NOVARTIS

Novartis Research and Development

QBW251

Clinical Trial Protocol CQBW251C12201
ClinicalTrials.gov Identifier: NCT04396366

A randomized, subject- and investigator-blinded, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of QBW251 in patients with bronchiectasis

Document type:	Amended Protocol Version
EUDRACT number:	2019-002840-26
Version number:	v03 (Clean)
Clinical Trial Phase:	II
Release date:	02-Dec-2022

Site Operations Manual (SOM)

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

Table of contents

List of tables

List of figures

List of abbreviations

AE	adverse event
AEMPS	Spanish Agency for Medicines and Medical Devices
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
b.i.d.	twice a day
BCRP	Breast Cancer Resistance Protein
BE	Bronchiectasis
BfArM	Federal Institute for Drugs and Medical Devices (Germany)
BMI	Body Mass Index
BUN	blood urea nitrogen
Cmin	Minimum concentration
CF	cystic fibrosis
CFR	Code of Federal Regulation
CFTR	Cystic fibrosis transmembrane conductance regulator
CFU	Colony-Forming-Unit
CMO&PS	Chief Medical Office & Patient Safety
COA	Clinical Outcome Assessments
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus identified in 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CRA	Clinical Research Associate
CSR	Clinical study report
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DDE	Direct Data Entry
DDI	Drug-Drug Interaction
DIN	Drug Inducted Nephrotoxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DRF	dose range finding
ECG	Electrocardiogram
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EoS	End of Study
EQ-5D-3L	Euro Quality of Life-5 Dimensions-3 level
E-RS	Evaluating Respiratory Symptoms in COPD

EU	European Union
eCRF	Electronic Case Report Form
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
EXACT-PRO	EXAcerbations of COPD Tool - Patient Reported Outcome
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
h	hour
HA	Health Authorities
hsCRP	High-sensitivity C-reactive Protein
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human Chorionic gonadotropin
HCV	Hepatitis C virus
HDL	high-density lipoproteins
HIV	human immunodeficiency virus
HRCT	High Resolution Computed Tomography
iABC	inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IL-6	Interleukin 6
IL-8	Interleukin 8
IN	Investigator Notification
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LABA	Long-acting β2 agonist
LAMA	Long-acting muscarinic antagonist
LDH	lactate dehydrogenase
LDL	low-density lipoproteins
LFT	Liver function test
LLOQ	lower limit of quantification
MCC	mucociliary clearance

MedDRA	Medical dictionary for regulatory activities
MHRA	The Medicines and Healthcare products Regulatory Agency (UK)
mg	milligram(s)
mL	milliliter(s)
NCFBE	non-CF bronchiectasis
NDA	New Drug Application
NOAEL	no-observed-adverse-effect-level
NTM	nontuberculous mycobacterial
NYHA	New York Heart Association
PCR	protein-creatinine ratio
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PoC	Proof of concept
PPM	potential pathogenic microorganisms
PRO	Patient Reported Outcomes
PT	prothrombin time
QMS	Quality Management System
QOL-B	Quality of Life Questionnaire for Bronchiectasis
QTcF	QT interval corrected by Fridericia's formula
rRNA	ribosomal ribonucleic acid
RoW	Rest of World
SABA	Short-Acting Beta-2 Agonists
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire
SMQ	Standardized MedDRA Query
SOC	Standard of care
SOM	Site Operations Manual
SOP	Standard Operation Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
ULN	upper limit of normal
US	United States of America
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study that contains different objectives or populations within that single study. Common parts within a study are a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly diagnosed disease.
Patient	An individual with the condition of interest
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.
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 medications or other intervention)
Screen Failure	A subject who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study 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

Amendment 03 (December 2022)

Amendment Rationale

This amendment removes the stopping rules for NOAEL threshold limits as recommended by both the sponsor and the Data Monitoring Committee (DMC) upon review of the full safety data set from all completed studies with QBW251 to date. No apparent correlation between drug exposure above the NOAEL threshold limits and safety signals has been observed in this safety review.

Further, this amendment discontinues the DMC involvement in the trial. The DMC was established as an independent review committee to monitor the exposure safety relationship and the benefit of the chosen exposure threshold. As the PK threshold monitoring has been eliminated given the lack of correlation with safety signals, the DMC is no longer required.

This protocol amendment clarifies the requirement of patient's completion of the EXAcerbations of COPD Tool - Patient Reported Outcome (EXACT-PRO) during screening/baseline period for the purpose of EXACT-PRO baseline score calculation to correctly set up EXACT-PRO alert after patient's being randomized. In addition, the exploratory objective and endpoints related to mucus burden are updated to be more specific. This change is made to ensure a baseline score can be correctly calculated and to ensure participants fully understand how to complete the EXACT-PRO, a questionnaire in place to measure exacerbations during the trial.

This amendment reduces the number of ECGs to one per visit versus in triplicate as results from the thorough QT study (CQBW251A2105) indicated that QBW251 at 300 mg b.i.d. did not have clinically relevant effects on studied ECG parameters, and reduction of ECGs will minimize time at study visits for participants.

This amendment updates the co-medication lists to include the most updated drug-drug interaction (DDI) information based on clinical DDI study (CQBW251A2107) and *in vitro* data.

This amendment also clarifies the inclusion/exclusion criteria, allowing patients with Primary Ciliary Dyskinesia (PCD) to participate which may facilitate recruitment to the study. Additional inclusion criteria are clarified, including the use of screening HRCT to satisfy inclusion in the study and the clarification that *Haemophilus parainfluenzae* alone is NOT permitted for inclusion as a pathogenic organism. These changes are made to increase understanding and simplify inclusion criteria in the study to facilitate recruitment.

This amendment introduces flexibility in the number of attempts for spontaneous sputum collection for each visit before attempting induced sputum collection.

This amendment allows participants at selected sites, upon approval of the sponsor, to forgo HRCT scanning. This change may facilitate participant recruitment at selected sites.

Additionally, this amendment made some other administrative and minor modifications to clarify or correct certain points, improving readability and to assure alignment between different protocol sections.

Changes to the protocol

- Protocol summary was updated to align with the changes in the protocol text.
- Table 2-1 Objectives and endpoints is updated to expand on the endpoints for the effect of QBW251 on HRCT outcome measures and to clarify biomarker endpoints.
- Section 3.1 Study visits and subsections are updated. Screening Visit subsection is updated to clarify the possibility to use the screening HRCT for diagnosis confirmation and to add the possibility for HRCT assessment to be optional at selected sites. Baseline/Randomization Day 1 subsection is updated to include information about mucous clearance regimen changes. Treatment period subsection is updated to provide flexibility in the number of attempts allowed for sputum collection and provide guidance on induced sputum, as well as to remove the need for triplicate ECGs based on CQBW251A2105 QT study results.
- Section 4.2 Rationale for dose/regimen and duration of treatment is updated to add DMC review conclusion and to remove PK threshold limits.
- Section 4.4 Purpose and timing of interim analyses/design adaptations is updated to remove the reference to the DMC.
- Section 4.5 Risks and benefits is updated to add advice for cautionary use of narrow therapeutic index substrates of CYP2C8, sensitive substrates of CYP2B6, CYP2C8, CYP2C19, OCT1, and MRP2, and prohibit use of narrow therapeutic index substrates of CYP2C19 and strong inducers mediating enzyme levels via PXR according to the updated information from CQBW251A2107 results and *in vitro* data. The triplicate ECGs were removed based on CQBW251A2105 QT study results. The PK threshold limits were removed, and more information was added about the DDI study CQBW251A2107.
- Section 5.1 Inclusion criteria is updated to clarify the possibility to use the screening HRCT for diagnosis confirmation and to exclude *H. parainfluenzae* alone as an acceptable pathogenic organism for inclusion.
- Section 5.2 Exclusion criteria is updated to clarify who determines certain exclusion criteria and to allow inclusion of patients with PCD with approval of Sponsor.
  The definition of an exacerbation in Excl #12 was updated. And Excl #22 was updated to clarify that only uncontrolled Type I and Type II diabetes are exclusionary. The timeframe for receiving medication that may influence treatment response was updated to within 4 weeks from Day 1.
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action is updated to include the most updated DDI information. The prohibition periods and action taken columns are reworded for more clarity and to remove the reference to -45min and -15min spirometry as the double spirometry is not required at each visit, only at screening.
- Table 6-4 is updated to clarify the action to be taken in case of the use of prohibited contraception methods.
- Table 6-5 Prohibited medication is updated to include additional prohibited medications that may influence the response to treatment and to clarify the duration of the prohibition period.
- Table 6-6 Prohibited Respiratory related medications and required washout periods prior to Day 1 is updated to remove redundancy with other tables.

- Section 6.4 Treatment blinding is updated to remove DMC-related activities.
- Table 6-7 Blinding levels is updated to remove DMC-related activities.
- Table 8-1 Assessment schedule is reformatted for all the visits to fit on the same page. It is also updated to clarify that patients need to complete the EXACT-PRO on at least 4 out of the past 7 days before patients begin the Baseline visit to calculate the EXACT-PRO baseline score. The Sparse PK Sample collection is removed at unscheduled visits. The footnotes have been updated to provide clarity and consistency with the rest of the document. The HRCT assessment is also made optional at selected sites with approval of Sponsor. For clarity, Concomitant medication and Adverse events were marked as assessments to be recorded in clinical database. Comments were marked as to be recorded in the source documentation.
- Section 8.1 Screening is updated to clarify that the sputum bacterial load assessment may be repeated twice prior to randomization if sputum bacterial load at screening is outside of the eligibility range.
- Section 8.3.1 Microbiological assessment is updated to allow participants to provide flexibility in the number of attempts allowed for sputum collection and provide guidance on induced sputum collection.
- Section 8.3.4 High Resolution Computed Tomography (HRCT) is updated to allow HRCT assessment to be optional at selected sites with approval of Sponsor. Additional details about secondary and exploratory HRCT assessments have also been included.
- Section 8.4.4 Bronchiectasis exacerbation is updated to include steroids as possible treatment for BE exacerbation treatment to be considered.
- Section 8.5.1 Clinical Outcome Assessment (COAs) was updated to remove that it should be completed before all other assessments for consistency with other recommendations in the protocol
- Section 8.5.2 Pharmacokinetics is updated to remove the need to collect additional PK samples for treatment-emergent SAEs.
- Section 8.5.3.1 Sputum biomarkers is updated to allow analysis flexibility depending on methods availability and emerging scientific knowledge.
- Section 8.5.3.2 Serum protein signatures is updated to add the description of serum protein profiling analysis
- Section 9.1.1 Discontinuation of study treatment is updated for discontinuation due to PK threshold-related SAEs. The EoS visit is specified for the assessments to be completed in case of discontinuation.
- Section 9.1.5 Early Termination by the sponsor is updated to remove exposure-driven decision.
- Section 10.2.3 Data Monitoring Committee is updated to specify that the DMC is no longer required.
- References were updated according to the latest guidance on Harvard style format

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulation prior to implementation. In addition, the changes herein will affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 02 (November 2021)

Amendment rationale

This protocol amendment addresses the following changes: two inclusion and one exclusion criteria were amended following investigators' feedback to improve study feasibility and recruitment. These changes will expand the number of eligible participants, but will not change the overall patient profile for the study.

1. Subjects with one documented exacerbation between January 2019 and study screening will be permitted. This will extend the window for historical exacerbations to pre-COVID-19 when subjects were potentially having exacerbations more typical of their disease state.
2. Subjects who are using mucolytics and hyperosmolar agents will be permitted. The study drug has a different mechanism of action compared to mucolytics and hyperosmolar agents, so use of mucolytics and hyperosmolar agents will not interfere with assessment of the study drug.

Additionally, this amendment made some other administrative and minor modifications to clarify or correct certain points, improving readability and to assure alignment between different protocol sections.

Changes to the protocol

- Key inclusion criteria in Protocol Summary, Section 5.1 Inclusion Criteria were updated to expanded timeframe for subject to have had defined, documented exacerbations between Jan 2019 and screening instead of 12 months prior to screening. This accounts for the reported reduction in exacerbations in this population due to presumed fewer exposures to triggers of exacerbation during the COVID-19 pandemic.
- Key inclusion criteria in Protocol Summary, Section 5.1 Inclusion Criteria were updated to allow patients to use mucolytics or hyperosmolar agents as maintenance therapy if they were treated with them before study start.
- Key exclusion criteria in Protocol Summary, Section 5.2 Exclusion Criteria and Table 6-6 Prohibited respiratory related medications and washout period prior to Day 1 were updated to remove mucolytics and hyperosmolar agents from the prohibited medication list.
- Section 3.1 Study visits and Section 8 Visit schedule and assessments and throughout the document were updated to extend the screening period from 35 days to 42 days to accommodate turn-around times for sputum in case of need to re-test during screening.
- Section 4.5 Risks and benefits was updated to remove advice for cautionary use of sensitive substrates of CYP2B6 and OATP1B3 according to the updated assessment based on the highest dose of 300 mg b.i.d. in IB version 13.
- Section 5.2 Exclusion criteria was updated to split exclusion criterion #18 into 3 separate criteria #18, #24 and #25, which was accidentally combined as one criterion.
- Section 6.2.4.1 Dietary restrictions and smoking was updated to allow smoking as smokers without severe emphysema are allowed to be enrolled.

- Section 8.1 Screening was updated to clarify in case of rescreening, patient does not need to retest HRCT at baseline if it has been done in the previous screening period within the past 12 months.
- Section 10.1.3 SAE reporting has been updated to include the latest requirement from BfArM in Germany.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulation prior to implementation. In addition, the changes herein will affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 01 (March 2021)

Amendment rationale

This protocol amendment addresses the following changes as requested by MHRA, BfArM, AEMPS and the EC in Germany:

1. To clarify that the dose to be used in the study is 300 mg and the respective dose rationale. During the independent Data Monitoring Committee (DMC) meeting held on 16-Apr-2020 for the QBW251 studies, the DMC recommended treatment with the 450 mg b.i.d. dose be discontinued in the ongoing dose-range-finding study, based on the statistical stopping rule pre-specified in the protocols (Section 10.2.3). Importantly, no safety findings contributed to this DMC recommendation. Accordingly, Novartis decided to use 300 mg b.i.d. dose in the present study instead of 450 mg b.i.d.
2. Remove the requirement for the serious adverse reactions to be similar in nature as a pre-requisite to put the study on hold.
3. Include a statement that any restart following a temporary hold due to stopping rules being met will require the Competent Authorities and Ethic Committees approval, as required per country regulations.
4. To clarify the primary analysis strategy as requested by the EC in Germany.

Additionally, this amendment made some other administrative and minor modifications to clarify or correct certain points, improving readability and to assure alignment between different protocol sections.

Changes to the protocol

- List of abbreviations was updated to include new abbreviations.
- Primary objective in protocol summary Section 2 and Section 8.3.1 were updated to clarify 1 CFU/mL = 1 CFU/g.
- Study design in protocol summary, Section 3.1 and Section 8.3.1 were updated to allow retesting of bacteria load during the screening period.
- Inclusion criteria in protocol summary and Section 5.1 was updated to clarify that chest CT (not only the chest HRCT) are acceptable for diagnosis of bronchiectasis (inclusion criterion #3).
- Inclusion criteria in protocol summary and Section 5.1 were updated to remove the requirement of steering committee's approval for including additional organisms to be measured and counted in the bacterial load (inclusion criterion #4).
- Exclusion criteria in protocol summary and Section 5.2 were updated to clarify the hepatitis exclusion criterion and requirements on liver function tests (exclusion criterion #5).
- Section 2 secondary objectives, Section 8.5.2 and Section 12.5.3 were updated to reflect the most accurate PK parameters to be assessed in this study.
- Section 3.1 was updated to clarify the requirement of HRCT assessment during screening.

