbation within 7 days prior to any spirometry study visit, the visit must be rescheduled to allow a washout of 7 days. Scheduled spirometry

[redacted]

[redacted]

8.4 Safety

Safety assessments are specified below in with the assessment schedule detailing when each assessment is to be performed in Table 8-1.

For details on AE collection and reporting, refer to the AE reporting information in Section 10.1.

Physical assessments are defined in below table:

Table 8-4 Assessments and Specifications

Assessment	Specification
Physical examination	A complete physical examination will be performed at Screening and at Week 24 or premature discontinuation visit. It should 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. 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 included in the Medical History part of the eCRF. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the eCRF.
Vital signs	Vital signs include blood pressure and pulse measurements. Vital signs are measured as per visit schedule indicated in Table 8-1. After the subject has been sitting for 5 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured 3 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 3 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.

[redacted]

Height and weight	Body height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at Screening. Body weight will be measured in addition at Week 24 or premature discontinuation visit.

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 patients 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 values are defined in Section 16.1.

Table 8-5 Laboratory parameters

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Clinical Chemistry	For all visits: Albumin, Alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Blood Urea Nitrogen (BUN), Calcium, Creatinine, Gamma-glutamyltransferase (GGT), Lactate dehydrogenase (LDH), Magnesium, Phosphorus, Potassium, Sodium, Total Bilirubin, [redacted] If the total bilirubin concentration is increased above 1.5 times the upper limit of normal range, total bilirubin should be differentiated into the direct and indirect reacting bilirubin At Day 1, Week 12 and Week 24/PSW only: HbA1c will also be measured
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 international normalized ratio (PT/INR) at Run In 1 and at Week 24/PSW only

[redacted]

Pregnancy Test	Serum/Urine pregnancy test for women of childbearing potential

Patient does not require fasting for the laboratory assessments

8.4.2 Electrocardiogram (ECG)

Triplicate ECGs (3 ECGs are collected within about a five-minute window) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline/according to the ECG investigator manual. 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.

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).

Triplicate ECGs are collected pre-dose and at 3 hours post-dose on Day 1, Day 15, and Day 169 as indicated in Table 8-1. For patients participating in the optional additional PK sampling sub-group, is should be 4 h post-dose on Day 1 and Day 15 instead of 3 hours post-dose.

Triplicate ECGs are collected at pre-dose at visits indicated in Table 8-1. All ECGs must be 12-lead ECGs. 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 patient'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

All pre-menopausal women who are not surgically sterile (women of childbearing potential) will have pregnancy testing. A serum or urine pregnancy test will be performed (urine test kits provided to the sites by the Central Laboratory/serum pregnancy tests conducted by the Central Laboratory) as per assessment schedule Table 8-1. A positive pregnancy test at any time during the study requires the patient to be discontinued from the study treatment. Refer to Section 9.1.1 for more details. Additional pregnancy testing can be performed if required by local authorities.

8.5 Additional assessments

8.5.1 Pharmacokinetics

Blood samples will be obtained from all subjects as per visits and timepoints indicated in Table 8-1 and Table 8-2.

In approximately 48 subjects, additional PK samples at Day 1 and Day 15 will be collected, as per Table 8-3, to examine the time-concentration profiles of QBW251 after single dose and multiple doses in the COPD patients. Furthermore, additional PK samples will be collected,

[redacted]

where possible, from patients 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 across all treatment arms including 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.

[redacted]

8.5.3.1 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 patients in this study (Jones et al 2009). It is completed by the patient at the beginning of the study visit before any other assessment to avoid influencing the responses. The CAT will be completed electronically by the patient at the investigator's site at the visit schedule indicated in Table 8-1.

It consists of 8 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, 11 - 20, 21 - 30 and 31 - 40 represent a mild, moderate, severe or very severe clinical impact of COPD upon the patient.

An example of the COPD Assessment Test (CAT) is provided in Section 16.10.

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of investigational treatment

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

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

Investigational treatment must be permanently discontinued 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
- Following emergency unblinding

[redacted]

- Emergence of a SAE that the Investigator suspects to be related to investigational drug shall lead to immediate stop of investigational treatment. A blood sample to assess the exposure level should be taken, where possible, for expedited assessment. Where no blood sample at the time of occurrence of the SAE can be obtained, the last sample taken prior to the start of the SAE will be assessed.
- Emergence of an AE that is of severe intensity and that the Investigator suspects to be related to investigational drug shall lead to immediate stop of investigational treatment.
- In case of emergence of a SAE that the Investigator does not suspect to be related to investigational drug, investigational treatment can be continued. A blood sample to assess the exposure level should be taken, where possible, for expedited assessment. If the SAE coincided with a verified exposure above the AUC threshold of $AUC_{0\text{-}24h}$ = 91 700 ng×h/mL, investigational drug needs to be permanently stopped as soon as possible upon receipt of the PK results.
- A patient with a verified exposure above the upper range of the individual animal (monkey) model exposure ($AUC_{0\text{-}24h}$ = 159 000 ng×h/mL). The investigator must permanently discontinue the investigational 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.
- In case of confirmed QTcF > 500 msec, as indicated in Section 6.5.1.1.

Investigational drug can be temporarily interrupted as a response to the occurrence of adverse events that do not fulfil the requirements above described for permanent discontinuation (refer to Section 6.5.1).

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

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code Section 6.6.2.

Subjects who have their investigational 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

[redacted]

the study visit schedule and at a minimum information on new/ concomitant treatments and adverse events /serious adverse events should be obtained.

9.1.1.1 Replacement policy

Discontinued patients will not be replaced on study.

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.

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 US and Japan: all biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and the rest of the world (RoW): 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 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 termination 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, patients may be instructed to stop taking the investigational drug QBW251 immediately. Else, patients may be instructed to continue QBW251 intake until they can return to the site for a final assessment. Background medication (LABA/LAMA/ICS) should be continued until the final visit. The patient 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.

9.1.4.1 Criteria for premature termination of treatment arm(s)

As described in the risks and benefits section (Section 4.5), this protocol features a PK monitoring plan to ensure that patients' exposures are generally consistent with an exposure threshold ($AUC_{0\text{-}24h}$ = 91 700 ng×h/mL), which was established based on animal (monkey) data. Therefore, the cohort stopping rules have been developed to comply with this goal. The independent Data Monitoring Committee (Section 10.2.3) will periodically review the cumulating PK data against these rules.

The 2 rules described below support 2 aims:

- Limit the proportion of patients that exhibits exposures (AUC) above the threshold

- Limit the number of patients with exposures that are above the upper range of the exposures (AUC) observed in the animals.

Based on these goals, a treatment arm will be permanently discontinued if:

1. At predefined safety interim read outs the observed proportion of patients above the threshold ($AUC_{0\text{-}24h}$ = 91 700 ng×h/mL) is significant greater than expected. Statistical details of this rule are described in Section 12.7.1.

and/or

2. More than one patient exhibits a projected AUC above the upper range of the individual animal (monkey) exposures ($AUC_{0\text{-}24h}$ = 159 000 ng×h/mL). In case the 2 patients are in separate treatment arms, the treatment arm with the lowest dose will determine all the treatment arms to be prematurely terminated.

Any treatment arm* fulfilling either one of these criteria will lead to the permanent discontinuation of study investigational drug for the patients in such treatment arm. New patients would be randomized to the remaining treatment arms.

[redacted]

PK exposure values above the threshold due to unverified sampling or analysis or the consequence of an accidental/voluntary overdosing will not be included in the determination of whether to stop a treatment arm.

* The affected treatment arm with the lowest dose will determine which treatment arm(s) will be discontinued (all the ones above it). For instance if the stopping rules impact the 300 mg b.i.d. treatment arm (but not the 450 mg b.i.d. treatment arm) both the 300 mg and the 450 mg arms will be discontinued as described above.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes his/her Follow-Up visit (study 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 when the last patient completes his/her premature termination visit (see Section 9.1.4).

Upon completion of a patient'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. Should there be patients with significant clinical benefit from QBW251 over approved treatment alternatives and the safety profile allow for treatment outside of the study, Novartis will consider to continue provision of the investigational treatment to these patients. Should there be a request from an investigator to provide post-trial treatment to a patient with evidence of significant clinical benefit from the use of QBW251 over the use of approved treatments, and the safety profile of the drug allow for treatment outside of the controlled environment of a study, Novartis will consider to continue providing the investigational treatment to this patient.

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

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events 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.

[redacted]

Adverse events must be recorded in the Adverse Events eCRF 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:
   a. mild: usually transient in nature and generally not interfering with normal activities,
   b. moderate: sufficiently discomforting to interfere with normal activities,
   c. severe: prevents normal activities.
2. 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.
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. action taken regarding with study treatment.
   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   a. Dose not changed,
   b. Dose Reduced/increased,
   c. Drug interrupted/withdrawn.
6. its outcome
   a. not recovered/not resolved,
   b. recovered/resolved,
   c. recovering/resolving,
   d. recovered/resolved with sequelae,
   e. fatal, or
   f. unknown.

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

Adverse events (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 clinical trial), 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.

[redacted]

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 adverse events 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 which are considered to be non-typical in subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

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 inpatient 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
  - elective or pre-planned treatment for a pre-existing 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 outpatient 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

[redacted]

emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met

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.

Upon reporting of an SAE, the investigator should make every attempt to bring the patient for an unscheduled visit to collect a PK blood sample at a minimum, unless a planned visit for this patient is occurring within a week time of the reported SAE.