- Further sections were updated throughout the document to emphasize the use of the dose of 300 mg b.i.d. and that the dose of 450 mg b.i.d. will not be used in this study.
- Figure 3-1 was updated to remove the dose of 450 mg.
- Section 4.2 Rationale for dose/regimen and duration of treatment was updated to clarify the reasons for using the dose of 300 mg b.i.d.
- The original Section 6.5.2 Dose Modifications and Section 9.1.4.1 Dose Reduction are integrated into Section 4.2, Section 4.5, Section 9.1.1 and Section 10.2.3. Redundant information related to the 450 mg dose was removed. Section 6.5.2.1 Dose Adjustments for QTcF Prolongation is promoted to the new Section 6.5.2.
- Section 6.2.1.1 was updated to reflect that induction of QBW251 by CYP2B6 and relevant change in exposure due to concomitant medicines are not expected at the anticipated exposure of QBW251 300 mg b.i.d. and remove sensitive substrates of CYP2B6 from Table 6-3.
- Section 6.2.3 was updated to accurately reflect the treatment for exacerbations instead of the rescue medication only.
- Section 6.4 was updated to clarify the blinding strategy.
- Table 8-1 was updated to include below changes to be aligned with the protocol body:
  - Add week number for each visit
  - Change time point “dose” to “0”.
  - List the requirement of drug accountability
  - List the assessment of coagulation
  - List sputum 16s rRNA PCR in a separate row
  - Add SGRQ, EQ-5D-3L, QOL-B and eDiary, EXACT-PRO to Unscheduled visit
  - Add respiratory assessment on Day 56
  - Combined individual cells for EXACT-PRO in to one for the treatment period to reflect that it needs to be completed every evening
  - Changed data capture requirement for telephone follow-up on day 14 from requiring in clinical database to only requiring in source data
  - Footer was updated to be aligned with the changes.
- Section 8.3.1 was updated to move the 16s rRNA PCR test to the Section 8.5.3.1.
- In Section 8.3.3, the method for fibrinogen analysis is removed as it will be defined by the central lab.
- Section 8.4.1 was updated to move fibrinogen from chemistry panel to coagulation panel; and to remove PTT from coagulation panel according to lab settings.
- Multiple sections throughout the document were updated to remove the mandatory serial PK sampling for selected sites. Now at selected sites, serial PK sampling is also optional to patients.
- Section 8.5.3.1 was updated to list all sputum biomarkers, including 16S rRNA PCR for bacterial load and 16S rRNA gene sequencing for bacterial profile, which are both optional to China.

- A statement for the restart of the study following a temporary hold due to stopping rules being met will require HA and EC approval as required per local regulations is added in Section 9.1.4 Study stopping rules.
- Section 9.1.4 was updated to remove the requirement for the serious adverse reactions to be similar in nature.
- Section 10.1.4 was updated to remove the requirement of following up male subject's female partner's pregnancy.
- Section 10.2.3 was updated to correct a typo in bullet point 1 from "The proportion of subjects" to "The number of subjects".
- Section 12.4.1, Section 12.4.2 and Section 12.4.3 were updated to clarify the analysis strategy for the primary estimand.
- Section 12.5.1 was updated to reflect the analysis plan for the secondary efficacy endpoints.
  - Updated the analysis in Section 12.5.1.3
  - Moved the description of the endpoint from Section 12.6.1 to Section 12.5.1.5.
- Reference was updated to reflect the correct URL for ICH-E2E.

Only the information referring to 450 mg has been deleted. All information that still concerns the 300 mg has been kept in the protocol. Sections that previously described the dose reduction and the steps to be taken have been distributed to other sections, as applicable (i.e. Section 4.2 and Section 9.1.1).

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulation prior to implementation. In addition, the changes herein will affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Protocol summary

Protocol number	CQBW251C12201
Full Title	A randomized, subject- and investigator-blinded, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of QBW251 in subjects with bronchiectasis
Brief title	Study of safety, tolerability, pharmacokinetics and pharmacodynamics of QBW251 in subjects with bronchiectasis
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine whether potentiating the cystic fibrosis transmembrane conductance regulator (CFTR) with QBW251 in patients with bronchiectasis will demonstrate clinical safety and efficacy related to improved mucociliary clearance with reduced bacterial colonization as potential drivers of airway obstruction, reduced airway inflammation, exacerbations and mucus load, improved lung function, clinical symptoms and quality of life to support further development in bronchiectasis.
Primary Objective(s)	The primary objective for this study is to determine the efficacy of QBW251 compared to placebo with respect to change from baseline in bacterial load of colony forming units (CFU/mL, 1 CFU/mL = 1 CFU/g) of potentially pathogenic microorganisms in spontaneous sputum at week 12.
Secondary Objectives	Objective 1: to assess the change on sputum bacterial clearance of QBW251 compared to placebo with respect to proportion of patients with absence of any CFU of potentially pathogenic bacteria in sputum culture after 12 weeks of treatment. Objective 2: to assess the change on patient reported outcomes on bronchiectasis symptom assessment of QBW251 compared to placebo with respect to change from baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B) after 12 weeks of treatment. Objective 3: to assess the change of fibrinogen plasma concentration of QBW251 compared to placebo after 12 weeks of treatment. Objective 4: to assess the change in rescue medication use of QBW251 compared to placebo after 12 weeks of treatment. Objective 5: to assess the effect of QBW251 after 12 weeks of treatment, on the change from baseline in lung function from measurement by spirometry of pre-bronchodilator FEV1 and FVC. Objective 6: to assess the effect of QBW251, after 12 weeks of treatment, on the change from baseline in airway structure and function from measurements by HRCT of airway wall, lumen parameters and the extent of global and regional air trapping. Objective 7: to assess the pharmacokinetic profile of QBW251 in subjects by measurement of concentrations of QBW251 in plasma and calculation of relevant PK parameters including Cmax, AUC on Days 1 and 28 (for a subset of patients at selected sites). Pre- and post- dose concentration (Ctrough and around Cmax) on Days 1, 28, 56 and 84 (for all patients).

	Objective 8: to assess the safety and tolerability of QBW251 by reporting the occurrence of adverse events, vital signs, ECG and safety laboratory changes during the study
Study design	This is a randomized, subject- and investigator-blinded, placebo-controlled, parallel-group study investigating the preliminary efficacy and safety of QBW251 administered orally for 12 weeks in subjects with bronchiectasis. Approximately 72 subjects will be randomized in a 1:1 ratio to receive either QBW251 or placebo in order to achieve 60 subjects who complete the treatment period based on the assumption of a 16% drop-out rate. The sample size assumptions will be reviewed in an interim analysis in a blinded manner when approximately 14 subjects complete the treatment period. The study consists of the following periods: Screening, baseline/Day 1, treatment period, and end of study assessments (EOS) visit followed by an additional post-treatment safety follow up via phone call. The total duration for each subject in the study is up to approximately 19 weeks. **Study visits** The study employs the following visits: **Screening visit (Day -42 to Day -1):** Screening assessments can be performed over a 6-week period maximum (up to 42 days). Informed consent must be obtained prior to implementing any study specific procedure. Inclusion and exclusion criteria will be checked to confirm patient's eligibility. Sputum will be collected once within the screening window to confirm bacterial load with at least one strain of potentially pathogenic bacteria (refer to Section 5.1). The sputum microbiology results at screening will need to be available prior to randomization. Retesting is allowed once. At screening, all subjects will be provided with an electronic diary (eDiary) and be trained on its use on how to record information about their rescue medication (salbutamol/albuterol), other concomitant medication use, how to complete questionnaires, how to record study medication intake (from Day 1 onwards) as well as symptoms. A HRCT assessment will be performed during screening period except at selected sites where HRCT is optional with Sponsor approval. **Baseline/Randomization Day 1:** Subjects who meet the eligibility criteria will be admitted to baseline/Day1 safety and efficacy evaluations before randomization. During baseline, sputum samples will be collected at the same time of the day (sputum collection procedure and timing will be detailed in the SOM and laboratory manual) for biomarker assessments (bacterial load and colonization as well as inflammatory markers). Subjects will be also asked to complete various scales and questionnaires (refer to Assessment Schedule type of questionnaires and time-points).

	There is no antibiotic intervention allowed between screening and baseline except for the use of macrolides for subjects who are on this medication before enrolment. In this case, macrolides are to be continued at the same dose and regimen during the study. Once all baseline assessments have been completed and subjects are again confirmed as being eligible for the study, they can be randomized on the same day (baseline/randomization Day 1). In the case that sputum sample cannot be collected or other assessments can't be completed at baseline visit for various reasons, the site must not randomize the subject on the same day. An unscheduled visit needs to be planned for sputum collection prior to randomization and treatment allocation. Once sputum is collected and other required assessments are completed, the subject can be randomized on the same day of the unscheduled visit. **Treatment Period (Day 1 to Day 84)**: The treatment period will be 84 days (Day 1 to Day 84), with dosing occurring on Days 1 through 84, and will include a Day 1 Visit, a Day 14 visit (via telephone check), a Day 28 Visit, a Day 56 Visit, and a Day 84 Visit. On Day 1, after completion of all pre-dose assessments (including the Concomitant medication therapy as per Table 6-2 and Table 6-6), eligible subjects will be randomized in a 1:1 ratio to receive QBW251 300 mg b.i.d. or matching placebo for 84 consecutive days. At randomization, stratification will be done according to the status of macrolides use and geographic region (sites from China/sites outside China) in order to balance patient distribution in treatment and placebo group. The first study medication for this treatment period should be administered in the clinic in the morning of Day 1, following the pre-dose pharmacokinetic blood sample collection as indicated in the Assessment Schedule. (NOTE: all PK sampling times are relative to the first dose of the treatment day). During treatment period, subjects will return to the site for scheduled visits for biomarker blood/sputum sample collections, PK, safety and efficacy assessments including completion of the questionnaires. On visit days, subjects will take their morning dose in the clinic after completion of pre-dose assessments. On scheduled sputum collection visits, sputum specimens are recommended to be collected in the morning at pre-dose time point and if possible before breakfast. In case subjects can’t produce enough sputum on the individual scheduled visits, they can come back to site up to 3 days after the scheduled visit to try to produce a sputum sample. If spontaneous sputum collection attempts are still not satisfactory, investigator may take decision to collect sputum sample after induction by the inhalation of saline. At Day 14, site will call the subject to evaluate the compliance and to check patient well-being. Pharmacokinetic blood sampling (pre-dose and 3 hr post dose) will be done at Day 1, Day 28, Day 56 and Day 84 visits. Additionally, although serial PK sampling is optional, efforts will be made to have a subset of approximately 30-40 subjects undergo serial PK sampling at pre- and up to 8 hours post-dose on Day 1 and Day 28.

	ECGs pre- and post-dose at Tmax will be performed at visits on Day 1, Day 28, Day 56 and Day 84 (end of treatment). These assessments will be complemented by PK sampling (trough and Cmax) on the matching time-points, at visits on Day 1, Day 28, Day 56 and Day 84. The morning dose on Day 84 will be the final dose administration for this treatment period. End of treatment assessment, e.g., safety assessment, lung function assessments and PROs will be performed on Day 84. If spontaneous sputum collection is not possible at Day 84, site needs to reschedule the visit within 3 days after Day 84 and subject has to continue to take study medication. Other assessments which have been completed on Day 84 do not need to be repeated. A second HRCT will be performed at Day 84 after the morning dose of study medication at site. If the HRCT can't be performed at Day 84 for any reason, the assessment needs to be planned within approximately the 3 coming days and patient must continue to take study medication. In case of symptom deterioration (via e-diary alert), subjects have to visit their study center to determine whether exacerbation criteria have been met and an immediate antibiotic treatment may be necessary (e.g. CRP increase over normal laboratory level). In addition, other markers of inflammation such as fibrinogen in blood will be taken to gain more information on systemic inflammation and sputum sample collection in order to determine if there are changes in pathogen or bacterial load that may have resulted in the exacerbation. Subjects experiencing an exacerbation during the treatment period will continue with the study treatment along with the standard of care (SOC) therapy for an exacerbation (i.e. antibiotics). **End of Study (EoS) visit (Day 91):** Approximately one week upon completion of the treatment period, subjects will be invited to the center for study visit completion (EOS) assessments. **Safety follow-up call (Day 114)** A follow-up phone call for safety will occur 30 days after the last dose administration. The safety follow-up includes adverse events safety monitoring. For a complete list of assessments, refer to the Assessment Schedule in Table 8-1.
Population	The study population will consist of approximately 72 male and female patients with bronchiectasis
Key Inclusion criteria	• Male or female patients aged ≥18 years at screening. • Proven diagnosis of bronchiectasis by chest CT at screening as determined by investigator • Evidence of sputum bacterial load of $\geq 10^6$ CFU/mL with at least one potentially pathogenic microorganism *(H. Influenzae, M catarrhalis, S aureus, S pneumoniae, Enterobacteriaceae, P aeruginosa, Stenotrophomonous maltophilia*, or any potential pathogenic non-fermenting Gram-negative bacteria measured by dilution/outgrowth). • Documented history of at least one bronchiectasis exacerbation between January 2019 and study screening.

	• Patients with bronchial hypersecretion, defined as productive cough that occurs on most days (defined as >50% days) for at least three consecutive months within 12 months prior to screening, as assessed by documentation of patient recollection (anamnesis) or documented in patients' record. • Patients are allowed to stay on fixed or free combinations of LABA/LAMA or LABA/ICS or LABA/LAMA/ICS as maintenance therapy if they are treated with them at a stable dose for the last 3 months prior to screening. Patients are also allowed to stay on macrolides as maintenance therapy if they are treated with them at a stable doses 3 months before screening. Patients will be allowed to use mucolytics or hyperosmolar agents if they were treated with them before study start. • If prescribed, patients are included in the study with unchanged chest physiotherapy for at least 4 weeks prior to screening. • Clinically stable pulmonary status in the opinion of the investigator and unlikely to require any change in the standard regimen of care during the course of the study

Key Exclusion criteria	• Patients with a history of long-QT syndrome or the QTcF interval at Screening and baseline is prolonged (QTcF >450 ms in males, >460 ms in females).
	• Patients with a history or current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure. A history of resolved Hepatitis A is not exclusionary. Patients with a prothrombin time international normalized ratio (PT/INR) of more than 1.5xULN at screening. Patients excluded for the PT/INR of more than 1.5xULN can be re-screened when the values have returned to normal.
	• History of lung transplant or malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin. Patients with segmentectomy for other reasons than cancer are allowed to be included in the study. 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.
	• Patients requiring long-term oxygen therapy for chronic hypoxemia. This is typically patients requiring oxygen therapy >12 h per day delivered by home oxygen cylinder or concentrator. *Note: Nocturnal oxygen therapy for transient oxygen desaturations during sleep is allowed.*
	• Patients with bronchiectasis who have had a pulmonary exacerbation with a deterioration in three or more of the following key symptoms for at least 48 h:
	  • cough;
	  • sputum volume and/or consistency;
	  • sputum purulence;
	  • breathlessness and/or exercise tolerance;
	  • fatigue and/or malaise;
	  • haemoptysis
	AND
	A clinician determines that a change in bronchiectasis treatment is required (e.g. requiring systemic glucocorticosteroid treatment and/or systemic or inhaled antibiotics) within 4 weeks prior to screening.

	In the event of an exacerbation occurring 4 weeks before screening, or between the screening and baseline (please see definition above), the patient must NOT be enrolled. The patient may be rescreened once, 4 weeks after the resolution of exacerbation.
	• Patients with bronchiectasis requiring therapy that may interfere with the assessment of QBW251 efficiency or that are unlikely to respond to QBW251 as follows:
	  • Patients with suspected active pulmonary tuberculosis or currently being treated for active pulmonary tuberculosis are not allowed. 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 baseline visit suggesting low probability of recurrent active tuberculosis
	  • Patients with active allergic bronchopulmonary aspergillosis and asthma as primary diagnosis.
	  • Patients with cystic fibrosis
	• Current or ex-smokers with severe emphysema.
	• Patients with another concomitant pulmonary disease according to the definition of the International ERS/ATS guidelines, including but not limited to interstitial pulmonary fibrosis (IPF), sarcoidosis or other granulomatous or infectious process. Concomitant COPD and asthma with characteristics of airway hyperresponsiveness as well as COPD-Asthma overlap syndrome are allowed as long as it is not the main, primary diagnosis in the opinion of the investigator. Primary ciliary dyskinesia (PCD) is allowed.
	• Patients currently receiving treatment for nontuberculous mycobacterial (NTM) pulmonary disease. If performed, patients with one or more positive cultures in the last 12 months for *M. avium complex, M. abscessus complex, M. kansasii, M. malmoense, M. xenopi, M. simiae* or *M. chelonae*, unless all subsequent NTM cultures (at least two) are negative and in the opinion of the investigator the patient does not meet ATS criteria for NTM-pulmonary disease.
	• Patients receiving any medication that may influence the response to treatment within 4 weeks prior to screening including systemic or inhaled steroids (ICS alone), or other systemic immunomodulators, recombinant human DNAse, any systemic or inhaled antibiotics.
	• Patients with a body mass index (BMI) of more than 40 kg/m^2

Study treatment	investigational and control drugs • QBW251 dose of 300 mg • Matching placebo
Efficacy assessments	• Microbiological assessment: Spontaneous sputum (if possible) will be collected for analysis of pathogenic bacterial colonization (CFU/mL) (e.g. *H influenzae, M catarrhalis, S aureus, S pneumoniae, Enterobacteriaceae, P aeruginosa, Stenotrophomonous Maltophilia*, or any potential pathogenic non-fermenting Gram negative bacteria). In addition, 16S rRNA PCR will be performed to measure the bacterial load. • Spirometry: FEV1, FVC • Plasma Fibrinogen

	• HRCT assessment on airway structure and function, mucus load • hsCRP
Pharmacokinetic assessments	• Cmax, Tmax, AUClast, AUC0-12h, T1/2, eff when feasible.
Key safety assessments	• Physical examinations • Vital signs • ECG • Safety laboratory • Adverse events, serious adverse events
Other assessments	• Bronchiectasis exacerbation • PROs: QOL-B, SGRQ, EQ-5D-3L, EXACT-PRO, eDiary • Sputum biomarkers: including but not limited to IL-6 and IL-8 • If feasible, sputum bacterial profile measured by 16s rRNA gene sequencing • Serum protein levels measured by SomaScan
Data Analysis	The primary endpoint will be analyzed using a Bayesian repeated measures model with change from baseline in CFU as response, adjusting for effect of treatment* visit interaction, status of macrolides use at screening as factor, and baseline CFU counts. In absence of informative data, non-informative priors for the model parameters will be used. The prior for placebo may be updated as a weakly informative prior and will be specified in the statistical analysis plan, should new relevant data become available before the database lock of this study. • A comparison of QBW251 vs. placebo at week 12 is of primary interest. Based on the fitted Bayesian model for repeated measures, the posterior probability of QBW251 effect over placebo for $\log_{10}$CFU will be calculated. Statistical evidence will be concluded if there is 90% probability that the true effect over placebo for $\log_{10}$CFU is >0.
Key words	• Bronchiectasis, QBW251, colony forming units

1 Introduction

1.1 Background

Bronchiectasis (BE) is defined as the irreversible dilatation of bronchi with destruction of elastic and muscular components of their walls. The gold standard method for diagnosis is via high resolution computerized tomography (HRCT) scan. Bronchiectasis is frequently idiopathic in origin, or may be a result of a number of post-infectious causes, congenital diseases (e.g., immunodeficiency, primary ciliary dyskinesia, cystic fibrosis), inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease) or anatomic obstruction, all of which predispose to a cycle of chronic infection and inflammation, and airways damage. While the cause of bronchiectasis is highly diverse, impaired mucociliary clearance is a shared mechanism across all phenotypes of the disease.

Bronchiectasis is often associated with bacterial infections that may be linked to higher morbidity and mortality. *Pseudomonas aeruginosa* infection in particular is associated with a 3 folds increased risk of death and a higher risk of hospitalization and exacerbation in bronchiectasis. The pathogens most frequently associated with bronchiectasis in addition to *P. aeruginosa* which accounts for 12-31% are: Haemophilus influenzae (30-47%), Streptococcus pneumoniae (7-11%), Staphylococcus aureus (4-7%), and Moraxella catarrhalis (2-20%) (O'Donnell 2008). Chronic infection with pathogenic microorganisms is associated with worse clinical outcomes including increased frequency of exacerbations (Chalmers et al 2014).

A high morbidity due to frequent exacerbations impair quality of life, facilitate resistance to antibiotics, and lead to reduced lung function in BE patients. Most frequent symptoms include cough, coughing up large amounts of thick mucus every day, hemoptysis, dyspnea, chest pain, fatigue, weight loss, frequent respiratory infections and exacerbations (~1.3 to 3 per patient per year). There is also a high socioeconomic impact through frequent use of primary and secondary healthcare with an economic burden estimated to be similar to COPD (Polverino et al 2017). It is estimated that there is an approximately 2-fold higher age-adjusted mortality compared to the general population (Quint et al 2016).

There is an increasing awareness of bronchiectasis and its impact on morbidity, mortality and health care costs. Bronchiectasis is likely underdiagnosed or misdiagnosed, the first international treatment guidelines were published in September 2017.

As Bronchiectasis is a progressive respiratory debilitating disease that evokes significant symptoms and poor quality of life for patients, there is a high unmet need for new therapeutic options beyond antibiotics and off-label use of bronchodilators.

The ERS 2017 guidelines for the management of adult bronchiectasis highlighted the lack of evidence for many treatments for bronchiectasis (Polverino et al 2017). Treatments to prevent exacerbations are also limited to antibiotics (inhaled or macrolides), airway clearance techniques and some mucoactive drugs such as isotonic or hypertonic saline for which there is limited evidence.

Chronic bronchitis, asthma and non-CF bronchiectasis (NCFBE) share many clinical and pathologic features with cystic fibrosis (CF), a lung disease potentially caused by gene mutations in the cystic fibrosis transmembrane conductance regulator (CFTR). CFTR, a cAMP regulated chloride channel is resident on the surface of epithelial cells in several body organs such as the airways, intestine, pancreas, bile ducts and kidney (Boucher 2007; O'Sullivan, Freedman 2009). Loss of CFTR function in the lung is associated with reduced mucociliary clearance (MCC), chronic bacterial infection and increased inflammation (Amaral, Kunzelmann 2007).

There is evidence that bronchiectasis may represent a spectrum of CFTR-related disorders as there are increased frequencies of CFTR mutations in patients in various studies (Bergougnoux et al 2015). In addition to the associations of CFTR mutant alleles in bronchiectasis, CFTR functional defects have been discovered in patients harboring no-CFTR mutant alleles using sweat chloride and nasal potential difference measurements (Bienvenu et al 2010). Thus, while the mechanisms of CFTR dysfunction in bronchiectasis and asthma are not well understood, there is evidence that certain subsets of patients demonstrate CFTR dysfunction. The association of CFTR dysfunction with complications of these diseases, however, is unknown (Solomon et al 2017).

The resulting mucus stasis is associated with excess mortality and a more rapid decline in pulmonary function (Hogg et al 2004; Fahy, Dickey 2010). While cystic fibrosis is caused by genetic dysfunction of CFTR, there is evidence that in bronchiectasis, COPD and other airways diseases, both genetic and acquired CFTR dysfunction in the airways are through mechanisms including chronic inflammation and cigarette smoking.

CFTR dysfunction may be a central disease mechanism and provides a potential joint therapeutic target. The discovery of CFTR potentiators, that can also potentiate even wild type of forms of CFTR, may therefore represent a new therapeutic strategy (Solomon et al 2017). The CFTR potentiator QBW251 represents a novel mechanism-of-action. QBW251 is a low molecular weight CFTR potentiator of both wild-type and mutated CFTR protein. The modulation of CFTR function may improve airway hydration, decrease mucus viscosity and thus enhance mucociliary clearance. CFTR also regulates airway surface liquid pH by bicarbonate secretion that is important in the fight against pathogens (Pezzulo et al 2012). Hence, CFTR potentiation may be effective in patients with bronchiectasis in reducing airway inflammation/infection and obstruction.

QBW251 is safe and well tolerated in healthy volunteers at doses up to 750 mg bid and in patients with CF at the 150 mg bid and 450 mg bid doses over 14 days. QBW251 demonstrated efficacy by promoting significant pharmacodynamic activity (decrease in sweat chloride and/or improvement in lung function) in heterozygous CF patients with a gating or residual function. Clinical data from patients homozygous for F508del mutation did not demonstrate clinical evidence of pharmacodynamic effect after treatment with QBW251.

In a 28-day randomized, placebo-controlled PoC study, QBW251 demonstrated in GOLD 2-3 COPD patients with chronic bronchitis and with various background inhaled therapies an improvement in lung function (FEV1) and sweat chloride over placebo. Furthermore, exploratory sputum analyses have suggested a trend for decreased bacterial colonization with QBW251. In addition, there was a significant reduction of fibrinogen,

a systemic inflammation marker, which is considered to be a prognostic biomarker for patients at increased risk for all-cause mortality or COPD exacerbation and approved as such by FDA (Mannino et al 2015).

This PoC in BE is proposed given similar pathophysiology to CF and COPD based on dysfunctional mucociliary clearance. CFTR potentiation may improve airway hydration, enhance mucociliary clearance, and reduce airway bacterial colonization in patients with BE; additionally, it may improve lung function in those patients with an obstructive ventilation defect. These benefits are thought to translate into a reduction of exacerbations and improvement of symptoms in BE patients with persistent mucus-related symptoms.

The study has been developed and will be executed as part of the iABC (inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis) project. iABC, as an IMI (Innovative Medicines Initiative) project, is a collaboration between EFPIA partners (including Novartis) and academic partners, with the managing entity being Queen's University Belfast. Novartis retains the role of the sponsor and as such is responsible for the regulatory and pharmacovigilance activities, and the conduct of this clinical trial.

1.2 Purpose

The purpose of this study is to determine whether potentiating the cystic fibrosis transmembrane conductance regulator (CFTR) with QBW251 in subjects with bronchiectasis will demonstrate clinical safety and efficacy related to improved mucociliary clearance with reduced bacterial colonization as potential drivers of airway obstruction, reduced airway inflammation, exacerbations and mucus load, improved lung function, clinical symptoms and quality of life to support further development in bronchiectasis.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the change on sputum bacterial colonization	• Change from baseline in bacterial load of colony forming units (CFU/mL, 1 CFU/mL = 1 CFU/g) of potentially pathogenic microorganisms in spontaneous sputum with QBW251 compared to placebo at week 12
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the change of QBW251 compared to placebo on sputum bacterial clearance	• Proportion of subjects with absence of any CFU of potentially pathogenic bacteria in sputum culture after 12 weeks of treatment

Objective(s)	Endpoint(s)
• To assess the change on patient reported outcomes on bronchiectasis symptom assessment	• Changes from baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B) (Respiratory symptoms domain) after 12 weeks of treatment.
• To assess the change of fibrinogen plasma concentration	• Change from baseline in fibrinogen plasma concentration after 12 weeks of treatment
• To assess the change in rescue medication use	• Change from baseline in rescue medication use (salbutamol/albuterol) after 12 weeks of treatment.
• To assess the change on lung function.	• Changes from baseline in pre-bronchodilator FEV1, FVC after 12 weeks treatment, measured by spirometry
• To assess the change in airway structure and function	• Change from baseline in airway wall and lumen parameters along with extent of global and regional air trapping after 12 weeks of treatment, as measured by HRCT.
• To assess the pharmacokinetics of QBW251 in patients with bronchiectasis	• Assessment of drug exposure (Cmax, AUC) and other PK parameters when feasible on Days 1 and 28 (for a subset of patients at selected sites). Pre- and post- dose concentration (Ctrough and around Cmax) on Days 1, 28, 56 and 84 (for all patients).
• To assess the safety and tolerability of QBW251 in patients with bronchiectasis	• All safety endpoints (including adverse events, vital signs, ECG, and safety laboratory changes) during the study
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To examine the change from baseline on sputum bacterial colonization after 12 weeks of treatment with QBW251 compared to placebo and at times of potential exacerbation for assessments of pathogens and bacterial load.	• Change from baseline in sputum bacterial colonization after 12 weeks of treatment measured by 16S rRNA PCR

Objective(s)	Endpoint(s)

• To assess the change on patient reported outcome	• Changes from baseline in the following PRO after 12 weeks of treatment
	  • St. George's Respiratory Questionnaire (SGRQ)
	  • Euro Quality of Life-5 Dimensions-3 level (EQ-5D-3L)

• To explore the effect of QBW251 on additional HRCT outcome measures	• Change from baseline in HRCT endpoints for distribution of mucus (whole lung and regional) after 12 weeks of treatment • IMI collaboration: HRCT scores and change from baseline in airway-artery ratios
• To assess the effect of QBW251 on bronchiectasis exacerbation	• Time to first event, • Annualized rate of exacerbations as defined by EXACT-PRO questionnaire

• To assess the change on biomarkers of inflammation	• Changes from baseline in blood and sputum after 12 weeks of treatment in markers that may include, but are not limited to:
	  • Serum hsCRP
	  • Blood inflammatory cells e.g. neutrophils, eosinophils
	  • Sputum inflammatory proteins e.g. IL-6, IL-8
	  • Serum protein levels measured by SomaScan

• To perform assessment of bacterial species profile in sputum	• Sputum samples will be biobanked for potential exploration of sputum bacterial profile measured by 16s rRNA gene sequencing
• To perform DNA assessments to examine whether individual genetic variation in genes relating to drug metabolism and transportation or individual genetic variations in CFTR genes or other disease-relevant genetic pathways confer differential response to QBW251 treatment or correlate with disease severity	• Genomic analysis in correlation with exposure to QBW251 or response to QBW251 or disease severity. DNA will be biobanked for potential future analysis of CFTR mutations and for genomic analysis

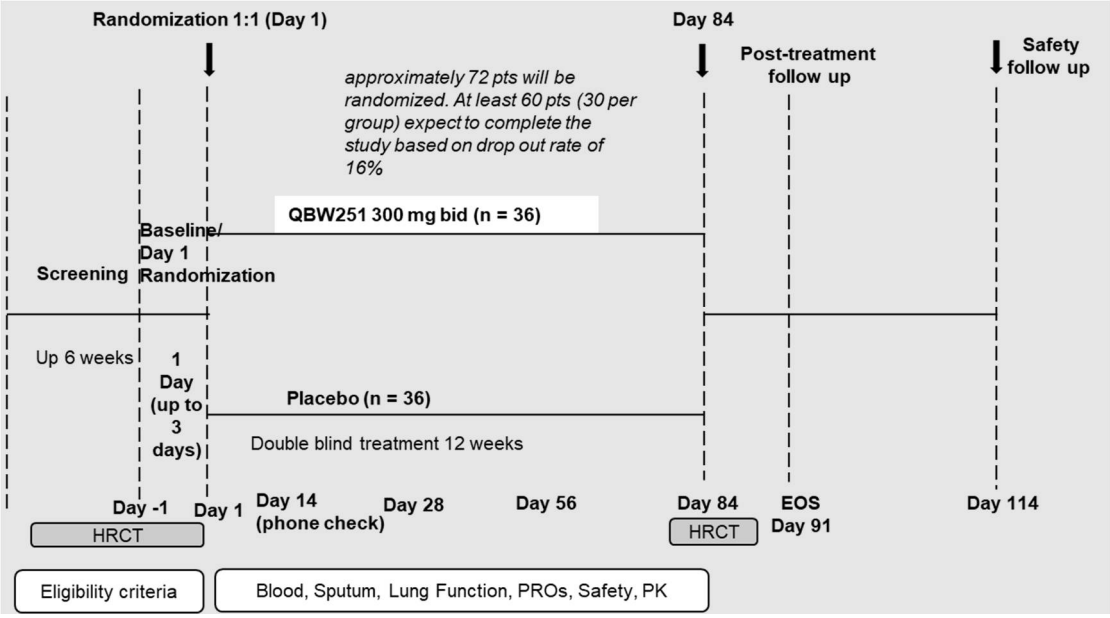
3 Study design

This is a randomized, subject- and investigator-blinded, placebo-controlled, parallel-group study investigating the preliminary efficacy and safety of QBW251 administered orally for 12 weeks in subjects with bronchiectasis. Approximately 72 subjects will be randomized in a 1:1 ratio to receive either QBW251 or placebo in order to achieve 60 subjects who complete the treatment period based on the assumption of a 16% drop-out rate. The sample size assumptions will be reviewed in an interim analysis in a blinded manner when approximately 14 subjects complete the treatment period.

The study consists of the following periods: Screening, baseline/Day 1, treatment period, and end of study assessments (EOS) visit followed by an additional post-treatment safety follow up via phone call. The total duration for each patient in the study is up to approximately 19 weeks.

The study design is described in Figure 3-1 below.

Figure 3-1 Study Flowchart



3.1 Study visits

The study employs the following visits:

Screening visit (Day -42 to Day -1):

Screening assessments can be performed over a 6-week period maximum (up to 42 days).

Informed consent must be obtained prior to implementing any study specific procedure. Inclusion and exclusion criteria will be checked to confirm patient's eligibility.

This check includes medical history, maintenance therapy of LABA/ICS or LABA/LAMA or LABA/LAMA/ICS and/ or macrolides, physical examination, ECG, vital signs, oxygen saturation, and clinical laboratory evaluations (hematology, blood chemistry, coagulation, urinalysis). Sputum will be collected once within the screening window to confirm bacterial

load with at least one strain of potentially pathogenic bacteria (refer to Section 5.1). The sputum microbiology results at screening will need to be available prior to randomization. Retesting is allowed once.