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 following the last administration of study treatment if there are post-treatment Follow-Up visits with no required procedures must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAEs occurring after the subject has provided informed consent until the time the subject is deemed a screen failure or run-in failure must be reported to Novartis.

For randomized subjects, SAEs occurring after the subject has provided informed consent until 30 days after the subject has discontinued or stopped study treatment (which usually would be the time of the Follow-Up visit) must be reported to Novartis.

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 within 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 Patient 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.

Any SAEs experienced after the 30 day period from the last treatment (usually marked by the Follow-Up visit) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

[redacted]

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 CMO&PS department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational study drug and 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 collected in the dose administration record (DAR) eCRF, 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 Dose Administration (DAR) eCRF (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

[redacted]

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
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.

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 2 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 completion of the respective eCRF pages as detailed in the CRF Completion Guidelines.

Please refer to 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 (ALT, AST, total bilirubin (TBL), PT/INR, alkaline phosphatase (ALP) and GGT) 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 reported on the local laboratory eCRF page,
- 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
- An investigation of the liver event which needs to be followed until resolution. 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 and imaging such as abdominal ultrasound, computer tomography (CT) or magnetic resonance imaging (MRI), as appropriate.

[redacted]

All follow-up information, and the procedures performed must be recorded as appropriate in the eCRF.

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 and Laboratory parameters in Table 8-5.

10.2.3 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate a trial. The DMC will furthermore assess at defined intervals the accumulating PK data and review these against the stopping rules (Section 9.1.4.1).

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulations (CFR) Part 11 requirements, Investigator site staff will not be given access to the Electronic Data Capture (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 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 Commercial Research Organization (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

[redacted]

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.

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. eSource Direct Data Entry (DDE) or 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 Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & 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

[redacted]

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

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

If not stated otherwise, all inferential analyses will not include the 450 mg dose due to early termination of the 450 mg b.i.d arm, resulting in very few or no data in some of the strata (covariates/factors in the model) during the later visits. All descriptive summaries will include the 450 mg b.i.d. dose.

12.1 Analysis sets

The Randomized Analysis Set (RAS) consists of all randomized patients. Patients will be analyzed according to the treatment they were assigned to at randomization.

The Full Analysis Set (FAS) will include all randomized patients who received at least one dose of randomized treatment. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization. It is reasonable to require that patients took randomized treatment for inclusion in the FAS because the decision on whether or not randomized treatment is started will not be influenced by the treatment group assignment due to effective treatment blinding procedures.

The Safety Set will include all patients who received at least one dose of double-blind treatment. Patients will be analyzed according to the treatment they received.

Note that the FAS and Safety Set are the same except that the Safety Set allows the inclusion of non-randomized patients who receive double-blind treatment in error. In addition, analyses based on the FAS assigns randomized treatment while analyses based on the Safety Set assigns received treatment.

The PK set will include all patients with at least one evaluable drug concentration data sample. The PK serial sub-group will include all patients with at least one evaluable drug concentration data sample and who consented to participate in the PK serial sub-group. Patients will be analyzed according to the treatment received for both sets.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data, including disease characteristics and relevant medical histories/current medical conditions, will be summarized descriptively by treatment group.

12.3 Treatments

The duration of exposure in days to each treatment group (QBW251 dose or placebo) will be summarized by means of descriptive statistics. The following summaries for COPD-related medications will be performed separately for medications prior to run-in (medications starting prior to screening and ending prior to or at the run-in visit) and for concomitant medications (medications which were taken anytime between the first dose and last dose of randomized treatment, inclusive). COPD-related medications will be summarized by pre-specified drug

[redacted]

categories, route of administration, preferred term, and treatment group. Non-COPD related medication prior to and after the start of randomized treatment will be summarized by route of administration, preferred term, and treatment group.

The number of patients who permanently discontinued from double blind treatment and the reasons will be summarized by treatment group.

12.4 Analysis of the primary endpoint(s)

The primary objective of this study is to characterize the DR (dose-response) efficacy relationship among QBW251 doses (25, 75, 150 and 300mg b.i.d.) and placebo with regards to the change from baseline in trough FEV_1 after 12 weeks of treatment. The goals associated with this objective are below.

- To confirm an overall DR signal
- To estimate the dose(s) that corresponds to the target effect over placebo based on the estimated DR curve

12.4.1 Definition of primary endpoint(s)

The primary estimand, defined below, quantifies a hypothetical on-treatment Week 12 effect during stable periods (i.e. outside episodes of COPD worsening that require rescue medication or systemic corticosteroids). This estimand targets the maximum treatment effect for QBW251 and allows selection of the best dose for those who take it for 12 weeks.

- **Population**: patients with moderate to severe COPD enriched for presence of chronic bronchitis and a history of exacerbations and treated with LABA/LAMA/ICS background therapy
- **Variable**: trough FEV_1 (average of the 2 values taken 15 and 45 min pre-dose) change from baseline after 12 weeks of treatment
- **Intervention effect of interest**: Effect of interventions initiated at randomization during stable periods (i.e. outside episodes of COPD worsening that require rescue medication or systemic corticosteroids) and that would have been observed had all patients remained on their assigned treatment for 12 weeks, with the following post-randomization events accounted for by assessing:
  - Intake of rescue medication or systemic corticosteroids (SCS): the effect outside of periods of worsening disease that necessitate rescue medication or SCS
  - Discontinuation of study treatment or study participation: hypothetical on-treatment trough FEV_1 value.
  - Missing data due to any reason prior to completion or discontinuation of treatment: on-treatment trough FEV_1 values.
- **Summary measure**: mean difference between treatment groups (QBW251 compared with placebo)

The baseline value is defined as the average of the FEV_1 values taken approximately 45 and 15 minutes prior to first dose of randomized treatment at Day 1. If one of the 2 values is missing (or is not confirmed to be pre-dose) then the remaining non-missing value will be taken as the baseline. If both values are missing (or are not confirmed to be pre-dose), then the measurements taken at the Run-In 1 visit will be used as the baseline.

[redacted]

12.4.2 Statistical model, hypothesis, and method of analysis

The Multiple Comparison Procedure – Modelling (MCP-Mod) methodology (see Bretz et al 2005 and Pinheiro et al 2014) will be employed to assess the primary objective. An overview of the steps for the MCP-Mod methodology is given below. Further details will be provided in the Statistical Analysis Plan (SAP).

Step 1 (Testing an overall dose-response signal - MCP part):

The (covariate) adjusted mean responses at each individual dose will be obtained from a mixed-effect linear model for repeated measures (MMRM) with terms for baseline FEV_1, visit, region, treatment, smoking status at screening, severity of airflow limitation, treatment-by-visit interaction, run-in post-bronchodilator FEV1, and baseline FEV_1-by-visit interaction as fixed effects. To allow adjustment for correlations between timepoints within patients, an unstructured variance-covariance structure will be used.

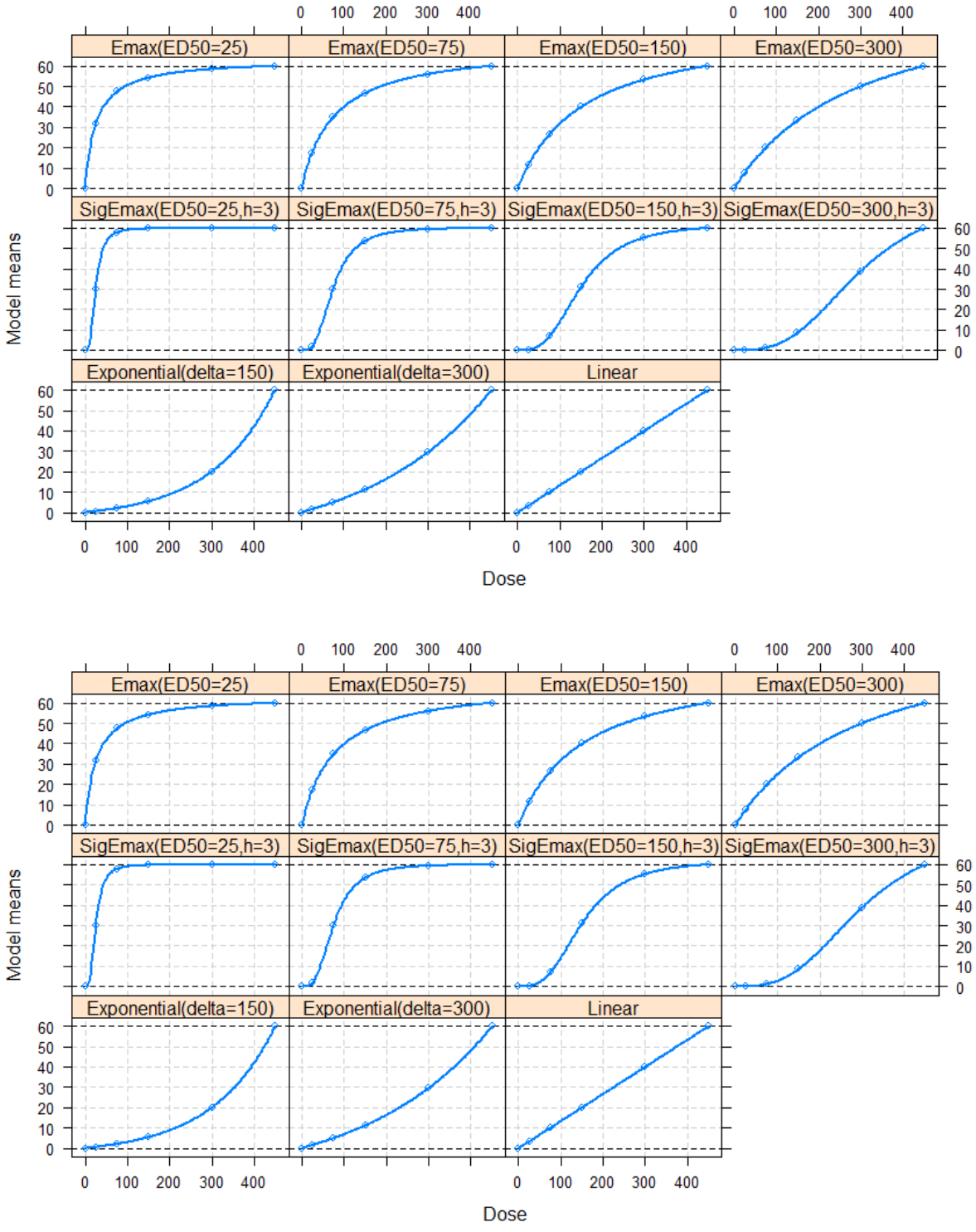
The adjusted treatment means from the MMRM will be used to test the null hypothesis of a flat DR relationship for the primary efficacy endpoint at a one-sided significance level of 5% against the alternative hypothesis of a non-constant DR curve. The testing will be performed with a multiple contrast test described in the MCP-Mod methodology.