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

A HRCT assessment will be performed during screening period except at selected sites where HRCT is optional with Sponsor approval. The screening HRCT can also be used to confirm the diagnosis of BE if no historical HRCT is available. At selected sites, where HRCT is optional, diagnosis of BE must be available from a historical scan.

Baseline/Randomization Day 1:

Subjects who meet the eligibility criteria will be admitted to baseline/Day1 safety and efficacy evaluations before randomization.

During baseline, sputum samples will be collected at the same time of the day (sputum collection procedure and timing will be detailed in the SOM and laboratory manual) for biomarker assessments (bacterial load and colonization as well as inflammatory markers). Subjects will be also asked to complete various scales and questionnaires (refer to the Assessment Schedule for the type of questionnaires and time points).

There is no antibiotic intervention or change of mucous clearance regimen allowed for pulmonary exacerbation between screening and baseline except for the use of macrolides for subjects who are on this medication before enrolment. In this case, macrolides are to be continued at the same dose and regimen during the study. Baseline mucous regimen should remain unchanged between screening and baseline.

Once all baseline assessments have been completed and subjects are again confirmed as being eligible for the study, they can be randomized on the same day (baseline/randomization Day 1). In the case that sputum sample cannot be collected or other assessments can't be completed at baseline visit for various reasons, the site must not randomize the subject on the same day. An unscheduled visit needs to be planned for sputum collection prior to randomization and treatment allocation. Once sputum is collected and required assessments are completed, the subject can be randomized on the same day of the unscheduled visit.

Treatment Period (Day 1 to Day 84):

The treatment period will be 84 days (Day 1 to Day 84), with dosing occurring on Days 1 through 84, and will include a Day 1 Visit, a Day 14 visit (via telephone check), a Day 28 Visit, a Day 56 Visit, and a Day 84 Visit.

On Day 1, after completion of all pre-dose assessments (including the Concomitant medication therapy as per Table 6-2 and Table 6-6) , eligible subjects will be randomized in a 1:1 ratio to receive QBW251 300 mg b.i.d. or matching placebo for 84 consecutive days.

At randomization, stratification will be done according to the status of macrolides use and geographic region (sites from China/sites outside China) in order to balance patient distribution

in treatment and placebo group. The first study medication for this treatment period should be administered in the clinic in the morning of Day 1, following the pre-dose pharmacokinetic blood sample collection as indicated in the Assessment Schedule (NOTE: all PK sampling times are relative to the first dose of the treatment day).

During treatment period, subjects will return to the site for scheduled visits for biomarker blood/sputum sample collections, PK, safety and efficacy assessments including completion of the questionnaires. On visit days, subjects will take their morning dose in the clinic after completion of pre-dose assessments.

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

At Day 14, site will call the subject to evaluate the compliance and to check patient well-being.

Pharmacokinetic blood sampling (pre-dose and 3hr post dose) will be done at Day 1, Day 28, Day 56 and Day 84 visits. Additionally, although serial PK sampling is optional, efforts will be made to have a subset of approximately 30-40 subjects undergo serial PK sampling at pre- and up to 8 hours post-dose on Day 1 and Day 28.

As the completed thorough QT study (CQBW251A2105) indicated that QBW251 at 300 mg b.i.d. did not have clinically relevant effects on studied ECG parameters, single ECGs pre- and post-dose at Tmax will be performed at visits on Day 1, Day 28, Day 56 and Day 84 (end of treatment). These assessments will be complemented by PK sampling (trough and Cmax) on the matching timepoints, at visits on Day 1, Day 28, Day 56 and Day 84.

The morning dose on Day 84 will be the final dose administration for this treatment period. End of treatment assessment, e.g. safety assessment, lung function assessments and PROs will be performed on Day 84.

If spontaneous sputum collection is not possible at Day 84, site needs to reschedule the visit within 3 days after Day 84 and subject must continue to take study medication. If spontaneous sputum collection attempts are still not satisfactory, investigator may take decision to collect sputum sample after induction by the inhalation of saline. Other assessments that have been completed on Day 84 do not need to be repeated.

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

In case of symptom deterioration (via e-diary alert), subjects must visit their study center to determine whether exacerbation criteria have been met and an immediate antibiotic treatment may be necessary. In addition, other markers of inflammation such as fibrinogen in blood will be taken to gain more information on systemic inflammation and sputum sample collection to determine if there are changes in pathogen or bacterial load that may have resulted in the exacerbation. Subjects experiencing an exacerbation during the treatment

period will continue with the study treatment along with the standard of care (SOC) therapy for an exacerbation (i.e. antibiotics).

End of Study (EoS) visit (Day 91):

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

Safety follow-up call (Day 114)

A follow-up phone call for safety will occur 30 days after the last dose administration. The safety follow-up includes adverse events safety monitoring.

For a complete list of assessments, refer to the Assessment Schedule in Table 8-1.

4 Rationale

4.1 Rationale for study design

This is a non-confirmatory, multi-center, randomized, placebo-controlled, subject- and investigator-blinded, parallel-group trial with a 12-week treatment period. Key efficacy endpoints will be evaluated over the time during the study period.

The design of this study addresses the primary objective to assess the effect of QBW251 compared to placebo administered for 84 days on sputum bacterial colonization. A reduction from baseline in colony forming units of potentially pathogenic microorganisms in spontaneous sputum by one log unit was associated with a significant reduction in risk of exacerbation by approximately 20% in patients with bronchiectasis, which is considered to be clinically relevant (Chalmers et al 2012).

In order to optimize the rigor and integrity of the study and minimize bias, a randomized, subject- and investigator-blinded parallel group is used. The design is well-established in respiratory clinical trials and enables the study treatment to be given for an appropriate and practical length of time to assess the efficacy and safety of the treatment. A parallel study design was chosen because a crossover design assumes patients will return to their own baseline levels of CFU in each period and this may not be the case in the study. It is more versatile in that a stable disease state is not a pre-requisite which is beneficial as also newly diagnosed patients with bronchiectasis may be included.

QBW251, an effective Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) potentiator, is hypothesized to be efficacious in patients with bronchiectasis based on improved mucociliary clearance (MCC), resulting in decreased bacterial colonization, decreased small airway inflammation, improved FEV1 and ultimately fewer exacerbations. Recent evidence suggests the molecular mechanism for reduced mucociliary clearance in bronchiectasis may relate to dysfunction of wild-type and mutated CFTR. Bronchiectasis patients may also have a component of ion channel dysfunction, including CFTR. COPD data suggests that QBW251 may decrease bacterial colonization and small airway inflammation (reduced fibrinogen). In addition, QBW251 demonstrated statistically important improvement in lung function

(FEV1) in cystic fibrosis (CF) following 2 weeks of treatment and in COPD following 4 weeks of treatment.

Therefore, in addition to the primary endpoint, several complementary endpoints will be used in this study to assess efficacy, including spirometry and patient reported outcomes (PROs) as well as pharmacokinetic parameters. These evaluations provide a comprehensive view of airway structure and function as well as an assessment of patients' well-being in addition to the safety and tolerability evaluation.

The study will also include the measurement of soluble biomarkers to provide additional information relevant to the endpoints.

4.1.1 Rationale for choice of background therapy

Not Applicable

4.2 Rationale for dose/regimen and duration of treatment

The selection of QBW251 300 mg b.i.d. oral dose as the relevant clinical dose in this study is based on the data previously collected in the QBW251 program.

Clinical activity was observed in CF and COPD patients in studies CQBW251X2101 (150 and 450 mg b.i.d.) and CQBW251X2201 (300 mg b.i.d. for 4 weeks), respectively. The COPD PoC study (CQBW251X2201) provided evidence of efficacy (FEV1 improvement) with a 300 mg b.i.d. regimen. Safety results from the COPD PoC study also demonstrated that 300 mg b.i.d. of QBW251 over 4 weeks was safe and well tolerated in COPD patients.

At completion of the dose range finding (DRF) study in COPD (CQBW251B2201) 300 mg b.i.d. was the highest dose administered to patients. Initially, five dose levels (25, 75, 150, 300, and 450 mg b.i.d.) were being tested in the DRF study. Following the DMC meeting in April 2020, the 450 mg b.i.d. dose was discontinued based on the statistical stopping rule pre-specified in the protocols. There were no safety findings in any of the treatment arms that contributed to this decision. Accordingly, Novartis has made the decision to use the 300 mg b.i.d. dose as the highest dose in the QBW251 program.

An independent DMC was established with the primary goal of performing periodic reviews of the accumulating PK and safety data from the DRF study in COPD (CQBW251B2201), Mode of Action study in COPD (CQBW251B2202) and bronchiectasis study (QBW251C12201) at pre-specified time intervals. Study data coming from these three studies was submitted to the DMC for consideration as to whether a proportion of patients have exceeded the NOAEL threshold (AUC0-24h=91,700 ng*h/ml) or more than one patient has exhibited a projected AUC0-24h above the upper range of the individual monkey exposures (AUC0-24h=159,000 ng×h/mL).

In May 2022, the DMC reviewed the data available from all clinical studies of QBW251 and concluded the following:

1. There were no substantial differences in the adverse event profiles of patients with exposure exceeding the previously specified NOAEL threshold values and those who did not. However, the comparison groups were of very different size and mean exposure data

for the 300 mg and 450 mg b.i.d. doses were not available. No AEs or SAEs occurred in the patients who exceeded the pre-specified threshold values.

2. There was a trend for elevations of the gamma glutamyl transpeptidase to occur more often in patients with higher plasma levels of QBW251 but the interpretation of these findings was limited by the small numbers of patients in each subgroup.
3. It was reasonable to dispense with PK monitoring in the ongoing studies and future phase 3 trials of the 300 mg b.i.d. dose as this would not provide more insight into the acceptability of treatment.

Accordingly, Novartis decided to stop further PK threshold monitoring in the present study, though planned PK measurements will continue. The selection of 300 mg b.i.d. as the maximum clinical dose is supported by both the animal chronic toxicology and the clinical study data currently available. The NOAEL dose in the 26-week rat and 39-week monkey chronic toxicology studies was 30 mg/kg/day and 150 mg/kg/day, respectively. Mean systemic exposure (AUC0-24h) at the NOAEL dose was 163,500 ng*h/mL for the rat at Week 26. For the monkey, the mean exposure (AUC0-24h) at the NOAEL dose (150 mg/kg/day) at Week 39 was 91,700 (range from 52,000 to 159,000) ng*h/mL. Based on the population PK modeling from COPD DRF study (CQBW251B2201), the mean steady-state daily exposure (AUC0-24h) of QBW251 following 300 mg b.i.d. dose in the COPD patients was 16,460 ng*h/mL, approximately 5-fold lower than the mean preclinical exposure threshold of 91,700 ng*h/mL.

The twice-daily dosing regimen was chosen based on the half-life of QBW251 (10-16 hours) and the intent to have a sustained effect on the ion channel. Additionally, a twice daily regimen is expected to provide a reduced Cmax/Ctrough fluctuation compared to once daily dosing. In comparison with a single dosing regimen designed to achieve the same trough concentrations, the proposed twice daily regimen is expected to yield higher average concentrations during the dosing interval. A twice daily regimen was therefore selected to maximize the opportunity of observing efficacy of QBW251 in bronchiectasis patients.

A study duration of 12 weeks is expected to provide clinically significant changes in mucociliary clearance allowing the assessment of safety and tolerability. Moreover, an adequate study duration of at least 3 months is especially important for patient reported outcomes such as quality of life to obtain significant treatment effects.

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

There is currently no approved CTFR potentiator for treatment of bronchiectasis that could serve as a comparator. Therefore, QBW251 is tested against placebo, 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

A blinded interim analysis is planned for this study when approximately 14 patients have completed Day 84 post treatment assessment. The purpose of this IA is to confirm sample size assumptions while assessing the variability in bacterial colonization of PPMs in this population.

One or more interim analyses for efficacy and safety may be conducted to support decision making in relation to the current clinical study, or the future of the sponsor's clinical development plan or in case of any exposure threshold criteria exceeded or safety concerns from this study or ongoing clinical studies.

4.5 Risks and benefits

Risks

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

Potential risks of QBW251

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

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

Risks associated with maintenance treatment (double or triple inhaled therapy) or macrolides

Adverse events associated with maintenance inhaled therapy include:

- Nasopharyngitis, hypertension, back pain and oropharyngeal pain, dyspepsia, gastroenteritis, chest pain, fatigue, peripheral edema, rash/pruritus, insomnia, dizziness, bladder obstruction/urinary retention, atrial fibrillation, palpitations, tachycardia, upper and lower respiratory tract infection, pneumonia, diarrhea, headache, gastroesophageal reflux disease, hyperglycemia, rhinitis, dysgeusia, cough, arthralgia, oral candidiasis (approved labels for Trelegy Ellipta, Breo Ellipta (EU name Relvar Ellipta), Incruse Ellipta and Utibron Neohaler US label)
- 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).
- The following additional adverse reaction of angioedema has been identified during worldwide post-approval use of indacaterol/glycopyrrolate at higher than the recommended dose (Utibron Neohaler US label)

Adverse events associated with macrolides include:

- The most common adverse effects associated with macrolide antibiotics (e.g. erythromycin products) are gastrointestinal. They include nausea, vomiting, abdominal pain, diarrhea and anorexia.
- Reversible hearing loss associated with doses of erythromycin usually greater than 4g per day has been reported.
- Treatment with macrolides may also result in cardiac arrhythmias such as QT prolongation

Other risks related to study procedures:

Procedural risks may include:

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

Risk mitigations:

Based on the above risk considerations, clinical monitoring will include the use of an electronic diary with the EXACT-PRO questionnaire to enable daily symptoms assessment, as well as safety assessments during visit days at the investigational site. These safety assessments include a careful assessment of adverse events, ECGs, hematologic and blood biochemistry laboratory assessments, urinalysis and vital signs measurements.

As the completed thorough QT study (CQBW251A2105) indicated that QBW251 at 300 mg b.i.d. did not have clinically relevant effects on studied ECG parameters, ECGs pre- and post-dose (at Tmax) will be performed at Day 1 and Day 28 (when steady state exposure is achieved), and at Day 56 and Day 84 (end of treatment). These assessments will be complemented by the corresponding PK sampling (Ctrough and Cmax).

In addition to the sampling described above, additional PK samples are requested to be taken in case of treatment-emergent serious adverse events.

Finally, although serial PK sampling is optional, efforts will be made to have a sub-group of approximately 30 - 40 patients undergo serial PK assessments to further characterize the PK profile of QBW251 in BE patients, which will provide important understanding of the 300 mg b.i.d. dose in BE patients. Women of childbearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study. In order to participate in the study, participants must agree to adhere to the contraception requirements outlined in the exclusion criteria throughout the study and for at least one week following the last administration of investigational medicinal product. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study. Based on the reproductive toxicity studies results, women of childbearing

potential are allowed to enter the study as long as they are using the effective method of contraception (see specific guidance in Section 5.2 Exclusion Criteria). This group of patients is relevant for the targeted disease and their inclusion is aligned with the ICHM3 (R2) guidance. In a hormonal contraception study (CQBW251X2102), it was demonstrated that QBW251 may enhance cytochrome P450 mediated degradation of contraceptive hormones; thus, hormonal contraception methods are not acceptable methods of contraception in the study. Based on clinical DDI study CQBW251A2107, at maximal QBW251 plasma concentrations achieved following oral administration of doses ≤ 300 mg b.i.d., QBW251 moderately inhibits the metabolic clearance of co-medications metabolized by CYP1A2 and CYP2C19. In addition, QBW251 was also found to weakly induce both CYP3A4 and CYP2C8. Based on *in vitro* data, QBW251 and its metabolites may also increase the exposure of drugs which are substrates for CYP2B6, BCRP, OCT1, OAT3 and MRP2.

Reflecting the current characterization of QBW251 potential for clinical drug-drug interactions, the protocol uses cautionary language for drugs that may potentially interact with QBW251, such drugs are sensitive substrates of CYP1A2, CYP2B6, CYP2C19, CYP3A4, CYP2C8, OAT3, BCRP, OCT1 and MRP2. These drugs are not prohibited but their substitution with alternative agents is advised; when not possible, closer monitoring is recommended. Additionally, use of co-medication which are sensitive substrates of CYP1A2 or CYP2C19 and have narrow therapeutic range are 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. As UGT mediated glucuronidation is likely a significant elimination pathway, use of certain UGT inhibitors and potential inducers is prohibited (see Table 6-5).