A wide range of possible dose-response relationship will be considered to take model uncertainty into account (Figure 12-1). A monotonic DR is assumed, supported by preclinical data and the observed DR of another CFTR-potentiator, ivacaftor. Eleven candidate DR curves (4 Emax, 4 Sigmoid Emax, 2 Exponential, and 1 Linear) will be used to derive the optimal model contrasts for the multiple contrast tests. Emax and sigmoidal Emax models are considered based on the observed DR of ivacaftor (FDA 2012). The ED50 values (the dose at which half of the maximum effect is reached) for the Emax models will be 25, 75, 150, and 300. The parameters of the sigmoidal Emax models (ED50, h) will be (25, 3), (75, 3), (150, 3) and (300, 3) where h is the Hill parameter that determines the steepness of the dose-response shape. Exponential models are considered since there is an over-proportional increase of exposures at the high end of the dose range tested. The parameter controlling the convexity of the Exponential models will be 150 and 300.

For each of the 11 candidate DR curves, a contrast test statistic will be derived that maximizes the power assuming the true mean response is the one assumed by the candidate DR curve. The detection of a significant DR signal is based on the maximum of the 11 contrast test statistics. The overall null hypothesis of no DR relationship is rejected if the multiplicity adjusted p-value for at least one contrast test is < 0.05 (one sided).

[redacted]

Figure 12-1 Candidate Dose Response Curves



Step 2 (Estimation of the dose-response curve and target dose – Mod part):

[redacted]

Once the DR signal is declared, the DR curve and the target dose(s) of interest will be estimated by model averaging. A large number of bootstrap samples from the multivariate normal distribution will be drawn with adjusted means from the MMRM and corresponding covariance matrix. For each sample:

- DR models from the candidate families (Emax, Sigmoid Emax, Exponential, Linear) will be fitted to the data and the best model according to the generalized Akaike information criterion (AIC) will be chosen.
- The predictions for dose-response will be obtained from the best model.

The final DR curve estimate is the median of these predictions while confidence intervals will be calculated from the quantiles. The final DR curve estimate with the model-based two-sided 90% confidence interval will be presented graphically. In addition, the plot will include the mean responses from the MMRM and the associated 90% confidence intervals for each of the studied dose groups.

The target dose(s) that corresponds to a clinically relevant effect over placebo can be estimated using inverse regression techniques (Bretz et al 2005). All data related to safety, efficacy and other assessments including PK exposure will be taken into consideration to propose a dose for Phase 3.

12.4.3 Handling of missing values/censoring/discontinuations

Since the estimand is related to an effect outside of rescue med intake, spirometry measurements within 6 hours of rescue medication or within 7 days of intake of SCS use will be set to missing.. If one of the values contributing to the trough FEV_1 variable is missing at a visit, the remaining non-missing value will be taken as trough FEV_1. If both values are missing, then their trough FEV_1 will be regarded as missing at that visit.

For the primary analysis, only on-treatment data (from date of first randomized dose up to 1 day after date of last randomized dose) will be used as the estimand specifies a hypothetical on-treatment effect. Missing on-treatment data will not be explicitly imputed as the MMRM model implicitly imputes missing data assuming the missing at random (MAR) mechanism.

The imputation procedure(s) related to the trough FEV_1 supportive analyses (Section 12.4.4) are "jump-to-reference" (J2R) and MAR (Carpenter et al 2013). The imputations will be based on all available data (i.e. from all scheduled timepoints) using all covariates as specified in the MMRM. For J2R, only placebo (reference) data will be used. For MAR, data from the same treatment arm will be used for building the imputation model. Imputation of intermittent missing observations before treatment discontinuation will be carried out following a MAR mechanism for all treatment arms. Additional details will be available in the SAP.

12.4.4 Supportive analyses

A supplementary analysis will be performed that quantifies the treatment effect in all randomized patients during stable periods (i.e. outside episodes of COPD worsening that require rescue medication or SCS) with an adherence to treatment like we would see in clinical practice in a world without COVID-19, with the following post-randomization events accounted for by assessing:

[redacted]

a. Intake of rescue medication or systemic corticosteroid: effect outside of periods of worsening disease that necessitate rescue med or systemic corticosteroid
b. Discontinuation of study treatment for non-COVID-19 reason with follow-up: actual off-treatment value. If no data was retrieved after study treatment discontinuation, missing data will be multiply imputed based on placebo arm data: J2R assumption for the QBW251 arms and MAR assumption for placebo arm.
c. Discontinuation of study treatment due to a COVID-19 related reason: on-treatment value. Missing data will be multiply imputed based on the MAR assumption.
d. Discontinuation of study participation due to any non-COVID-19 related reason: off-treatment value. Missing data will be multiply imputed based on placebo arm data: J2R assumption for the QBW251 arms and MAR assumption for placebo arm.
e. Any other event leading to missing data prior to completion or discontinuation of study treatment: on-treatment value. Missing data will be multiply imputed based on the MAR assumption.

Additional sensitivity and/or supportive analyses may also be added to explore the impact of COVID-19 in the SAP.

A supportive exposure-response analysis may also be performed.

12.5 Analysis of secondary endpoints

No multiplicity adjustment will be carried out for secondary analyses described below. In addition, the treatment effect of QBW251 compared to placebo that would have been observed had all patients remained on their assigned treatment will be estimated. Only data obtained while patient is on-treatment (from date of first randomized dose up to 1 day after date of last randomized dose) will be used. Missing data for any reason will not be explicitly imputed and will be handled by the respective mixed effects model which implicitly imputes missing data assuming MAR.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

12.5.1.1 COPD symptoms

12.5.1.1.1 Respiratory symptoms from E-RS

The E-RS assesses both overall daily respiratory COPD symptoms (Total score) and specific respiratory symptoms using 3 subscales (Breathlessness, Cough & Sputum, and Chest Symptoms). Higher scores indicate more severe symptoms.

The mean baseline E-RS Total and subscale scores will be the average of the corresponding daily scores from the run-in period. The last 14 days of the run-in period, i.e. the scheduled duration of run-in period, will be considered. A patient needs to have at least 8 days of data from the run-in period in order for the mean baseline score to be calculated.

The daily scores post-randomization will be averaged for each week (Week 1, Week 2, etc.). A patient needs to have at least 4 days of data in any week in order for the mean score to be calculated.

[redacted]

Monthly means over a 4-week period will also be calculated. A patient needs to have at least 3 weekly means in that month in order for the monthly mean score to be calculated.

E-RS Cough & Sputum score

The change from baseline in the E-RS Week 12 Cough & Sputum mean scores will be analyzed using the same MCP-Mod approach described in Section 12.4 for the primary analysis of the primary variable. The change from baseline in the E-RS Cough & Sputum weekly mean scores will be analyzed using a similar MMRM as described in Section 12.4 for the primary variable, with the appropriate baseline score replacing the baseline FEV_1 value in the model. The estimated treatment difference (QBW251 – placebo) at each week will be reported along with the associated 90% confidence interval.

The proportion of patients who achieve a clinically important improvement (decrease) of at least 0.7 (Leidy et al 2014b) in the weekly mean score will be analyzed using a repeated measurements logistic regression. The model will include the same terms as for the MMRM analysis of the weekly scores. The estimated odds ratios will be displayed over time along with the associated 90% confidence intervals.

The change from baseline in the monthly mean scores will be analyzed using a similar MMRM as described above. The proportion of patients who achieve a clinically important improvement (decrease) in the monthly mean score will also be analyzed as described above.

E-RS Total, Breathlessness, and Chest Symptoms scores

The change from baseline in the E-RS weekly mean Total, Breathlessness, and Chest Symptom scores will be analyzed using a similar MMRM as described in Section 12.4 for the primary variable with the appropriate baseline E-RS score replacing the baseline FEV_1 value. The estimated treatment difference (QBW251 – placebo) will be reported along with the associated 90% confidence interval.