QBW251 may also impact the systemic exposure of the individual components of maintenance therapy.

However, efficacy of the inhaled therapies (such as LABA/LAMA, LABA/ICS, LABA/LAMA/ICS) is not expected to be impacted due to the delivery directly to the lungs. In addition to the inhaled therapies, as a perpetrator, QBW251 is not expected to have significant impact on the PK exposure of the macrolides (such as erythromycin and clarithromycin) as they are not sensitive substrates of metabolite enzymes of CYP1A2, 3A4, 2B6, 2C8, 2C19 or UGTs.

Please refer to the respective labels of the maintenance therapy for additional information on drug interactions. Any concomitant medications should be noted in the CRF. When additional clinical drug interaction information becomes available during the QBW251 development, this information will be further updated and reflected in the QBW251 Investigator Brochure.

No SARs are considered expected by the sponsor for the purpose of expedited reporting of suspected unexpected serious adverse reactions (SUSARs). Refer to the Investigator's Brochure for further details.

Benefits

A transient benefit may be observed if QBW251 provides efficacy. A positive outcome from this study may lead to further development of QBW251 for eligible patients with bronchiectasis.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected from each subject during Screening, Baseline, during the 12 weeks of the treatment period and at the end of the study.

For the subset of patients who will undergo serial PK sampling at pre- and up to 8 hours post-dose on Day 1 and Day 28, the additional blood samples will be collected.

Additional samples may be required for safety monitoring.

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

A summary blood log is provided in the SOM. Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and central laboratory manual.

See the Section 8.5.3.3 on the potential use of residual samples.

5 Population

The study population will consist of approximately 72 male and female patients with bronchiectasis.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female patients aged ≥18 years at screening.
3. Proven diagnosis of bronchiectasis by chest CT at screening as determined by the investigator. The screening HRCT can be used to confirm the diagnosis if no historical chest CT is available.
4. Evidence of sputum bacterial load of $\geq 10^6$ CFU/mL with at least one potentially pathogenic microorganism at screening *(H. Influenzae, M catarrhalis, S aureus, S pneumoniae, Enterobacteriaceae, P aeruginosa, Stenotrophomonous maltophilia*, or any potential pathogenic non-fermenting Gram-negative bacteria measured by dilution/outgrowth.) NOTE: *H. parainfluenzae* is not considered pathogenic in this study and therefore growth of this organism alone does not satisfy this criterion.
5. Documented history of at least one bronchiectasis exacerbation between January 2019 to study screening.
6. Patients with bronchial hypersecretion, defined as productive cough that occurs on most days (defined as >50% days) for at least three consecutive months within 12 months prior to screening, as assessed by documentation of patient recollection (anamnesis) or documented in patients' record.
7. Patients are allowed to stay on fixed or free combinations of LABA/LAMA or LABA/ICS or LABA/LAMA/ICS as maintenance therapy if they are treated with them at a stable dose for the last 3 months prior to screening. Patients are also allowed to stay on macrolides as maintenance therapy if they are treated with them at a stable dose 3 months before screening. Patients will be allowed to use mucolytics or hyperosmolar agents if they were treated with them before study start.

If prescribed, patients are included in the study with unchanged chest physiotherapy for at least 4 weeks prior to screening.

8. Clinically stable pulmonary status in the opinion of the investigator and unlikely to require any change in the standard regimen of care during the course of the study.
9. Able to perform reliable, reproducible pulmonary function test maneuvers per American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines at screening. At screening, patients who have failed to meet ATS/ERS requirements for acceptability and reproducibility for spirometry will be allowed one additional repeat testing session during the screening period.
10. Able to communicate well with the investigator, to understand and comply with the requirements of the study. Patients should be able to understand and sign the written informed consent.

5.2 Exclusion criteria

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

1. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations. Current or planned participation in another clinical trial during this study.
2. History of hypersensitivity to the study drugs or to drugs of similar chemical classes or excipients.
3. Patients with a history of long-QT syndrome or the QTcF interval at screening or baseline is prolonged (QTcF >450 ms in males, >460 ms in females).
4. Patients who have a clinically significant ECG abnormality before randomization, as determined by the investigator.

   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).
5. Patients with a history or current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure. A history of resolved Hepatitis A is not exclusionary. Patients with prothrombin time international normalized ratio (PT/INR) of more than 1.5xULN at screening. Patients excluded for the PT/INR of more than 1.5xULN can be re-screened when the values have returned to normal.
6. History of lung transplant or malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin. Patients with segmentectomy for other reasons than cancer are allowed to be included in the study. 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.
7. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory blood test.

8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using acceptable effective methods of contraception during study participation. Acceptable effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six 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.

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

   Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.
9. Use of prescription drugs prohibited as stated in the Section 6.2.2 within 1 week prior to Day 1.
10. Clinically significant laboratory values abnormalities (including GGT, AST, ALT, total bilirubin or creatinine) in the opinion of the investigator at screening. For additional guidance on hepatic parameters refer to exclusion criterion #5.
11. Patients requiring long-term oxygen therapy for chronic hypoxemia. This is typically patients requiring oxygen therapy >12 h per day delivered by home oxygen cylinder or concentrator. **Note: Nocturnal oxygen therapy for transient oxygen desaturations during sleep is allowed**.

12. Patients with bronchiectasis who have had a pulmonary exacerbation with a deterioration in three or more of the following key symptoms for at least 48 h:
    - cough;
    - sputum volume and/or consistency;
    - sputum purulence;
    - breathlessness and/or exercise tolerance;
    - fatigue and/or malaise;
    - haemoptysis

    AND

    A clinician determines that a change in bronchiectasis treatment is required (e.g. requiring systemic glucocorticosteroid treatment and/or systemic, inhaled antibiotics or change in mucous clearance regimen) within 4 weeks prior to screening.

    In the event of an exacerbation occurring 4 weeks before screening, or between the screening and baseline (please see definition above), the patient must NOT be enrolled. The patient may be rescreened once, 4 weeks after the resolution of exacerbation.
13. Hemoptysis, requiring medical intervention at any time within 4 weeks prior to screening.
14. Bronchiectasis predominantly characterized by isolated cavitary lung lesions.
15. Patients with bronchiectasis requiring therapy that may interfere with the assessment of QBW251 efficiency or that are unlikely to respond to QBW251 as follows:
    - Patients with suspected active pulmonary tuberculosis or currently being treated for active pulmonary tuberculosis are not allowed. 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 baseline visit suggesting low probability of recurrent active tuberculosis
    - Patients with active allergic bronchopulmonary aspergillosis and/or asthma as primary diagnosis
    - Patients with cystic fibrosis
16. Current or ex-smokers with severe emphysema as determined by the investigator.

    Bidi or other similar non-filtered cigarette may be considered applicable to smoking history. They should be counted in the same way as standard cigarettes.
    Occasional smoking of cigars, pipes, e-cigarettes, or inhaled nicotine products are not relevant to smoking history (Dinakar, O'Connor 2016).

    Note: An ex-smoker may be defined as a subject who has not smoked for ≥ 6 months at screening or at the time of assessment.
17. Patients with another concomitant pulmonary disease according to the definition of the International ERS/ATS guidelines, including but not limited to interstitial pulmonary fibrosis (IPF), sarcoidosis or other granulomatous or infectious process. Concomitant COPD and asthma with characteristics of airway hyperresponsiveness as well as COPD-Asthma overlap syndrome are allowed as long as it is not the main, primary diagnosis as

determined by the investigator. Patients with a diagnosis of primary ciliary dyskinesia (PCD) **may** be allowed to participate with approval of the Sponsor.

18. Patients currently receiving treatment for nontuberculous mycobacterial (NTM) pulmonary disease. If performed, patients with one or more positive cultures in the last 12 months for *M. avium complex, M. abscessus complex, M. kansasii, M. malmoense, M. enopi, M. simiae or M. chelonae*, unless all subsequent NTM cultures (at least two) are negative and in the opinion of the investigator the patient does not meet ATS criteria for NTM-pulmonary disease.
19. Patients with a known history of non-compliance to medication or who are unable or unwilling to complete an electronic patient diary or patient reported outcome questionnaire.
20. Recent (within three years of screening) or recurrent history of clinically significant autonomic dysfunction (e.g., recurrent episodes of fainting, palpitations, etc...) as determined by the investigator.
21. Patients with a major vascular surgery in the 6 months prior to the screening visit.
22. Patients who have clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction), neurological, endocrine, immunological, psychiatric, gastrointestinal, or hematological abnormalities, which could interfere with the assessment of the efficacy and safety of the study treatment, or patients with uncontrolled Type 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.
23. Known or suspected history of ongoing, chronic or recurrent infectious disease of HIV, Hepatitis B/C.
24. Patients receiving any medication that may influence the response to treatment within 4 weeks prior to Day 1 including systemic or inhaled steroids (ICS alone), other systemic immunomodulators, recombinant human DNAse, any systemic or inhaled antibiotics other than chronic macrolides.
25. Patients with a body mass index (BMI) of more than 40 kg/m^2 at screening.

6 Treatment

6.1 Study treatment

The study treatment includes:

- Investigational drug QBW251 dose of 300 mg
- Matching placebo

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

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

6.1.1 Investigational and control drugs

Table 6-1 presents the details of the investigational drug and its control.

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 300mg b.i.d.	Capsule[1]	Oral use	Double-blind supply; bottles	Novartis Pharma AG (global)
QBW251 placebo b.i.d.	Capsule	Oral use	Double Blind supply; bottles	Novartis Pharma AG (global)

All capsules are of identical appearance to ensure blinding
[1] QBW251 is a film coated tablet over-encapsulated as final pharmaceutical dosage form to maintain double-blind

6.1.2 Additional study treatments

Rescue medication

Rescue medication for pulmonary exacerbations (including systemic antibiotics) are allowed.

All subjects will also be provided with a short-acting beta2 agonist, (salbutamol 100 µg/puff or albuterol 90 µg/puff or equivalent dose). Patients will be instructed to use it throughout the study on an "as needed" basis. (No other rescue medication is permitted during the study). Rescue medication will be sourced locally (see Section 6.2.3 for rescue medication further information).

Sites will be instructed to record the short-acting beta agonist rescue medications dispensation in the eDiary. Use of rescue medications must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.1.3 Treatment arms/group

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

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

6.2 Other treatment(s)

6.2.1 Concomitant therapy

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

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. 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 and an overview regarding actions to be taken for antibiotics.

Table 6-2 Medications permitted under certain conditions

Rationale/Group	Medication	Prohibition Period	Action Taken
Maintenance therapy	Free or fixed combination of LABA/LAMA, LABA/ ICS or LABA/LAMA/ICS	Washout period before spirometry assessments: 12 hours for twice-daily and 24h for once-daily	Reschedule spirometry assessment accordingly. Trough spirometry should be done after the washout period is complete. Otherwise, postpone visit to the next day where washout criteria can be fulfilled.
Rescue medication only	Short-Acting Beta-2 Agonists (SABA)	Hold treatment at least 6 hours prior to each Spirometry measurement	If possible, postpone spirometry measurement on the same day until the washout criterion is fulfilled. Trough spirometry should not be done within 6 hours after last rescue medication intake
Antibiotics for treatment of exacerbations and macrolides as maintenance medication	Antibiotics, e.g. amoxicillin; Macrolides, e.g. erythromycin	Systemic and/or inhaled antibiotics are allowed for treatment of acute infections, or are allowed for the treatment of acute exacerbations (but not as permanent prophylactic treatment, with the exception of macrolides at stable doses as maintenance therapy per inclusion #7). Topical treatment (e.g. use of intraocular, intraconjunctival antibiotic treatments, topical use of creams, etc.) is permitted.	No action required

Patients are allowed to have macrolides at stable doses as maintenance therapy throughout the study.

If a patient experiences a pulmonary exacerbation and/or worsening of the disease condition, he/she will be treated as deemed appropriate by the investigator. Antibiotics (systemic or inhaled) are allowed for the treatment of pulmonary exacerbations as dictated by the patient's condition.

QBW251 moderately inhibits the metabolic clearance of co-medications mainly metabolized by CYP1A2 or CYP2C19. Thus, drugs that are sensitive substrates of CYP1A2 or CYP2C19 are expected to have an increased exposure upon co-administration of 300 mg b.i.d QBW251. In addition, QBW251 was observed to weakly induce both CYP3A4 and CYP2C8 based on results from a clinical drug interaction study. QBW251 is a time-dependent inhibitor and inducer of CYP3A4/5. The net effect of QBW251 on CYP3A4/5 is anticipated to be induction based on results of a perpetrator drug-drug interaction study of QBW251 (450 mg b.i.d.) with an oral contraceptive that resulted in a decrease in exposure of the substrate.

Weak *in vitro* inhibition of CYP2B6, BCRP, OCT1, OAT3 and MRP2 was also observed. QBW251 may increase the exposure of drugs which are substrates of the transporters or enzymes.

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

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

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

Medications that may have decreased exposure due to co-administration with QBW251	
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.
Narrow therapeutic index substrates of CYP2C8	dabrafenib, erlotinib, paclitaxel
Sensitive substrates of CYP2C8	daprodustat, dasabuvir, paclitaxel, repaglinide

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
Sensitive Substrates of CYP2B6	bupropion, efavirenz, nevirapine, sibutramine
Sensitive Substrates of CYP2C19	clobazam, diazepam, gliclazide, (R)-(-)-hexobarbital, (R)-lansoprazole (dexlansoprazole), (S)-lansoprazole, (S)-mephenytoin, (R)-mephobarbital, (R)-omeprazole, omeprazole, pantoprazole, proguanil, rabeprazole, tilidine, voriconazole
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.
OCT1 substrates	amantadine, cephalexin, ipratropium, lamivudine, oxyplatin, oxybutynin, phenformin, picoplatin, sorafenib, procainamide, ranitidine, thiamine, tropisetron, trospium, varenicline, umeclidinium
MRP2 substrates	irinotecan, mycophenolic acid, lopinavir, methotrexate, pravastatin, cabozantinib

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). Furthermore, patients should be instructed not to take grapefruit, Seville oranges or their juice for 14 days prior to dosing, during the 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 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 as acceptable means of contraception as efficacy may be compromised by QBW251 administration

Medication	Period during which contraceptive effect may be compromised	Action taken
Drospirenone Ethinyl estradiol Etonogestrel Levonorgestrel Medroxyprogesterone acetate Norelgestromin Norethindrone Norgestimate Norgestrel	Use of these drugs is not prohibited, but in combination with QBW251 these may no longer constitute means of contraception, and thus their use does not fulfill the requirements of contraception stipulated in the exclusion criteria (risk of contraceptive failure). Patient is at risk to experience a pregnancy due to the interaction between systemic contraceptive and QBW251.	Pause study treatment and perform a urine pregnancy test. In order to resume study treatment, patient must have a negative urine pregnancy test and must use an approved contraception method (Section 5.2 – Exclusion #8). If urine pregnancy test is positive, refer to Section 9.1.1.

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.

Table 6-5 Prohibited medication

Rationale/Group	Medication[1]	Prohibition period
Medication with a narrow therapeutic range and potential for increased exposure with QBW251 due to inhibition of CYP1A2	Theophyline Tizanidine	1 week prior to Day 1 until End of Study visit
Medication with a narrow therapeutic range and potential for increased exposure with QBW251 due to inhibition of CYP2C19	Amitriptyline Clomipramine Imipramine	1 week prior to Day 1 until End of Study visit
Medications lacking information on metabolizing enzymes	Pirbuterol	1 week prior to Day 1 until End of Study visit
Strong uridine diphosphate glucuronosyl transferase (UGT) inhibitors, which will potentially increase systemic concentrations of QBW251	Mefenamic acid Probenecid Valproic acid	1 week prior to Day 1 until End of Study visit

Rationale/Group	Medication[1]	Prohibition period
Strong inducers mediating enzymes levels via PXR, which will potentially decrease systemic concentrations of QBW251	Valproic acid Apalutamide Avasimibe, Carbamazepine Enzalutamide Ivosidenib Lumacaftor Mitotane Phenytoin Rifampicin Rifapentine St. John's wort (*Hypericum perforatum*)	1 week prior to Day 1 until End of Study visit
Any medication that may influence the response to treatment	Systemic or inhaled steroids (ICS alone), other systemic immunomodulators, recombinant human DNAse, any systemic or inhaled antibiotics, with the exception of oral macrolides mucolytics or hyperosmolar agents as noted in Table 6-2.	4 weeks prior to Day 1 until End of Study visit

Table 6-6 Respiratory related medications and required washout periods

Prohibited respiratory-related medications and washout period prior to Day 1	
Class of medication[1]	**Minimum washout period prior to Day 1**
Long-acting muscarinic antagonists (LAMA) (other than as ingredient of study maintenance therapy)	12 hours for twice-daily LAMAs 24 hours for once-daily LAMAs
Short-acting muscarinic antagonists (SAMA)	6 hours
Long-acting β_2 agonists (LABA)(other than as ingredient of study maintenance 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 maintenance therapy)	28 days
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.