The minimum clinically important improvements (decrease) for the scores are defined below (Leidy et al 2014b).

- Total ≥ 2.0
- Breathlessness ≥ 1.0
- Chest Symptoms ≥ 0.70

The proportion of patients who achieve a clinically important improvement in the weekly mean scores will be analyzed using a repeated measurements logistic regression. The model will include the same terms as for the MMRM analysis of the weekly mean scores. The estimated odds ratios will be displayed over time along with the associated 90% confidence intervals.

The change from baseline in the monthly mean scores will be analyzed using a similar MMRM as described above. The proportion of patients who achieve a clinically important improvement (decrease) in the monthly mean score will also be analyzed as described above.

12.5.1.1.2 Cough and sputum symptoms from CASA-Q

CASA-Q assesses cough and sputum symptoms and their impact with 4 domain scores (cough symptoms, cough impact, sputum symptoms, and sputum impact). The change from baseline in the domain scores will be analyzed using the MMRM described in Section 12.4 for the primary

[redacted]

variable with the appropriate baseline domain score replacing the baseline FEV_1 value in the model. The estimated treatment difference (QBW251 – placebo) at each visit will be reported along with the associated 90% confidence interval.

12.5.1.1.3 Severity of symptoms from PGI-S

The PGI-S rates the severity of the respiratory symptoms and of cough and mucus. Shift tables will be used to compare baseline to Weeks 12 and 24 for each PGI-S value. The proportional odds model for repeated measures with the same terms as for the MMRM analysis described in Section 12.4 for the primary variable with the baseline PGI-S value replacing the baseline FEV_1 value. The estimated odds ratios will be displayed over time along with the associated 90% confidence intervals.

12.5.1.2 Health-related quality of life from SGRQ

SGRQ measures health impairment. A total score is produced, along with the domain scores of symptoms, activity, and impacts. The Weeks 12 and 24 change from baseline in the SGRQ total and domain scores will be analyzed using the MMRM described in Section 12.4 for the primary variable with the appropriate baseline SGRQ score replacing the baseline FEV_1 value in the model. The estimated treatment difference (QBW251 – placebo) at each visit will be reported along with the associated 90% confidence interval.

The proportion of patients who achieve a clinically important improvement (decrease) of at least 4 in the total score will be analyzed using a repeated measurements logistic regression. The model will include the same terms as for the MMRM analysis of the total scores. The estimated odds ratios will be displayed over time along with the associated 90% confidence intervals.

12.5.1.3 Lung function

The change from baseline in trough FEV_1 at visits other than Week 12 will be analyzed using the same MMRM as described in Section 12.4 for the primary analysis of the primary variable. The estimated treatment difference (QBW251 – placebo) at each visit will be reported along with the associated 90% confidence interval. The change from baseline in trough FEV_1 at Week 24 will also be analyzed using the same MCP-Mod approach described in Section 12.4.

The change from baseline in trough FVC after 4, 8, 12, 16, 20, and 24 weeks of treatment will be analyzed using the MMRM model described in Section 12.4 for the primary variable. The estimated treatment difference (QBW251 – placebo) at each visit will be reported along with the associated 90% confidence interval.

12.5.2 Safety endpoints

Safety summaries 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).

Adverse events

The on-treatment period for adverse events lasts from the date of first administration of double-blind study treatment to 30 days after the date of the last actual administration of randomized

[redacted]

study treatment. Adverse events will be summarized by treatment group. Summary tables for AEs will summarize only on-treatment events (also known as treatment-emergent AEs).

The number (and percentage) of subjects with treatment-emergent adverse events 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.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events and other significant adverse events leading to discontinuation.

A subject with multiple adverse events within a primary system organ class or preferred term is only counted once towards the total of the primary system organ class or preferred term.

In addition, treatment emergent AEs and SAEs will be presented by treatment, system organ class and preferred term, showing exposure adjusted event rates (i.e., the number of events expressed in rates per 100 patient years).

Vital signs

The on-treatment period for vital signs will be defined in the SAP. Summary statistics will be provided by treatment and visit/time for each vital signs variable. Notable values (to be defined in the SAP) and change from baseline will also be summarized. The baseline value is the last value prior to first dose of double-blind treatment.

12-lead ECG

The on-treatment period for ECG will be defined in the SAP. Summary statistics will be provided by treatment and visit/time for each ECG variable. Categorical analysis of QTc interval data based on the number of subjects meeting or exceeding predefined limits (to be defined in the SAP) in terms of absolute QTc intervals or changes from baseline will be presented. The baseline value is the last value prior to first dose of double-blind treatment.

Clinical laboratory evaluations

The on-treatment period for labs will be defined in the SAP. Summary statistics will be provided by treatment and visit/time by each lab variable.

For selected laboratory tests, the number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria (to be defined in the SAP) will be summarized by laboratory parameter. Change from baseline will also be summarized. The baseline value is the last value prior to first dose of double-blind treatment.

12.5.3 Pharmacokinetics

Descriptive summary statistics of QBW251B plasma concentration data will be provided by treatment and visit/sampling timepoint, including the frequency (n, %) of concentrations below the lower limit of quantification (LLOQ). Summary statistics will include mean (arithmetic and geometric), standard deviation, coefficient of variation (arithmetic and geometric), median,

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

Descriptive summary statistics of pharmacokinetic parameters will include mean (arithmetic and geometric), standard deviation, and coefficient of variation (arithmetic and geometric), median, minimum and maximum. An exception to this is T_{max} where median, minimum and maximum will be presented. In addition, the plasma concentration data from this study be combined with data from other studies to perform a population PK analysis, which will follow the principles outlined in the FDA Guidance for Industry 1999.

[redacted]

12.7 Interim analyses

12.7.1 Safety

IAs are planned for the monitoring of PK and safety data and do not inflate the type I error for the primary efficacy hypothesis testing. Thus no adjustment for multiplicity is required. These analyses will be performed by an external Independent Statistician and an Independent Programmer for an independent external safety DMC. Persons directly involved in the conduct of the clinical trial will not be involved in performing the IA or reviewing the results. The DMC will be provided with reports which are semi-blinded. If necessary, the study treatment can be unblinded by the chair of the DMC. The DMC will review PK and safety data and make recommendations regarding the conduct of the trial and/or alteration of the current protocol, including termination of a treatment arm. As mentioned in Section 9.1.4.1, a treatment arm (along with all other treatment arms with higher doses administered) will be terminated if the observed proportion of patients above the exposure threshold ($AUC_{0\text{-}24h}$ = 91 700 ng×h/mL) is significant greater than expected. It is expected that < 5% of patients on 300 mg or 450 mg b.i.d. will exceed the threshold based on a conservative scenario. An α-spending function with Pocock type stopping boundary (as implemented in East 6.4) will be used to construct the stopping boundaries (Lan et al 1983) using the p-value scale such that the overall significance level across all analyses is maintained at 0.05. At each interim analysis, an exact test on the proportion of subjects who exceed the exposure threshold will be performed to test the following hypotheses for these 2 treatment arms.

- Null hypothesis (Ho): the proportion of patients exceeding the exposure threshold < 5%
- Alternative hypothesis (Ha): the proportion of patients exceeding the exposure threshold ≥ 5%

The interim analyses are proposed to occur when 20%, 40%, 60%, 80%, and 100% of subjects have completed at least 4 weeks of treatment, which should be long enough to determine if the patient's exposure will exceed the threshold or not. The corresponding stopping boundaries in the p-value scale are 0.015, 0.016, 0.017, 0.018, and 0.019 for the interim analyses. For example, when the first interim analysis is performed after 20% patients have completed 4 weeks of treatment in the 450 mg b.i.d. arm, the observed (i.e. nominal) p-value has to be equal to or smaller than 0.015 in order to reject Ho and terminate the treatment arm.

If the true proportion of patients in the 300 mg or 450 mg b.i.d. treatment arm exceeding the exposure threshold is < 5%, then the probability of rejecting Ho would be very low (< 5%) with this group sequential test for the treatment arm. If the true proportion is 10% then the probability of rejecting Ho and stopping the treatment arm early would be high (≥77%). If the timing of the actual interim analyses deviate from the proposed schedule (20%, 40%, 60%, 80%, and 100% completed at least 4 weeks of treatment), stopping boundaries will need to be recalculated using the pre-specified α-spending function and based on the actual sample size at each interim analysis. The observed p-values at the interim analyses will then be compared against the re-calculated stopping boundaries.

After reviewing the exposure data from the first interim analysis, the DMC informed the sponsor that the 450 mg b.i.d. arm had crossed the stopping boundary and recommended termination of the treatment arm. The DMC confirmed that the arm was well tolerated in this patient population and the stop was not based on adverse reactions to the 450 mg b.i.d. regimen.

[redacted]

The sponsor followed the DMC's advice and discontinued investigational treatment from all patients randomized to the 450 mg b.i.d. arm.

More detailed criteria will be outlined in the DMC charter.

12.7.2 Efficacy

Up to 2 IAs on efficacy data may be conducted and the timing will correspond to 1 or 2 safety DMC analyses. The purpose of these IA(s) is to have an early assessment of the data for planning future studies in the QBW251B program. The efficacy IA results will not trigger any change or decision in the conduct of this study.

An internal Novartis committee, external to the study team, will be set up to review the both the efficacy and safety data. Once team members are exposed to the unblinded IA data, they will no longer be involved in the further execution of the study. A charter will provide further details.

The first IA will be conducted when approximately 645 to 680 patients, including ~102 patients randomized to the 450 mg b.i.d. arm, have either discontinued or completed 12 weeks of treatment. This IA will have acceptable precision for the estimated trough FEV_1 dose-response curve. The average half-length of the 90% confidence interval is around 26 mL and 32 mL for the estimated dose-response curve and the estimated placebo-adjusted dose-response curve, respectively. If the first IA does not lead to a clear decision for the planning of the QBW251B program, a second IA may be performed when all randomized patients have either discontinued or completed 12 weeks of treatment.

12.8 Sample size calculation

A total of 956 patients will be randomized to one of the 6 groups including 5 QBW251 dose groups (450, 300, 150, 75, 25 mg b.i.d.) and placebo. This includes the ~102 patients randomized to the 450 mg b.i.d. arm prior to its discontinuation. Prior to the discontinuation of 450mg b.i.d., patients were randomized to QBW251 450, 300, 150, 75, 25 mg b.i.d., or placebo with an allocation ratio of 2:2:1:1:1:2. After discontinuation of 450mg b.i.d., patients were randomized to QBW251 300, 150, 75, 25 mg b.i.d., or placebo with an allocation ratio of 2:1:1:1:2. This sample size of 854 (956 total minus approximately 102 patients already randomized to 450 mg b.i.d.) achieves at least 80% power for dose-response signal detection on key endpoints for all models from the candidate set based on the MCP-Mod methodology and also to ensure an acceptable precision for the DR curve estimation. The calculations in Table 12-1 exclude 450 mg b.i.d. from the analysis and are based on a 20% dropout rate, a one-sided significance level of 5%, and the following standard deviation assumptions.

- Pre-dose trough FEV_1: A common standard deviation of 200 mL based on previous Novartis COPD studies.
- E-RS Cough & Sputum weekly mean score: A common standard deviation of 1.3 based on the FLAME study (Wedzicha et al 2016).

Table 12-1 Power and Precision

Variable	Power to detect a DR signal	Average half-length of 90% confidence interval

	Maximum improvement over placebo		Estimated DR curve	Estimated placebo-adjusted DR curve
Trough FEV_1	60 mL	92%	21 mL	26 mL
	50 mL	81%		
E-RS Cough & Sputum	0.35	86%	0.14	0.17
	0.30	76%		

Power calculations were performed using ADDPLAN-DF-4.0 and the precision estimates (half-length of confidence interval) were obtained from simulations.

The randomization ratio was based generally on D-optimality criteria, which maximize the information on the dose response curve, for the MCP-Mod analysis. The D-optimal allocation ratio randomizes approximately twice as many patients to placebo and the highest dose, compared to the middle doses.

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 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 (defined as last patient last visit) 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.).

[redacted]

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.

[redacted]

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[redacted]

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 ≥ 450 msec for males or ≥ 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 patient by the Investigator.

[redacted]

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 PT/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 • Complete appropriate eCRFs	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	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
	• Complete appropriate eCRFs	
> 3 × ULN and PT/INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete appropriate eCRFs	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 • Complete appropriate eCRFs	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete appropriate eCRFs	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	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 • Complete appropriate eCRFs	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 • Fractionation into direct and indirect bilirubin is required	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
	• Complete appropriate eCRFs	Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete appropriate eCRFs	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 • Complete appropriate eCRFs	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 3 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.

[redacted]

16.3 Appendix 3 Spirometry guidance

Equipment

Spirometers must meet the specifications and performance criteria recommended in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry[1]. Spirometers must have the capacity to print FVC tracings. All spirometry values should be reported at body temperature, pressure, saturated with water vapor (BTPS) by the method established by the manufacturer.

Calibration

The spirometer should be calibrated every morning before any spirometric measurements for the study are performed. Calibration reports should be printed and stored as source data at the site.

Preparing the test subject

On study days when spirometry will be performed, patients should refrain from the following:

- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods and ice-cold beverages for 4 hours prior to spirometry
- Alcohol for 4 hours prior to spirometry
- Strenuous activity for 12 hours prior to spirometry
- Smoking within at least 1 hour of testing
- Exposure to environmental smoke, dust or areas with strong odors

Every effort should be made to assure consistent testing conditions throughout the study. A seated position with nose clips is recommended to reduce risks related to dizziness or syncope. When possible, spirometry should be conducted by the same technician using the same spirometer. To minimize the effects of diurnal variation on lung function, spirometry visits should start at approximately the same time of day at each visit.

Performing Spirometry

The subject's age, height and gender will be entered into the spirometer. It is important that the height is measured accurately at the study site. Spirometry, an effort-dependent test, requires careful instruction and cooperation of the subject. The technician should ensure a good seal around the mouthpiece, and confirm that the subject's posture is correct. The subject should be instructed to perform a maximal inspiration, followed by maximum forced expiration until no more air can be exhaled or for at least 6 seconds. Expiration must be rapid with exertion of maximal effort. The results of spirometry should meet the ATS/ERS criteria for acceptability (one retest may be performed for patients that don't meet the acceptability criteria).

Number of trials

A minimum of 3 acceptable forced vital capacity (FVC) maneuvers should be performed. If a subject is unable to perform a single acceptable maneuver after 8 attempts, testing should be discontinued.

Acceptability

An acceptable maneuver has the following characteristics:

[redacted]

- No hesitation or false start;
- A rapid start;
- No cough, especially during the first second of the maneuver;
- No glottic closure or obstruction by tongue or dentures
- No early termination of exhalation (minimum exhalation time of 6 seconds is recommended, or no volume change for at least 1 second) or the subject cannot continue to exhale further

Repeatibility

The 2 largest FVC and FEV_1 values from 3 acceptable maneuvers should not vary by more than 0.150 L.

Recording of data

The highest FEV_1 and FVC from any of the acceptable curves are recorded. (The highest FEV_1 and FVC may not necessarily result from the same acceptable curve).

Predicted normal

This study will utilize the spirometric predication equation standards for the European Community for Coal and Steel [2] or Nhanes[3] or Japanese Respiratory Society[4]. Further details will be provided in a specification document for the central spirometry assessments.

Reversibility

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing[1].

Administer 400µg of salbutamol/albuterol following the completion of the pre-bronchodilator assessment. Post-bronchodilator spirometry assessment is then performed 30 - 60 minutes after administration of the salbumatol/albuterol.

Reversibility is calculated as:

100 x FEV_1 (post-bronchodilator) – FEV_1 (pre-bronchodilator)

FEV_1 (pre-bronchodilator)

Following the reversibility testing assessment for post-bronchodilator FEV_1, if lung function has been observed to have deteriorated (i.e. there is a decrease in post bronchodilator FEV_1 compared to pre-bronchodilator FEV_1 *as opposed to an increase*) after administration of salbutamol/albuterol, then the patient should repeat the visit, allowing at least 24 hours between visits (one retest may be performed in patients that demonstrate a deterioration in lung function post-bronchodilation).

Patients with COPD demonstrating a high reversibility may require further clinical evaluation by the investigator to rule out a diagnosis of asthma.

References

1 Miller MR et al, Standardization of Lung Function Testing. Eur Resp J 2005;26:153-161.

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16.4 Appendix 4 CASA-Q

The sample provided here is for illustrative purposes only (US English version).

[redacted]

Cough And Sputum Assessment Questionnaire (CASA-Q)

- With this questionnaire, we would like to learn from you how your cough and your phlegm affect your day-to-day life.
- Please read each question carefully.
- Answer as best as you can without the help from anyone by marking the box that best corresponds to your answer (☒ or ☑).
- There are no right or wrong answers.
- All of the information you provide will be kept confidential.
- This questionnaire will take about 10 minutes to complete.

[redacted]

Cough

The following questions ask about your cough. Please try to think only about your cough when answering these questions.

1. Over the last 7 days, how much did you cough when you woke up in the morning?

Not at all	A little	Somewhat	Quite a bit	A lot
☐1	☐2	☐3	☐4	☐5

2. Over the last 7 days, how often did you cough during the day?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

3. Over the last 7 days, how often did you have coughing bouts?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

4. Over the last 7 days, how often were you tired after coughing?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

5. Over the last 7 days, how often did coughing make you short of breath?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

[redacted]

6. Over the last 7 days, how annoyed were you by your cough?

Not at all	A little	Somewhat	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. Over the last 7 days, how often did you avoid going to public places because of your cough (for example, movie theaters, restaurants, etc)?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

8. Over the last 7 days, how often were your usual activities interrupted by your cough (for example, driving, hobbies, working around the house)?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

9. Over the last 7 days, how often did your cough interrupt your conversations with others (for example, phone conversations and face-to-face)?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

10. Over the last 7 days, how often did your cough wake you up, prevent you from falling asleep or falling back to sleep?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

[redacted]

11. Over the last 7 days, how often were you uncomfortable about bothering other people while coughing?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

Phlegm

The following questions ask about your phlegm. Please try to think only about your phlegm when answering these questions.