6.2.3 Treatment for exacerbations and for bronchospasm

Pulmonary exacerbations:

Treatment for pulmonary exacerbation (including systemic corticosteroids, antibiotics) is allowed. Use of treatment for pulmonary exacerbations must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Bronchospasm:

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. The rescue medication will be supplied to the investigator sites locally by Novartis or provided by the study center and reimbursed by Novartis. No other rescue medication for bronchospasm 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 prior concomitant medication page of the eCRF.

6.2.4 Restriction for study subjects

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

6.2.4.1 Dietary restrictions and smoking

Dietary restrictions

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

- It is recommended not to take the investigational drug in together with high-fat meals (refer to SOM for details). The definition of high-fat meals follow the definition suggested by FDA in the draft guidance on Assessing the Effects of Food on Drugs in INDs and NDAs (FDA 2019): a meal containing at least 1000 kcal (4184 kJ), and at least 50% of that energy content from fat.

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

  - of which from proteins: 150 kcal
  - of which from carbohydrates: 250 kcal
  - of which from fats: 600 kcal.
- 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 as inhibitors of CYP3A.

Smoking

Smoking is not prohibited during the study.

6.2.4.2 Other restrictions

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 beverage for 4 hours prior to spirometry
- Alcohol for 4 hours prior to spirometry
- Strenuous activity for 12 hours prior to spirometry
- Exposure to environmental smoke, dust or areas with strong odors

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

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

6.3.2 Treatment assignment, randomization

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

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 but will be used by the IRT system. The patient will retain the Subject Number throughout the study as the unique identifier. If the subject fails to be treated for any reason, the IRT should be notified within 2 days that the subject was not treated, and the reason will be entered into the CRF.

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

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

Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of subjects.

Randomization will be stratified by macrolides use status and geographic region (from China/not from China).

6.4 Treatment blinding

Subjects, investigator staff, persons performing the assessments, will remain blinded 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, statistician and programmer supporting the CQBW251C12201 study.

(2) The identity of the treatments will be concealed by the use of identical packaging, labeling, schedule of administration, appearance, taste and odor for both QBW251 and placebo.

The sponsor will remain blinded until study completion except Trial Statistician and Trial Programmer who will be responsible for any interim analyses conducted at any time for efficacy and safety. Unblinding this study to the sponsor will happen in the case of subject emergencies that will be deemed necessary to evaluate the safety outcome to safeguard all subjects. The randomization codes associated with subjects from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until data base lock.

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

Table 6-7 Blinding levels

	Time or Event		
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**
Subjects	B	B	UI
Site staff	B	B	UI
Unblinded site staff e.g. pharmacy staff (see text for details)	B	UI	UI
Global Clinical Supply and Randomization Office	UI	UI	UI
Unblinded sponsor staff e.g. for study treatment re-supply, unblinded monitor(s), sample analyst(s) (see text for details),	B	UI	UI

	Time or Event		
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**
Statistician/statistical programmer/ data analysts (e.g. biomarker, PK)	B	B	UI
All other sponsor staff not identified above	B	B	UI

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

6.5 Dose escalation and dose modification

Investigational treatment dose adjustments are permitted under specific circumstances described in Section 6.5.1 and Section 6.5.2.

Temporary dose interruptions are permitted under specific circumstances described in Section 6.5.1.

6.5.1 Dose Interruptions

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

Any interruption of study medication 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.

6.5.2 Dose Adjustments for QTcF Prolongation

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

- Assess the quality of the ECG recording and the QT value and repeat, if needed
- Interrupt study investigational treatment
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities
- If possible, collect a time-matched PK sample on that visit (if not already scheduled per Table 8-1) and record time and date of last study treatment intake

If QTcF interval > 500 msec is confirmed:

- Permanently discontinue the study treatment.
- Take a blood sample for PK analysis. Timepoint should be as close as possible to the ECG recording in question

- Consult with a cardiologist (or qualified specialist)
- Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 msec
- Review concomitant medication use for other causes for QT prolongation (refer to http://www.qtdrugs.org for known QT prolonging drugs), and for drugs with the potential to increase the risk of drug exposure related QT prolongation
- Check the dosing schedule and treatment compliance

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Study drug compliance should be assessed by the investigator and/or center personnel at all visits. 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 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 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs).

Treatment of adverse events should be symptomatic. In case of questions regarding treatment of AEs caused by investigational product the investigator may contact the sponsor. Study drug discontinuation criteria as provided in Section 9.1.1 must be followed.

In case of exacerbations of bronchiectasis, adequate treatment of exacerbation as per national or international recommendations or current clinical practice should be instituted. These include administration of antibiotics and supervision until the patient is considered stable.

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

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

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/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.

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

6.7 Preparation and dispensation

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

6.7.1 Instruction of prescribing and taking study medication

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

- QBW251/ placebo is an oral capsule.
- One capsule should be taken twice a day at approximately the same time each day, with about 12 hours between each dose administration (approximately in the morning between 7 and 10 a.m. and in the evening between 8 and 11 p.m.)
- Refer to Section 6.2.4.1 Dietary restrictions relevant to QBW251 intake.
- 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.

Instructions for the maintenance treatment 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 maintenance therapy doses prior to the site visit to ensure compliance with the pre-dose PK sampling procedure and spirometry pre-dose measurements. The morning dose on the visit days should be taken after the pre-dose PK sampling and spirometry assessments have been completed within 15 min approximately.

Of note, spirometry on visit days shall be conducted

- 10-14 hours after the last intake of investigational drug on the evening before for b.i.d. drugs, and
- 22-26 hours after the last inhalation of daily maintenance medication on the morning before o.d. drugs (see also Section 8.3.2).

7 Informed consent procedures

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

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

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

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

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

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

The study includes optional sub studies/ DNA component/serial PK sampling component which requires a separate signature if the subject agrees to participate. It is required as part of this protocol that the Investigator presents this option 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 these optional assessments (DNA, serial PK 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.

Refer to the SOM for a complete list of ICFs included in this study.

8 Visit schedule and assessments

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

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final 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 CRF.

Table 8-1 Assessment Schedule

EPOCH	**Screening**		**Treatment**																			**End of Study**		**Unscheduled**
Visit Name	**Screening**	**Baseline**[2]	**Treatment**																			**End of Study**	**Safety Follow Up**	**Unscheduled**
Visit Numbers[1]	**1**	**20**	**100**							**110**[3]	**120**							**130**	**140**			**1999**		**150**
Days	**-42 to -1**	**1 -3 +1**	**1**							**14**	**28 ±3**							**56 ±3**	**84 ±3**			**91 ±3**	**114 ±3**	**-**
Weeks			**1**							**2**	**4**							**8**	**12**			**13**	**17**	**-**
Time (post-dose)	**-**	**-**	**0h**[4]	**1h**	**2h**	**3h**	**4h**	**6h**	**8h**	**-**	**0h**[4]	**1h**	**2h**	**3h**	**4h**	**6h**	**8h**	**0h**[4]	**3h**	**0h**[4]	**3h**	**-**	**-**	**-**
Informed consent	X																							
Inclusion / Exclusion criteria	X	X																						
Demography	X																							
Medical history/current medical conditions	X																							
Bronchiectasis exacerbation history	X																							
Smoking history	X																							

EPOCH	Screening		Treatment																			End of Study		Unscheduled
Visit Name	Screening	Baseline[2]	Treatment																			End of Study	Safety Follow Up	Unscheduled
Visit Numbers[1]	1	20	100							110[3]	120							130		140		1999		150
Days	-42 to -1	1 -3 +1	1							14	28 ±3							56 ±3		84 ±3		91 ±3	114 ±3	-
Weeks			1							2	4							8		12		13	17	-
Time (post-dose)	-	-	0h[4]	1h	2h	3h	4h	6h	8h	-	0h[4]	1h	2h	3h	4h	6h	8h	0h[4]	3h	0h[4]	3h	-	-	-
Randomization			X																					
Study drug administration[5]			b.i.d. dosing																					
In-clinic study drug administration			X								X							X		X				
Rescue medication dispensation[6]	S																							
Drug accountability			S																					
Concomitant medications	X																							
Physical Examination[7]	S	S									S							S		S		S		S
Body Height	X																							
Body Weight	X																					X		
Body Temperature	X	X	X								X							X		X		X		X
Blood Pressure	X	X	X								X							X		X		X		X
Pulse rate	X	X	X								X							X		X		X		X
Clinical Chemistry[8]	X		X								X							X		X				X
Coagulation[8]	X		X								X							X		X				X
Hematology	X		X								X							X		X				X
Urinalysis	X		X								X							X		X				X
Pregnancy and assessments of fertility[9]	X		X								X							X		X		X		X

EPOCH	Screening		Treatment																			End of Study		Unscheduled
Visit Name	Screening	Baseline[2]	Treatment																			End of Study	Safety Follow Up	Unscheduled
Visit Numbers[1]	1	20	100							110[3]	120							130		140		1999		150
Days	-42 to -1	1 -3 +1	1							14	28 ±3							56 ±3		84 ±3		91 ±3	114 ±3	-
Weeks			1							2	4							8		12		13	17	-
Time (post-dose)	-	-	0h[4]	1h	2h	3h	4h	6h	8h	-	0h[4]	1h	2h	3h	4h	6h	8h	0h[4]	3h	0h[4]	3h	-	-	-
Electrocardiogram (ECG)[10]	X		X			X					X			X				X	X	X	X	X		X
St. George's Respiratory Questionnaire (SGRQ)		X																		X				
EQ-5D-3L		X																		X				
Quality of Life Questionnaire for Bronchiectasis (QOL-B)		X									X							X		X				
eDiary	X																							X
EXACT-PRO[11]	X[12]																							X
HRCT[13]	X[14]																			X[15]				
Spirometry	X		X								X							X		X				X
Spirometry reversibility test	X																							
Oxygen Saturation	X																							
Sputum bacterial load[15]	X	X									X							X		X				X
Sputum 16S rRNA PCR		X									X							X		X				
Exploratory Biomarkers in Sputum		X									X							X		X				
Exploratory sputum bacterial profile		X																		X				

EPOCH	**Screening**		**Treatment**																			**End of Study**		**Unscheduled**
Visit Name	**Screening**	**Baseline**[2]	**Treatment**																			**End of Study**	**Safety Follow Up**	**Unscheduled**
Visit Numbers[1]	**1**	**20**	**100**							**110**[3]	**120**						**130**		**140**			**1999**		**150**
Days	**-42 to -1**	**1 -3 +1**	**1**							**14**	**28 ±3**						**56 ±3**		**84 ±3**			**91 ±3**	**114 ±3**	**-**
Weeks			**1**							**2**	**4**						**8**		**12**			**13**	**17**	**-**
Time (post-dose)	**-**	**-**	**0h**[4]	**1h**	**2h**	**3h**	**4h**	**6h**	**8h**	**-**	**0h**[4]	**1h**	**2h**	**3h**	**4h**	**6h**	**8h**	**0h**[4]	**3h**	**0h**[4]	**3h**	**-**	**-**	**-**
Exploratory Biomarkers in Blood		X									X									X				
Sparse PK samples collection			X			X[17]					X			X[17]				X	X[17]	X	X[17]			
Serial PK samples collection (optional at selected sites)			X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X			
Exploratory DNA consent (optional)	X																							
Exploratory DNA Sampling (optional)[18]		X																						
Telephone follow-up										S														
Adverse Events	X																						X	X
Comments	S																							
Safety Follow up Call																							S	
Study completion information																						X		

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only

[2] When Baseline and Day 1 visits occur on the same day, assessments assigned to both visits should be done only once.
[3] Day 14 visit will be conducted via telephone
[4] Unless otherwise specified, assessments at 0h must be done pre-dose
[5] On visit days, subjects will take their morning dose in the clinic after completion of all pre-dose assessments. All the other doses will be taken at home.
[6] SABA will be provided to patients as rescue medication
[7] A complete physical examination will be conducted at screening and end of treatment on Day 84. For the rest of visits with assessment scheduled, a short physical examination will be conducted
[8] hsCRP assessment is included in the chemistry panel and fibrinogen is included in the coagulation panel
[9] Serum assessment is required at screening, both serum and urine assessments are acceptable for all other visits. A positive urine test requires immediate interruption of study treatment until a serum test is found to be negative.
[10] Single ECG measurement
[11] It is to be completed by the patient at the end of every day at bedtime until the day before the last dose (Day 84)
[12] In order to set up the eCOA handheld device, patients need to complete the EXACT-PRO on at least 4 out of the past 7 days before patients begin the Baseline visit to calculate the EXACT-PRO baseline score. If less than 4 out of the past 7 days are completed, the baseline visit will need to be postponed until that requirement is met.
[13] Optional at selected sites with pre-approval of Sponsor.
[14] If patients have no historical CT assessment report, the investigator can make the diagnosis of bronchiectasis based on the screening HRCT scan for eligibility check. When the screening HRCT is performed, it is recommended the assessment to be performed after patient has passed all the other screening criteria, prior to randomization.
[15] The HRCT at Day 84 must be performed after the morning dose. If screening HRCT was not performed, no Day 84 HRCT should be performed.
[16] In the case that patient cannot produce enough volume of sputum on the scheduled visit, it is allowed that they can return to site within 3 days after the scheduled visit for sputum sample collection. Induced sputum process may be considered provided that the spontaneous attempts are not satisfactory

[17] 3h post-dose PK sample should be taken after the 3h post-dose ECG is performed.
[18] Genetic informed consent (optional) must be signed before a genetic sample is collected. Sample may be taken at assigned visit or any visit thereafter

8.1 Screening

It is permissible to re-screen a subject once if he/she fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

In the case where a safety laboratory or spirometry assessment at screening and/or baseline is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to randomization. In the case where sputum bacterial load at screening is lower than the threshold specified in the eligibility criteria, the assessment may be repeated **twice** prior to randomization. If the repeat value remains outside of the specified ranges, the subject must be screen failed. The subject can be rescreened as detailed below. If the subject has already taken the required baseline HRCT during the previous screening period within the past 12 months, the subject does not need to take the baseline HRCT again during the rescreening period.

If a subject re-screens for the study, then the subject must sign a new ICF and be issued a new subject number prior to any screening assessment being conducted. The investigator/qualified site staff will record if the subject was re-screened on the re-screening CRF along with the screening number the subject was issued prior to the current screening number.

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

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

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure.

The reason for the screening failure will be entered on the screening disposition page. If the patient fails to be randomized, the IRT must be notified within 2 days of the screen fail that the patient was not randomized.

Information on what data must collected for screening failures and further information on re-screening is outlined in the SOM.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent.

Smoking history information will be collected. Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to informed consent signature.

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

Details are outlined in the SOM.

8.3 Efficacy

The efficacy assessments selected are standard for this indication/subject population. Blood and sputum samples will be collected and evaluated in all patients at the time points defined in the Assessment Schedule (Table 8-1). Follow instructions outlined in the SOM regarding sample collection, numbering, processing, and shipment. Number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol. For all completed scales/questionnaire described below, the Investigator will be required to review and examine responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the scale but also for any unsolicited comments written by the patient. If the occurrence of AEs or SAEs is confirmed, the investigator/physician should record the events as per instructions given in Section 9.

Pharmacodynamic (PD) samples will be obtained and evaluated in all subjects at all dose levels, including the placebo group.

8.3.1 Microbiological assessment

Spontaneous or induced sputum will be collected for analysis of pathogenic bacterial colonization (CFU/mL) (e.g. *H influenzae, M catarrhalis, S aureus, S pneumoniae, Enterobacteriaceae, P aeruginosa, Stenotrophomonous Maltophilia*, or any potential pathogenic non-fermenting Gram negative bacteria).

On scheduled sputum collection visits, at least one sputum specimen is recommended to be collected in the morning at pre-dose timepoint and before breakfast (including drinks) if possible. If spontaneous sputum collection attempts are not satisfactory, an investigator may take the decision to collect sputum sample after induction by the inhalation of saline. If patients can't produce enough sputum on the individual scheduled visits, they can come back within 3 days after the scheduled visits to try to produce sputum sample. Retesting is allowed once during the screening period.