12. Over the last 7 days, how thick was your phlegm?

Not at all	Slightly	Somewhat	Quite	Extremely
☐1	☐2	☐3	☐4	☐5

13. Over the last 7 days, how often did you bring up phlegm?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

14. Over the last 7 days, how often did your phlegm make it difficult for you to breathe?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

15. Over the last 7 days, how difficult was it for you to bring up phlegm?

Not at all	A little	Somewhat	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

[redacted]

16. Over the last 7 days, how often did you feel uncomfortable about bothering other people while bringing up phlegm?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

17. Over the last 7 days, how annoyed were you by your phlegm?

Not at all	A little	Somewhat	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

18. Over the last 7 days, how often did your phlegm interfere with your ability to speak?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

19. Over the last 7 days, how often did your phlegm prevent you from going to public places (for example, movie theaters, restaurants, etc)?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

20. Over the last 7 days, how often did you have to interrupt your usual activities to get rid of your phlegm (for example, driving, hobbies, working around the house)?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

Thank you for your help.

[redacted]

[redacted]

[redacted]

[redacted]

16.6 Appendix 6 EXACT questionnaire

(The sample provided here is for illustrative purposes only)

The EXACT Total score is computed across 14 questions and has a theoretical range of 0 to 100, with higher values indicating a more severe condition. The Total score is used in the determination of exacerbation frequency, severity and duration of exacerbation. Specifically, changes in the Total score are used to define onset and recovery from an exacerbation event and the magnitude of the event.

The EXACT provides information on 3 exacerbation-related outcomes: frequency (counts), severity (score) and duration (days). Time to first event may also be examined.

Study site and patient training

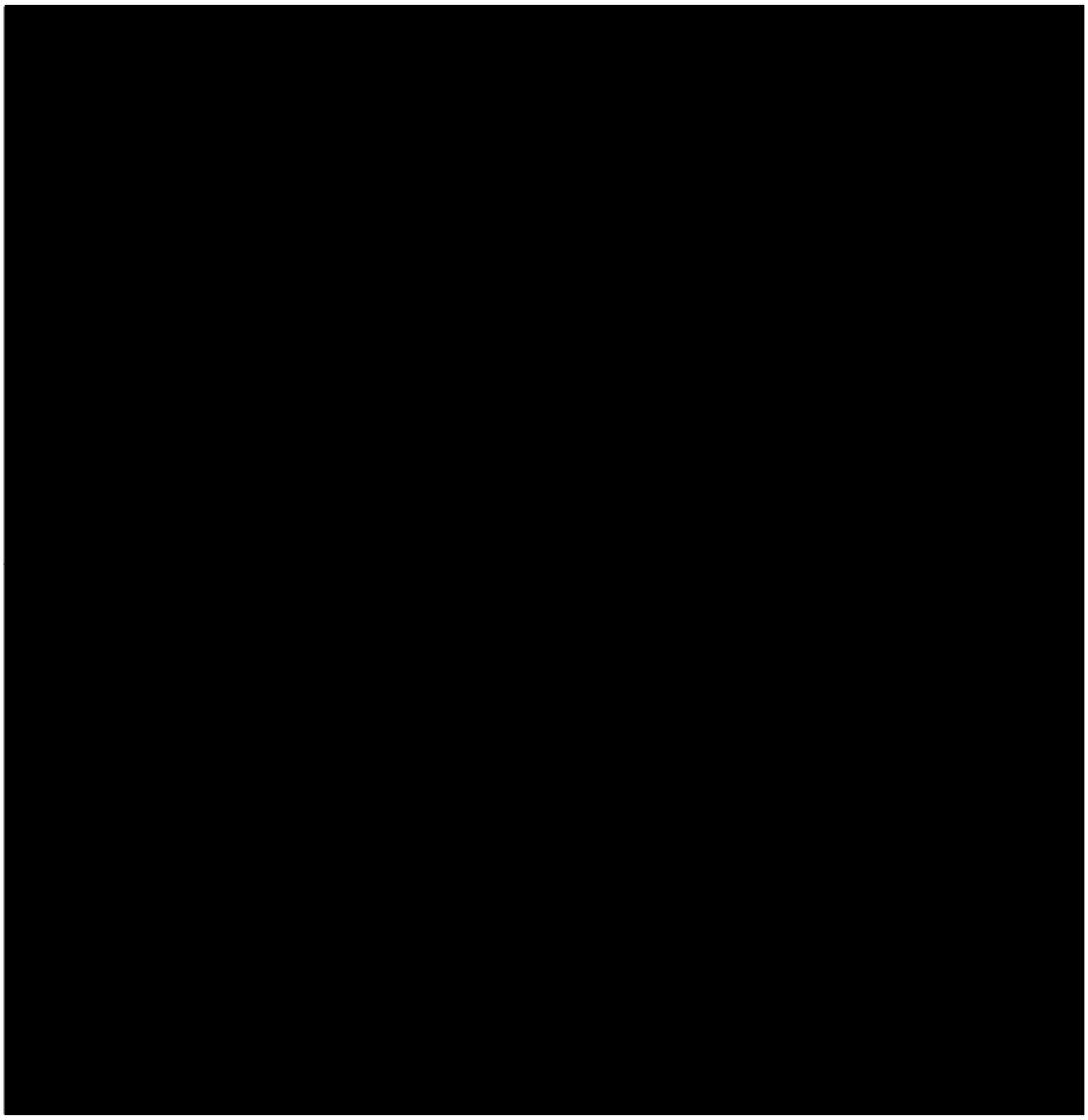
Study personnel should be trained on the following procedures to introduce a patient to the EXACT:

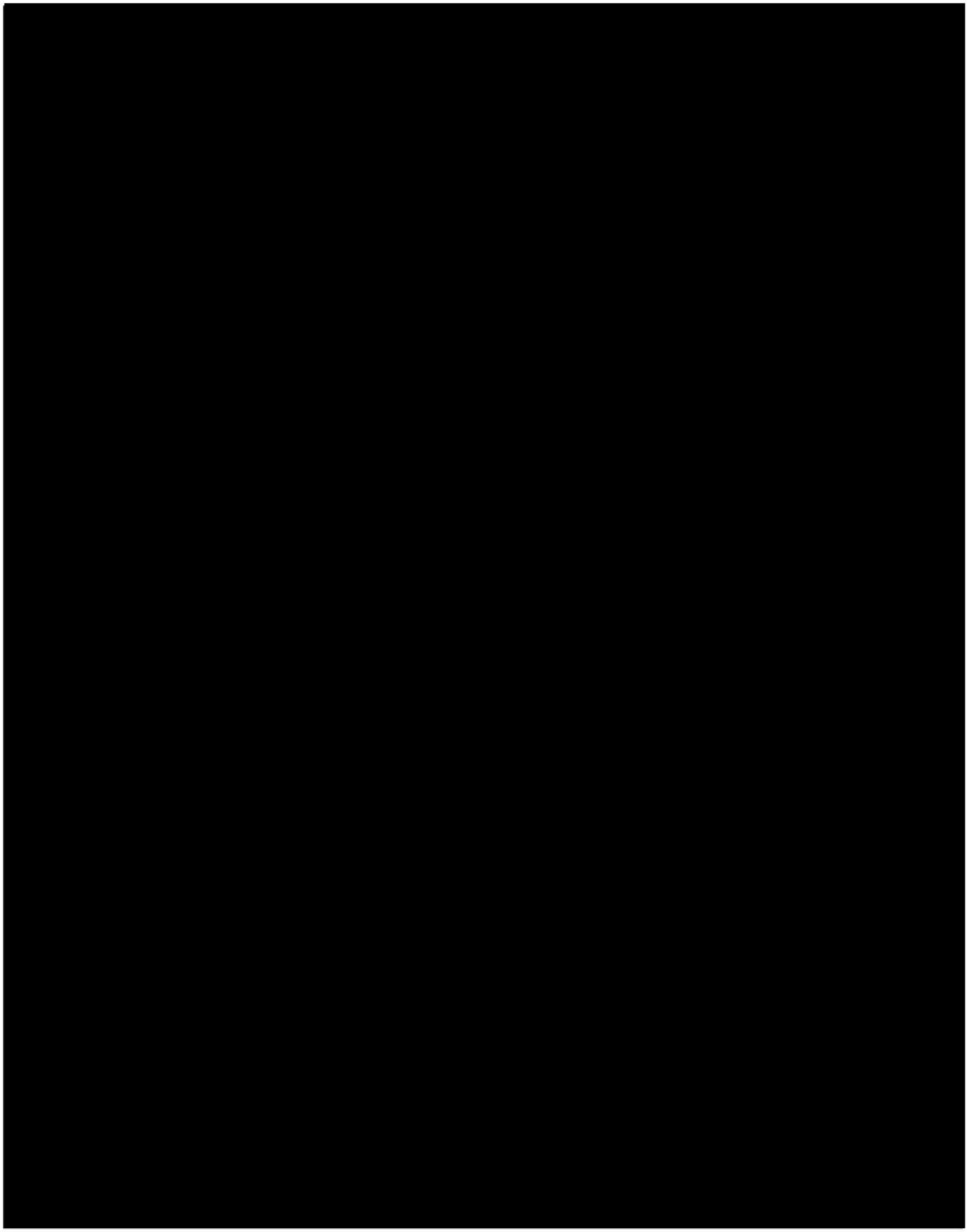
- Sit down with the patient at the beginning of the study and show them an example of the EXACT diary in the device on which it is to be administered.
- Inform the patient that the EXACT is to be completed every evening, just before going to bed.
- Instruct patients to reflect on their day and answer the questions based on how they felt over the day.
- Instruct a patient to respond in a way that is representative of the entire day.
- Remind patients that there are no right or wrong answers.
- Highlight for patients that the EXACT has 14 items.
- All 14 items are to be answered daily for the study period, as specified in the protocol.
- Point out that answers cannot be skipped.
- If a patient is unsure how to answer an item, instruct the patient to select the answer that best describes how they feel.