Treatment emerging pathogens will be determined at all visits.

Microbiological analyses, including bacterial colonization and bacterial load profiling, will be performed at qualified microbiology laboratory(ies). Depending on different laboratories, the unit of bacterial load CFU/mL is considered equal to CFU/g.

Furthermore, all patients with signs of an exacerbation will have to come to the study center where additional sputum sample will be collected. The analysis of this sample would help to determine whether the bacteria load and/ or bacterial colonization may change with an exacerbation.

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

8.3.2 Spirometry

Spirometry testing will be performed with the MasterScope system (manufactured by eResearch Technology GmbH) according to the ATS/ERS guidelines (Miller et al 2005a; Miller et al 2005b) at screening to assess patients' lung function at the visits detailed in the assessment schedule in Table 8-1.

The spirometry evaluation should be performed at the site prior to the morning investigational drug intake and the daily maintenance therapy, such as LABA, LAMA, LABA/LAMA, as pre-bronchodilator. 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 for b.i.d drugs, and 22-26 hours for once daily drugs after the last inhalation of daily maintenance medication on the prior morning.

The spirometry equipment used during the trial will be provided to all study sites by a Central Spirometry vendor. The equipment must meet or exceed the minimal ATS/ERS recommendations for diagnostic spirometry equipment as defined in the guideline provided by the vendor. Calibration of the spirometry equipment is mandatory on all visit days and must be performed before the first 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 spirometry assessment attempt depends on the overreader's judgement for compliance with and acceptability according to the ATS/ERS criteria.

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

8.3.3 Fibrinogen

Fibrinogen is a glycoprotein, which is the most abundant clotting factor in plasma. It is associated with severity of disease and quality of life in bronchiectasis (Saleh et al 2017). For details on the collection, handling and storage/shipment of samples, refer to the Laboratory Manual. Samples will be collected at the time points defined in the Assessment Schedule (Table 8-1).

8.3.4 High Resolution Computed Tomography (HRCT)

High Resolution Computed Tomography (HRCT) will be performed at screening period and at Day 84 (12 weeks). At the time points specified in the schedule, a HRCT scan of the lung, without contrast agent, will be acquired. The acquisition will include inspiratory and expiratory image sets at both assessment time points. In all subjects, the baseline and follow-up HRCT scan should be performed where possible on the same scanner.

HRCT assessment is optional at selected sites only with pre-approval from the Sponsor. Patients who opt out of the HRCT assessment must have a historical chest CT to confirm the diagnosis of bronchiectasis.

Protocol-specific requirements of the HRCT and machine settings are provided to all sites as part of a separate Imaging Manual. Additionally, the imaging vendor will provide centralized review of the HRCT scans.

In summary, HRCT scans will be analyzed to determine both at baseline and week 12, along with the associate change from baseline:

- As secondary objectives: airway structure (airway wall and lumen parameters) and function (global and regional air trapping)
- As exploratory endpoints: mucus load (whole lung and regional)

As additional endpoints, airway-artery ratios (airway lumen area and airway outer area to the area of the accompanying vessel) and HRCT scores (based on the presence and extent of BE, airway wall thickening, trapped air, parenchymal abnormalities and nodules) will be determined in the context of the IMI collaboration

Note: The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

8.3.5 High-sensitivity C-reactive protein (hsCRP)

Serum biomarkers (e.g. hsCRP) will be analyzed to determine the effect of QBW251 treatment on inflammation in peripheral blood. C-reactive protein (CRP) is substance produced by the liver in response to inflammation.

hsCRP levels are assessed as part of the clinical chemistry panel for patient safety but will also be assessed as a biomarker for bronchiectasis.

8.3.6 Appropriateness of efficacy assessments

The sputum bacterial colonization and the lung function assessment such as FEV1 and FVC in pre-bronchodilator are standard outcome measurement in bronchiectasis disease trials.

8.4 Safety

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

For details on AE collection and reporting, refer to AE section.

Table 8-2 Assessments and Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be at all visits starting from Day 1 visit except where a complete physical examination is required (see footnote 6 of Assessment Schedule). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include BP and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Appendix 1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured, mass index (BMI) will be calculated as (Body weight (kg) / [Height M)]^2) (Screening only).

The methods for each assessment and data recording details are specified in the SOM.

8.4.1 Laboratory evaluations

Central or local laboratories 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.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant. Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE CRF /eCRF page as appropriate.

Clinically notable laboratory findings are defined in Section 16.1.

Table 8-3 Laboratory evaluations

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

8.4.2 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the SOM.

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

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening to assess eligibility. See the SOM for additional details.

Clinically significant abnormalities must be reported as adverse events.

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 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 might be performed if requested by local requirements.

8.4.4 Bronchiectasis exacerbation

Bronchiectasis exacerbations are defined as a deterioration in three or more of the following key symptoms for at least 48 hours:

- cough
- sputum volume and/or consistency;

- sputum purulence;
- breathlessness and/or exercise tolerance;
- fatigue and/or malaise;
- haemoptysis

  AND

  A clinician determines that a change in bronchiectasis treatment is required (e.g. requiring systemic glucocorticosteroid treatment and/or systemic or inhaled antibiotics).

A worsening of symptoms that either does not meet the above symptom definition but is treated by the investigator with antibiotics or steroids or both, or that meets the symptom definition but is not treated with antibiotics or steroids or both, is not considered a pulmonary exacerbation for the study.

For the above reported signs and symptoms, additional information will be collected to document if the reported signs and symptoms last for more than 48 hours.

Patients should contact the site when experiencing a pulmonary exacerbation. An unscheduled visit should occur within 2 working days of the event to confirm the diagnosis, unless the patient is hospitalized and thus unable to attend the site. AEs/SAEs, concomitant medications, and safety laboratory exams should be captured, as appropriate.

The start date for a pulmonary exacerbation recorded in the CRF should be the first day of treatment with antibiotics or steroids or both, as defined above. The end of a pulmonary exacerbation episode is marked by the end of treatment with antibiotics or steroids or both.

An exacerbation might result in missed or rescheduled visit(s) and missing associated CRF data in some circumstances.

Patients who develop a pulmonary exacerbation between screening and prior to treatment will be screen failed but will be permitted to be re-screened once the inclusion/exclusion criteria have been met (see Section 5.2 Exclusion criteria).

8.4.5 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO)

The impact of bronchiectasis on a subject's health status will be assessed by the following patient-reported questionnaires (PROs) completed on the handheld electronic device which also contains the eDiary (see below):

- The St. George Respiratory Questionnaire (SGRQ) providing the health status measurements
- The Quality of Life Questionnaire for Bronchiectasis(QOL-B) (Respiratory Symptoms domain) assessing symptoms for patients with bronchiectasis

- The European Quality of Life-5 Dimensions- 3 level (EQ-5D-3L) measuring global health status
- EXAcerbations of COPD Tool - Patient Reported Outcome (EXACT-PRO) evaluating frequency, severity, and duration of exacerbations.

The appropriate language version of the questionnaires will be used in each participating country. Subject questionnaires will be completed in the language most familiar to the subject. 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 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.

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

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

Completed measures and any unsolicited comments written by the subject should be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in the patient's source records. If AEs or SAEs are confirmed, the study investigator should not encourage the subject to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 10 (e.g. reference Section 10.1.1 Adverse Events) of the study protocol.

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 the Assessment Schedule (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 SOM.

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

The SGRQ contains 50 items divided into two parts covering three aspects of health related to Bronchiectasis: Part I covers "Symptoms" and is concerned with respiratory symptoms, their frequency and severity; Part II covers "Activity" and is concerned with activities that cause or are limited to breathlessness; Part II is also concerned with "Impacts", which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease. A score will be calculated for each of these three subscales and a "Total" score

will also be calculated. In each case the lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of health status.

Quality of Life Questionnaire for Bronchiectasis (QOL-B) (Respiratory Symptoms)

The Quality of Life Questionnaire for Bronchiectasis (QOL-B) (Respiratory Symptoms scale) will be used to assess respiratory symptoms for patients in this study (Quittner et al 2015). It is a self-administered patient-reported outcome (PRO) measure.

QOL-B will be electronically completed by the patient at the investigator's site at the visits indicated in the Assessment schedule (Table 8-1).

A detailed guide relating to the administrative procedures of the questionnaire are given in SOM.

Instrument scoring and handling of missing item data will be conducted in accordance with the user guide for the QOL-B. The Respiratory Symptoms scale contains **9** items.

European Quality of Life-5 Dimension-3 Level (EQ-5D-3L)

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

EXACT Questionnaire

The EXACT-PRO is a validated 14-item electronic questionnaire designed to detect the frequency, severity, and duration of exacerbations. 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 disease and detect worsening indicative of an exacerbation.

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

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

Electronic Diary (eDiary)

At screening, all patients will be provided with an electronic diary (eDiary).

The eDiary will record rescue medication, medication intake (dose) after randomization, as well as the study questionnaires at prespecified timepoints.

The patients will be instructed to routinely complete the rescue medication information in the eDiary twice daily at the same time in the morning and evening (before taking the study drug), approximately 12 hours apart. The eDiary 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 eDiary device.

A list of eDiary questions is provided in the SOM.

8.5.2 Pharmacokinetics

PK samples will be collected as per visits and time points indicated in the Assessment Schedule (Table 8-1). Instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment shall be followed.

PK sampling (pre-dose and 3 hour post-dose) will be conducted and evaluated in all subjects on Days 1, 28, 56 and 84 (end of treatment).

Additionally, although serial PK sampling is optional, efforts will be made to have approximately 30-40 patients from selected sites undergo serial PK sampling up to 8 hours post-dose at Day 1 and Day 28 visits as per Table 8-1 to further characterize the PK profile of QBW251 in BE patients, which will provide important understanding of the 300 mg b.i.d. dose in BE patients.

Furthermore, in case a patient prematurely discontinued treatment but continue participation in the study, the first visit after the discontinuation should have a PK trough assessment and thereafter subsequent PK sampling should be suspended.

Plasma PK samples will be evaluated only in subjects who have been administered QBW251. QBW251 concentration will be determined by a validated LC-MS/MS method with an anticipated lower limit of quantification (LLOQ) of 1 ng/mL of QBW251.

Concentrations below the LLOQ will be reported as zero and missing data will be labeled as such in the bioanalytical report.

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8 or higher): Cmax, Tmax, AUClast, AUC0-12h, T1/2,eff when feasible.

Residual plasma samples remaining after the determination of QBW251 may be used for exploratory assessment of metabolites or other bioanalytical purposes (e.g. cross check between different sites, stability assessment).

8.5.3 Biomarkers

Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 8-1).

Follow instructions for sample collection, numbering, processing, and shipment provided in the laboratory manual.

DNA sampling / Pharmacogenetics

The study includes an optional genetic research component which requires a separate informed consent signature if the subject agrees to participate. As permitted by local governing regulations and by IRB/EC, it is required as part of this protocol that the Investigator presents these options to the subject.

The purpose of genetic research may be to better understand the safety and efficacy of QBW251, or to learn more about human diseases, or to help develop ways to detect, monitor and treat diseases.

As technology changes over time, the most appropriate technology will be used at the time the exploratory genetic research is performed. This may include the study of the entire genome.

Laboratory manuals will be provided with detailed information on sample collection, handling, and shipment.

DNA samples

The use of DNA to search for biomarkers of disease and drug action is exploratory. Any results from this DNA study will not be placed in the subject's medical records.

To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the subject's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the subject's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

8.5.3.1 Sputum biomarkers

The examination of QBW251 effect on inflammatory markers, which may include but are not limited to IL-6 and IL-8 will be done in sputum.

16S rRNA PCR may be performed to measure the bacterial load. If feasible, the analysis will be performed using remaining sputum samples collected for microbiology assessment.

Sputum samples will be biobanked for potential exploratory sputum bacterial profile measured by 16s rRNA gene sequencing.

Both 16S rRNA PCR and 16s rRNA gene sequencing are optional to China.

8.5.3.2 Serum protein levels

Protein profiling applying highly multiplexed exploratory analytical platform and hypothesis free data analysis (SomaScan) may be applied to identify biomarker signatures, related to disease and/or QBW251 mode of action. Given the exploratory nature of the work, the analytical method used for this assessment is not validated and the results from this exploratory analysis will not be included in the clinical study report. This assessment is optional to China.

8.5.3.3 Use of residual biological samples

Any residual samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis related to the purpose of this study. This may include but is not limited to using residual samples for protein binding, metabolite profiling, biomarkers of transporters or other bioanalytical purposes (e.g., cross check between different sites and/or stability assessment). Residual PK plasma samples remaining after the determination of QBW251 may be used for exploratory assessment of metabolites or other bioanalytical purposes (e.g., cross check between different sites, stability assessment).

Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

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

Subjects may voluntarily discontinue study treatment for any reason at any time.

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

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy: a positive urine pregnancy test after start study drug requires immediate interruption of study drug until serum hCG is performed and found to be negative. If positive, the subject must discontinue study medication.
- Use of prohibited treatment outlined in Section 6.2.2.
- Any situation in which study participation might result in a safety risk to the subject.
- Following emergency unblinding
- Emergence of an AE reported as severe and suspected to be related to investigational drug or an SAE reported and suspected to be related to the investigational drug.

- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study.
- Any liver event requiring immediate discontinuation of study treatment, as specified in Table 16-2
- Individual serum creatinine increase ≥ 50% compared to baseline (must be confirmed). Please refer to Section 16.3 for discontinuation criteria due to emerging renal abnormalities.
- Study drug can be temporarily interrupted as a response to the occurrence of adverse events that do not fulfill the requirements above described for permanent discontinuation (refer to Section 6.5.1).

Discontinuation of study treatment will be at the discretion of the Investigator under the following circumstances:

- Any other protocol deviation that results in a significant risk to the subject's safety.
- Emergence of adverse event(s) or laboratory abnormalities that in the judgement of the Investigator, taking into account the subjects' overall status, prevent the subject from continuing participation in the study.

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently. Unblinding for emergency reasons requires study drug discontinuation.

If a female subject of childbearing potential withdraws from the study prematurely, the investigator should recommend her to maintain contraceptive measures for at least 7 days after the last dose of the study drug.

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

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2 'Withdrawal of Informed Consent'). Where possible, they should return for the assessments indicated for EOS (V1999) in the Assessment Schedule (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 (Section 9.1.3). This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

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

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

9.1.2 Withdrawal of informed consent

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

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

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

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

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

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

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

For EU and 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 or until the end of the study.

9.1.4 Study stopping rules

The study may be put on hold pending a full safety data review, if one of the following criteria is met:

1. Three or more study medication-related serious adverse events (SAE) reported
2. The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.

The study may resume following the safety review if Lead Investigator(s) and sponsor agree it is safe to proceed.

Any restart following a temporary hold due to stopping rules being met will require the Competent Authorities and Ethic Committees approve the study to proceed, as required per country regulations.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. 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 and treated as a prematurely withdrawn subject and undergo all assessments of the premature withdrawal visit. 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. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their 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 of that decision (e.g. Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

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

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject 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.

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

1. The severity grade:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - 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 study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/withdrawn

6. Its outcome
    - not recovered/not resolved
    - recovered/resolved
    - recovering/resolving
    - recovered/resolved with sequelae
    - fatal
    - 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 study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

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

Abnormal laboratory values or test results constitute 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 Appendix 1.

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2E Guidelines 2004).

- 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 emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2E Guidelines 2004).

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.

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 must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

- Screen Failures (e.g. a subject who is screened but is not treated or randomized)*:* SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis
- Baseline Failures (e.g. A subject who is screened but not randomized/treated after the baseline visit): SAEs collected between time subject signs ICF until time that subject is determined to be a baseline failure.
- Randomized OR Treated Subjects: SAEs collected between time subject signs ICF until 30 days after the subject has discontinued or stopped study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, and under no circumstances later than 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). 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 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 (following the last administration of study treatment) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

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

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

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

For more information on AE and SAE definition and reporting requirements, please see the respective Section 10.1

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

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

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

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

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

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF
- 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 Section 9.1.1 Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include

- These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease and imaging such as abdominal ultrasound, computer tomography (CT) or magnetic resonance imaging (MRI), as appropriate.
  - All follow-up information and procedures performed must be recorded as appropriate in the CRF.

Refer to the SOM for additional details.

10.2.2 Renal safety monitoring

Renal safety monitoring for the investigational drug will be performed in the study. This includes baseline measurements of serum creatinine, calcium, potassium and urine dipstick and at subsequent visits as indicated in the Schedule of Assessments Table 8-1 and Laboratory parameters in Table 8-3.