The EXACT total score is the sum of the raw score of the EXACT 14 items.

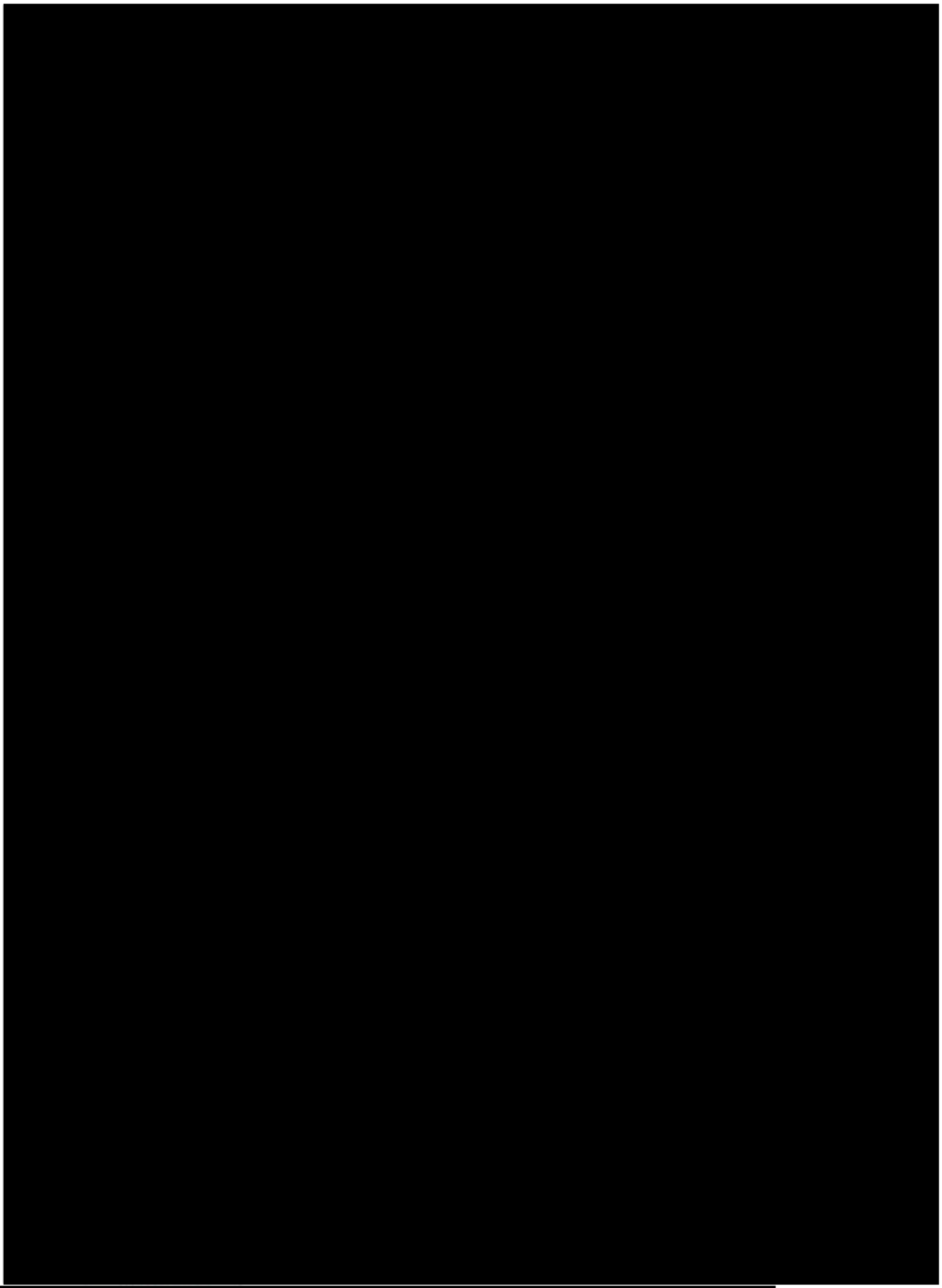
The following lists the raw score values associated with each response category for the EXACT items.

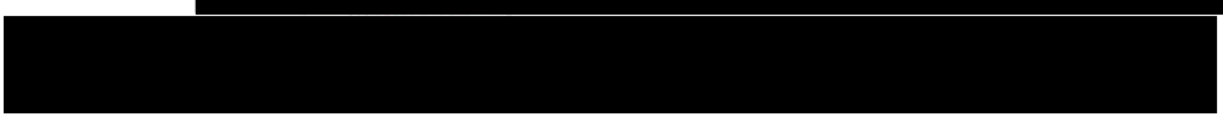
[redacted]





[redacted]





16.8 Appendix 8 PGI

The sample provided here is for illustrative purposes only.

The PGI-S consists of PGI-S - general question and PGI-S - specific question:

PGI-S - general question:

Overall, how would you rate the severity of your respiratory symptoms in the last 7 days? (Please check one only)

0 Not at all

1 Slightly

2 Moderately

3 Severely

4 Extremely

PGI-S - specific question:

Overall, how would you rate the severity of your cough and mucus in the last 7 days? (Please check one only)

0 No cough and mucus

1 Very Mild

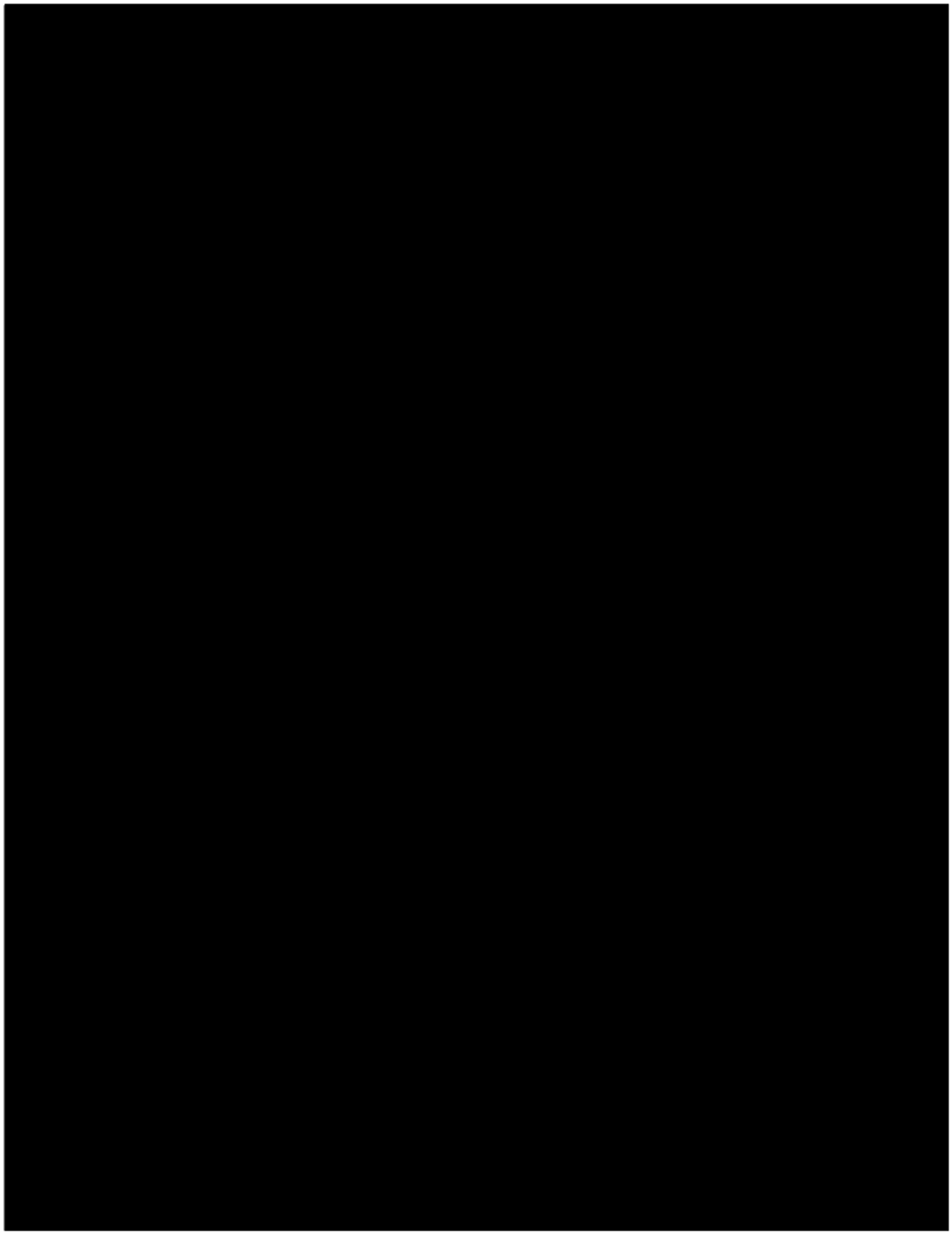
2 Mild

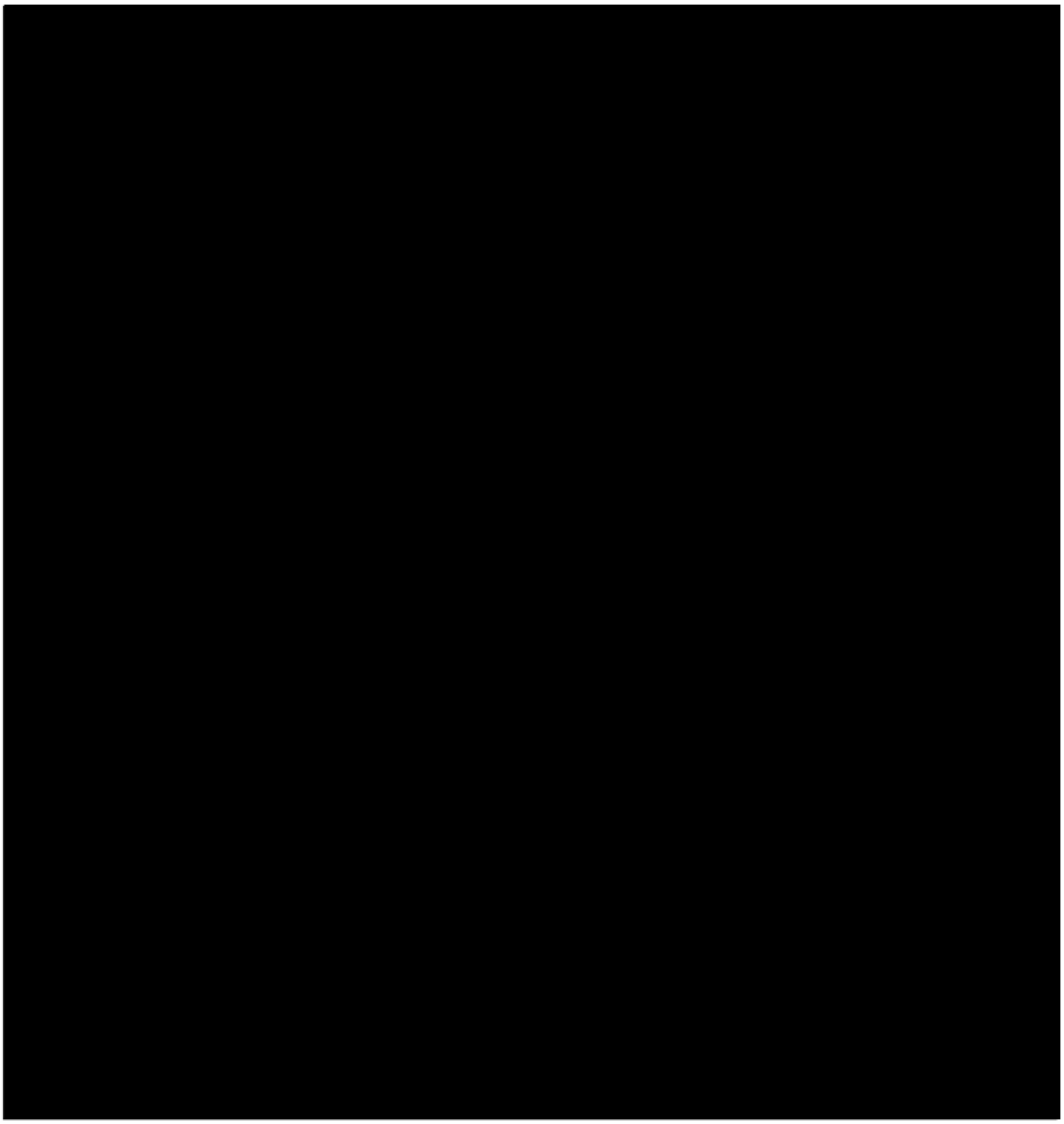
3 Moderate

4 Severe

5 Very Severe

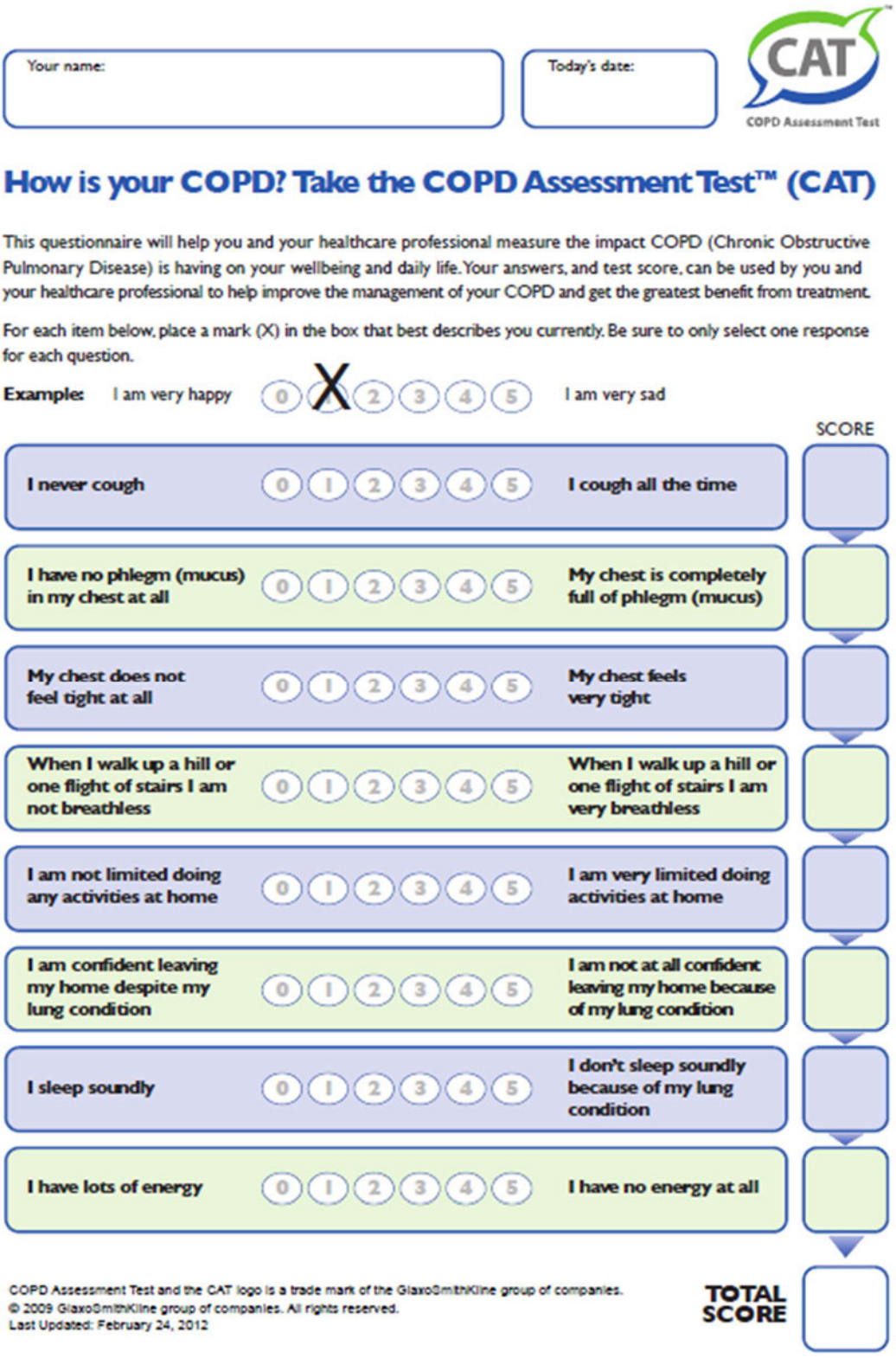
[redacted]





16.10 Appendix 10 CAT

(The samples provided here are for illustrative purposes only)



Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE	

Last Updated: February 24, 2012

[redacted]

16.11 Appendix 11 e-Diary (for rescue medication)

The following information will be captured twice daily before taking study medication. In addition, patient will register any study medication interruptions.

In the MORNING (pre-medication)	In the EVENING (pre-medication)
Number of puffs of rescue medication during the past 12 hours	Number of puffs of rescue medication during the past 12 hours

16.12 Appendix 12: SGRQ

The sample provided here is for illustrative purposes only.

[redacted]

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ENGLISH FOR THE UNITED STATES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

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

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

Before completing the rest of the questionnaire:

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

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

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[redacted]

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

Please check (✓) *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:
- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:
- No ☐
- Yes ☐

[redacted]

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

Please check (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problems ☐

If you have ever held a job:

Please check (✓) *one*:

- My respiratory problems made me stop working altogether ☐
- My respiratory problems interfere with my job or made me change my job ☐
- My respiratory problems do not affect my job ☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days.</u>

For each statement please check (✓) ***the box*** that applies to you ***these days***:	True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

continued...

[redacted]

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath <u>these days</u>.

	For each statement please check (✓) ***the box*** that applies to you ***these days***: True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you <u>these days</u>.

	For each statement, please check (✓) ***the box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbors	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

	For each statement, please check (✓) ***the box*** that applies to you ***these days:*** True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

continued…

[redacted]

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your respiratory problems.

	For each statement, please check (✔) ***the box*** that applies to you ***because of your respiratory problems***: True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

	For each statement, please check (✔) ***the box*** that applies to you ***because of your respiratory problems***: True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

continued...

[redacted]

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Sexual intercourse

Going to a place of worship, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐

It stops me from doing one or two things I would like to do ☐

It stops me from doing most of the things I would like to do ☐

It stops me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

[redacted]