Abnormal renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment.

Every renal laboratory trigger or renal event as defined in Table 16-3 and Table 16-4 should be followed up by the investigator or designated personnel at the trial site as summarized in Section 16.3, Appendix 3.

Refer to the SOM for additional details.

10.2.3 Data Monitoring Committee

Following the data review in May 2022, it was concluded that the Data Monitoring Committee is no longer required.

10.2.4 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial, i.e. not being Novartis/sponsor representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

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

Randomization codes and data about all study treatment(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The 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/delegated CRO representative will review the protocol and data capture requirements (i.e. eSource 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/delegated CRO/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 CRFs 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 CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

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

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

12.1 Analysis sets

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

The Safety Set includes all subjects who received at least one dose of study treatment whether or not being randomized. The safety set will be used in the analysis of all safety variables.

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

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

12.2 Subject demographics and other baseline characteristics

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

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

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

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to each treatment group (QBW251 dose or placebo) will be summarized by means of descriptive statistics using the safety set.

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

12.4 Analysis of the primary endpoint(s)

The primary objective of the study is to assess the change from baseline of QBW251 compared to placebo on the total number of bacteria over all strains after 12 weeks of treatment. The PD Analysis Set will be used for analysis of the primary variable, unless otherwise specified.

12.4.1 Definition of primary endpoint(s)

The primary estimand targets the hypothetical effect as if all patients had stayed on treatment for 12 weeks and as if antibiotics other than macrolide had not been available.

- **Population**: patients are defined by the study inclusion and exclusion criteria. The protocol defines the use of allowed maintenance therapy for this target population, as well as medications that are prohibited.
- **Variable**: change from baseline in bacterial load as measured by the number of colony forming units (CFU/ml) of potentially pathogenic microorganisms in sputum at week 12. A $\log_{10}$ transformation is applied to the CFU counts before forming the change from baseline computing therefore the log ratio to baseline of the bacterial load.
- **Intervention effect** of interest:
- Intake of antibiotics other than macrolide and intake of rescue medication
- Treatment discontinuation or study participation: hypothetical on treatment CFU counts
- **Summary measure**: difference in variable means (QBW251 compared with placebo)

12.4.2 Statistical model, hypothesis, and method of analysis

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

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

The primary endpoint will be analyzed using a Bayesian repeated measures model with change from baseline in CFU counts (on log10-transformed scale) as response, including the fixed factors and covariates but are not limited to: treatment group, visit, effect of treatment*visit interaction, status of macrolides use at screening, and baseline CFU counts (on log10-transformed scale) by time interaction. In absence of informative data, non-informative priors for the model parameters will be used. The prior for placebo may be updated as a weakly informative prior and will be specified in the statistical analysis plan, should new relevant data become available before the database lock of this study.

A comparison of QBW251 vs. placebo is of primary interest. Based on the fitted Bayesian model for repeated measures, the posterior probability of QBW251 effect over placebo for $\log_{10}$CFU will be calculated. Statistical evidence will be concluded if there is 90% probability that the true effect over placebo for $\log_{10}$CFU is >0.

The posterior probabilities of efficacy will be assessed according to the following criteria:

1. **Go / success criteria** at final: Better than placebo with high confidence (at least 90% probability that the change from baseline in $\log_{10}$CFU for QBW251 is better than placebo, i.e. Posterior Prob (delta > 0) > 0.90)

Due to the nonconfirmatory nature of this study, no multiplicity adjustment will be applied.

In addition, the mean and corresponding two-sided 80% credible interval for the QBW251 difference to placebo from the posterior distribution will be presented.

12.4.3 Handling of missing values/censoring/discontinuations

Since the primary estimand is related to an effect outside of antibiotics intake, the CFU counts assessed within 2 weeks after pulmonary exacerbations or during or after last dose of antibiotics, other than macrolide, would not be included in the primary estimand. They will be excluded from the primary estimand, if a valid unscheduled assessment did not happen at the time point for the primary analysis. This is because of the potential confounding effect were expected from the use of antibiotics.

If a valid unscheduled assessment happened at the time point for the primary analysis, then the CFU data collected during the unscheduled visit will be included in the primary estimand. Details about the definition of unscheduled visit is provided in the site manual.

However, the CFU counts at the following visits (if there is no antibiotics use and no pulmonary exacerbation) are assumed not to be confounded and will be included in the primary estimand of interest.

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 related to primary endpoint will not be explicitly imputed. If endpoint measurements are missing at random, an analysis of the available data provides consistent estimates of model parameters.

12.4.4 Sensitivity and Supportive analyses

The primary estimand described in Section 12.4.1 is complemented by two supplementary estimands. This would allow to assess the robustness of the QBW251 treatment effect on bacterial load drop with and without antibiotics use / pulmonary exacerbations that would be deemed to affect the outcome of interest.

- To estimate the effect of study drug versus placebo without potential confounding due to the antibiotics use for exacerbation. All visits after receiving antibiotics other than macrolide will not be included in the CFU analysis (they will be set as missing). Note that this approach will lead to less data being used than the primary estimand.
- To estimate the effect regardless of antibiotic use. This estimand follows the treatment policy strategy where antibiotics are used as needed basis on top of study treatment as in clinical practice. Thus, the CFU measurements collected during the intake of antibiotics will be included in the analysis. The estimate of treatment actually means (treatment + any antibiotics) in this context.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

12.5.1.1 Proportion of patients with absence of any CFU or CFU counts below the limit of quantification

The proportion of patients with absence of any CFU or CFU counts below the limit of quantification at week 12 will be analyzed using a logistic regression. The model will include treatment, baseline macrolide use as fixed class effects and the number of bronchiectasis exacerbations in the 12 months prior to screening as a categorical variable. The estimated odds ratios will be displayed along with the associated 80% confidence intervals.

12.5.1.2 Change from baseline in fibrinogen plasma concentration

The change from baseline in fibrinogen is assumed normally distributed. An MMRM will be fitted to the changes from baseline in fibrinogen for all time points until Day 84 visit including the following fixed factors: treatment group, visit, treatment group by visit interaction, baseline macrolide use, and baseline fibrinogen value by time interaction.

12.5.1.3 Change from baseline in rescue medication use (salbutamol/albuterol)

The mean night-time/day-time number of puffs of rescue medication will be calculated for each subject for each visit interval.

The total number of puffs of rescue medication will be divided by the total number of (full or half) days with non-missing rescue data to derive the mean daily number of puffs of rescue medication taken for the patient for each given visit interval. If the number of puffs is missing for part of the day (either morning or evening) then a half day will be used in the denominator. No imputation will be used for missing rescue therapy.

The change from baseline in the mean monthly daily number of puffs of rescue medication will be analyzed using a similar MMRM as described in Section 12.5.1.2, with the appropriate baseline mean daily number of puffs replacing the baseline fibrinogen value. The total count of rescue medication use over the 12 week treatment period may be analyzed using a generalized linear model assuming a negative-binomial distribution. Details will be provided in the SAP.

Mean daily number of puffs will be summarized descriptively by monthly interval.

12.5.1.4 Changes from Baseline in pre-bronchodilator FEV1, FVC, measured by spirometry

The descriptive statistics for each variable will be provided by treatment.

Change from baseline in FEV1 and FVC will be analyzed using the similar statistical method with the same factors of interest described for the secondary efficacy endpoint (Section 12.5.1.2). A MMRM will be handled in the statistical model accordingly.

12.5.1.5 Change from baseline in airway wall and lumen parameters along with extent of global and region air trapping as measured by HRCT

Change from baseline in airway wall and lumen parameters will be analyzed using the same model as for the efficacy endpoint in Section 12.5.1.2. Global and region air trapping changes will be summarized. Contrasts for treatment differences will be provided together with two-sided 80% confidence intervals.

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

12.5.2 Safety endpoints

All safety endpoints will be analyzed based on safety set and will be summarized by actually received treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment (30 days after the last actual administration of study treatment) deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

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

Adverse events

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

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

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

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

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

Vital signs

All vital signs data will be summarized with standard descriptive statistics by treatment and visit/time. The number of patients with vital signs meeting the definition of notably abnormal will be presented by parameter.

12-lead ECG

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

Clinical laboratory evaluations

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

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

12.5.3 Pharmacokinetics

PK analysis set will be used for the analysis of all pharmacokinetic parameters.

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

The PK parameters which will be determined from the plasma concentration time data include (but not limited to), where possible: Cmax, Cmin, Tmax, AUClast, AUC0-12h, and T1/2,eff when feasible. Pharmacokinetic parameters will be determined using WinNonlin Phoenix (version 8 or higher).

12.5.4 PK/PD relationships

An exploratory analysis of the relationship between pharmacokinetic and pharmacodynamic measures may be performed using a model-based approach, if the data measures permit.

12.5.5 Patient reported outcomes

Quality of Life Questionnaire for Bronchiectasis (Respiratory symptoms) will be summarized by treatment groups and visit.

12.6 Analysis of exploratory endpoints

Statistical analysis for exploratory variables will be described in the statistical analysis plan.

12.6.1 Changes from baseline in SGRQ, and EQ-5D-3L

Change from baseline will be provided by treatment group and visit.

12.6.2 Bronchiectasis exacerbation

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

12.6.2.1 Time to first bronchiectasis exacerbations

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

The time to the first on-treatment bronchiectasis exacerbation (event) is defined as the earliest start date of a bronchiectasis exacerbation minus the date of randomization +1. Patients who do not experience an exacerbation or discontinued earlier without an exacerbation will be considered as censored for analyses purpose at the end of the treatment period. Events which occur after randomization and during the treatment period will be included in the analysis.

The hazard ratios for QBW251 compared with placebo and their corresponding 80% confidence intervals will be computed using Kaplan-Meier method. The stratification factor may include number of exacerbations in the last 12 months as =1 and >1.

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

12.6.2.2 Annualized rate of bronchiectasis exacerbations

Using data from EXACT questionnaire, the number of bronchiectasis exacerbations will be analyzed using a generalized linear model assuming a negative binomial distribution. The time at risk for a patient is defined as the length of time the patient is on treatment and the log (length of time) will be used as the offset variable in the model. The model will include treatment, baseline macrolides use, and the number of bronchiectasis exacerbations in the 12 months prior to screening as categorical variables. An estimate of the rate ratio together with 80% confidence intervals and corresponding p-value will be presented.

12.6.3 Biomarkers

Exploratory biomarkers such as change from baseline in inflammatory markers in sputum, bacterial load of sputum as well as their association with primary and secondary efficacy endpoints will be analyzed. Summary statistics for biomarkers of interest will be provided by treatment and visit.

12.6.4 DNA

Exploratory DNA studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests are used for the analyses. Additional data, from other clinical trials, are often needed to confirm associations. Alternatively, if the number of subjects enrolled in the study is too small to complete proper statistical analyses, the data may be combined, as appropriate, with those from other studies to enlarge the dataset for analysis.

Data generated on hypothesis-free platforms will be reported separately (e.g. CSR addendum).

12.7 Interim analyses

A blinded interim analysis will take place when approximately 14 patients complete Day 84 assessments to review the sample size assumptions related to bacterial load. The variability of primary endpoint (change from baseline in CFU counts) will also be assessed at that time.

Additional interim analyses may be conducted to support decision making concerning the current clinical study, or the future of the sponsor's clinical development plan.

All enrolled subjects and the participating investigators will remain blinded during the entire study. Only the sponsor may be unblinded at the interim as necessary.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

This study will enroll approximately 72 patients who will be randomized in a 1:1 ratio to receive either QBW251 300 mg or placebo in order to achieve 60 patients who complete the treatment period based on the assumption of a 16% drop-out rate. There will be approximately 79% power to show that QBW251 is superior to placebo in reducing bacterial load with 10% level of significance, assuming a true difference of 1.5 $\log_{10}$ CFU count and a standard deviation of 2.8 for the change from baseline to Day 84 on $\log_{10}$ scale. Regarding the assumption on the standard deviation of the change from baseline in bacterial load ($\log_{10}$ scale), this is derived from two historical trials in bronchiectasis and COPD patients with a conservative view. There will be about 10% chance to erroneously declare positive PoC (Type 1 error).

The sample size assumptions will be reviewed in a blinded manner when approximately 14 patients complete the treatment period.

If deemed appropriate, in the case of a higher dropout rate than assumed or a higher variability of the primary endpoint in either region, or if there is foreseen a significant imbalance between sites in Europe and China, up to 108 subjects may be randomized in order to achieve an adequate number of completers.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (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.).

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.

15 References

References are available upon request

Amaral MD, Kunzelmann K (2007) Molecular targeting of CFTR as a therapeutic approach to cystic fibrosis. TRENDS in Pharmacological Sciences; 28(7):334-341

Bergougnoux A, Viart V, Miro J, et al (2015) Should diffuse bronchiectasis still be considered a CFTR-related disorder. J Cyst Fibros; 14(5):646-653

Bienvenu T, Sermet-Gaudelus I, Burgel PR, et al (2010) Cystic fibrosis transmembrane conductance regulator channel dysfunction in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med; 181(10):1078–1084

Boucher RC (2007) Cystic fibrosis: a disease of vulnerability to airway surface dehydration. Trends Mol Med; 13(6):231-240

Chalmers JD, Smith MP, McHugh BJ, et al (2012) Short- and Long-Term Antibiotic Treatment Reduces Airway and Systemic Inflammation in Non–Cystic Fibrosis Bronchiectasis. Am J Respir Crit Care Med; 186(7):657-665

Chalmers JD, Goeminne P, Aliberti S, et al (2014) Derivation and validation of the bronchiectasis severity index: an international multicentre observational study. Am J Respir Crit Care Med; 189:576–585

Dinakar C, O'Connor GT (2016) The Health Effects of Electronic Cigarettes. N Engl J Med; 375(14):1372-1381

EuroQol Group (1990) EuroQol-a new facility for the measurement of health-related quality of life. Health Policy; 16:199-208

Fahy JV, Dickey BF (2010) Airway mucus function and dysfunction. N Engl J Med; 363(23):2233-2247

Hogg JC, Chu F, Utokaparch S, et al (2004) The Nature of Small-Airway Obstruction in Chronic Obstructive Pulmonary Disease. N Engl J Med 2004; 350(26):2645-2653

ICH-E2E Guideline 2004. [Viewed 12 January 2021] Available from: https://database.ich.org/sites/default/files/E2E_Guideline.pdf

Jones PW, Quirk FH, Baveystock CM et al (1992) A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis. 145(6):1321-7

Mannino D.M. Singer R.T. Lomas D.A. et al (2015) Plasma Fibrinogen as a Biomarker for Mortality and Hospitalized Exacerbations in People with COPD. Chronic Obstr Pulm Dis.; 2(1):23-34

Miller M.R, Hankinson J. et al (2005)a Standardisation of spirometry. Eur Respir J. 26(2):319-38

Miller M.R, Crapo R.J. et al (2005)b General considerations for lung function testing. Eur Respir J. 26:153–161

O'Donnell AE (2008) Bronchiectasis. Chest; 134(4):815–823

O'Sullivan BP, Freedman, SD (2009) Cystic fibrosis. Lancet; 373(9673), 1891-904.

Pezzulo AA, Tang XX, Hoegger MJ et al (2012) Reduced airway surface pH impairs bacterial killing in the porcine cystic fibrosis lung. Nature; 487(7405):109-13.

Polverino E, Goeminne PC, McDonnell MJ et al (2017) European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Resp J; 50:1700629;

Quint JK, Millett ER, Joshi M et al (2016) Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. Eur Respir J; 47(1):186-93

Quittner AL, O'Donnell AE, Salathe MA et al (2015) Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. Thorax; 70:12–20

Saleh AD, Chalmers JD, Soyza DA et al (2017) The heterogeneity of systemic inflammation in bronchiectasis. Respir Med; 127:33-39

Solomon GM, Fu L, Rowe SM, Collawn JF, et al (2017) The therapeutic potential of CFTR modulators for COPD and other airway diseases. Curr Opin Pharmacol; 34:132-139

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 and require assessment for clinical relevance and continuance of the patient by the Investigator.

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

Table 16-1 Liver event and laboratory trigger definitions

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

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

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

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (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 • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (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 • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

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

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

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase 50 % + **OR if <18 years old, eGFR ≤ 35 mL/min/1.73 m²**	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	Assess & document • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

+ Corresponds to KDIGO criteria for Acute Kidney Injury

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

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

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

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

Table 16-4 Renal Event Follow Up

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