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QBW276

Clinical Trial Protocol CQBW276X2201

A randomized, double blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of inhaled QBW276 in patients with cystic fibrosis

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

Notification of serious adverse events

Refer to Section 9.2 of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Chief Medical Office & Patient Safety Department and notify the Clinical Trial Leader).

Contact information is listed in the SOM.

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
b.i.d.	twice a day
BMI	Body Mass Index
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CF	Cystic Fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFR	Code of Federal Regulations
CK	creatinine kinase
CMO & PS	Chief Medical Office & Patient Safety
CRF	Case Report/Record Form (paper or electronic)
CO_2	carbon dioxide
CRO	Contract Research Organization
CTCAE	Common terminology criteria for adverse events
CTRD	Clinical Trial Results Database
CV	coefficient of variation
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
DMC	Data Monitoring Committee
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
GCP	Good Clinical Practice
γ-GT	Gamma-glutamyl transferase
h	hour
HIV	human immunodeficiency virus

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LCI	Lung Clearance Index
LFT	Liver function test
LDH	lactate dehydrogenase
LLN	lower limit of normal
MedDRA	Medical dictionary for regulatory activities
NCDS	Novartis Clinical Data Standards
NOVDD	Novartis Data Dictionary
OC/RDC	Oracle Clinical/Remote Data Capture
PA	posteroanterior
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRO	Patient Reported Outcome
RBC	red blood cell(s)
REB	Research Ethics Board
RV	Residual Volume
SAE	serious adverse event
s.c.	subcutaneous
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SD	standard deviation
SOM	site operations manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TLC	Total Lung Capacity

ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization

Pharmacokinetic definitions and symbols

AUClast	Area under the blood concentration-time curve from time zero to the last sampling time with a quantifiable concentration
AUCtau	Area under the blood concentration-time curve from time zero to the end of the dosing interval tau
Cmax	Maximum blood concentration
Clast	The last measurable concentration
Racc	The accumulation ratio
T1/2	Half-life
Tmax	Time postdose when maximum concentration occurs
Tlast	Time of last measurable concentration (when Clast occurs)

Protocol synopsis

Protocol number	CQBW276X2201
Title	A randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of inhaled QBW276 in patients with cystic fibrosis
Brief title	Safety, pharmacokinetics and pharmacodynamics study of inhaled QBW276 in patients with cystic fibrosis
Sponsor and Clinical Phase	Novartis Phase Ib/IIa (non-confirmatory)
Intervention type	Drug
Study type	Interventional
Purpose and rationale	To assess the clinical profile including safety, tolerability, pharmacokinetics of multiple doses of inhaled QBW276 in patients with cystic fibrosis to support potential clinical development in this indication.
Primary Objective(s)	Cohorts 1 and 2: To assess the safety, tolerability, and pharmacokinetics (PK) of multiple doses of inhaled QBW276 and its metabolites, over 1 or 2 weeks of treatment in patients with cystic fibrosis regardless of the underlying mutation Cohort 3: To evaluate the pharmacodynamic (PD) response to multiple doses of inhaled QBW276 in lung function (percent of predicted FEV_1) over 4 weeks of treatment compared with placebo in patients with cystic fibrosis that are homozygous for the F508del mutation
Secondary Objectives	Cohorts 1 and 2: To evaluate the PD response to multiple doses of inhaled QBW276 on change in lung function over 1 or 2 weeks of treatment from baseline compared with placebo in patients with cystic fibrosis Cohort 3: To assess the safety, tolerability, PK, and PD of multiple doses of inhaled QBW276 and its metabolites over 4 weeks of treatment per period in patients with cystic fibrosis who are homozygous for the F508del mutation.
Study design	Cohorts 1 and 2: Randomized, double-blind, placebo-controlled, multi-cohort, parallel arm, multiple dose study of inhaled QBW276 to assess its safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with cystic fibrosis over one or two weeks of therapy Cohort 3: Randomized, double-blind, placebo-controlled, cross-over study of inhaled QBW276 over 4 weeks of therapy to assess its pharmacodynamics, safety, tolerability, and pharmacokinetics in patients with cystic fibrosis who are homozygous for the F508del mutation
Population	Cohorts 1 and 2: 8 adults (≥ 18 years old) per cohort (N = 16), male and female patients with a diagnosis of cystic fibrosis, on standard of care treatment, regardless of their genotype Cohort 3: 24 adult (≥ 18 years old) male and female patients who are homozygous for the F508del mutation, on standard of care treatment (Up to 40 may be randomized to ensure 24 completers)

Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. 2. Male and female patients of age 18 and above with a confirmed diagnosis of cystic fibrosis as per the Cystic Fibrosis Foundation consensus guidelines (Farrell et al 2008). 3. For Cohort 3, male and female patients of age 18 and above with a confirmed diagnosis of cystic fibrosis, who are homozygous for the F508del mutation. 4. Should be on stable medical regimen in the 4 weeks prior to screening and baseline visits (Cohorts 1 & 2: Screening; Cohort 3: Screening (v1) and Baseline (v2)). 5. Should be established as "clinically stable to participate in the study" in the judgment of a site investigator at the screening and baseline visits. 6. FEV_1 must be between 40 and 100% predicted (inclusive) by NHANES/Hankinson standards at screening and baseline visits (may be repeated once at screening and once at baseline) (Cohorts 1 & 2: Screening; Cohort 3: Screening (v1) and Baseline (v2)). 7. $LCI_{2.5} \geq 8$ at screening if $FEV_1 > 80\%$ of predicted (Cohorts 1 & 2 only). 8. Must pass the metabolite screening assay prior to baseline visit 9. Must demonstrate ability to communicate well with the investigator, to understand and comply with the requirements of the study.
Exclusion criteria	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. The only exception to this is QBW276. If a patient has participated in cohort 1 of CQBW276X2201, he/she may qualify to participate in cohort 2 contingent upon approval from the sponsor, as long as he/she has been through a 4 week wash-out between dosing in the two cohorts, and has not experienced any significant AEs since enrollment in cohort 1. This will ensure that no patient receives more than 4 weeks of the investigational drug QBW276 in his/her lifetime until further supportive toxicology studies are conducted in the drug's development program. Note that patients who participate in cohorts 1 or 2 cannot participate in cohort 3. 2. History of significantly uncontrolled or untreated cardiovascular, adrenal or electrolyte abnormalities. 3. History of 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. 4. History of lung transplant. 5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation. 6. A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening or baseline visits: • PR > 200 msec • QRS complex > 120 msec • QTcF > 450 msec (males) • QTcF > 460 msec (females)

	7. History of adverse reaction or hypersensitivity to any of the study drugs, excipients (e.g. lactose) or to drugs of similar chemical classes, such as amiloride. 8. Any upper respiratory tract infection (e.g. common cold, influenza, sinusitis) or signs or symptoms thereof within 4 weeks prior to dosing that, in the opinion of the investigator, may jeopardize the patient or the study data in case of the patient's participation in the study. 9. Clinical evidence of liver disease or liver injury as indicated by clinically significant abnormal liver function tests as judged by the investigator, such as SGOT, SGPT, GGT, alkaline phosphatase, or serum bilirubin at screening or baseline visits. 10. Clinical evidence of significantly impaired renal function (i.e., CLr <30 mL/min) as indicated by abnormal creatinine or BUN values or clinically significant abnormal urinary constituents (e.g. albuminuria) at screening or baseline visits. 11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception for the duration of the study and for at least 3 days after the last dose of the study drug or until the end-of-study visit, whichever occurs later. 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) or tubal ligation at least six weeks prior to enrollment. In the case of oophorectomy alone, the reproductive status of the woman must have been confirmed by follow up hormone level assessment to be considered not of child-bearing potential. 12. Smokers (use of inhaled tobacco products in the previous 3 months). Urine cotinine levels will be measured during screening and at baseline for all patients. Smokers will be defined as any patient who reports inhaled tobacco use in the previous 3 months and/or who has a urine cotinine ≥ 500 ng/mL. (E-cigarettes and nicotine patches are permitted concomitant medications). 13. Sexually active males unless they agree to use a condom during intercourse for the duration of the study and for at least 3 days after the last dose of the study drug or until the end-of-study visit, whichever occurs later, and agree to not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of drug or its metabolites via seminal fluid. 14. Recent (within the last one year) and/or recurrent history of autonomic dysfunction (e.g. recurrent episodes of fainting, palpitations, etc.). 15. A positive HIV, Hepatitis B Ag or Hepatitis C Ab test result (unless previously treated and confirmed Hepatitis C cleared.) 16. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening and baseline visits. 17. Any changes in concomitant medications during the 4 weeks prior to screening and baseline visits. Over-the-counter oral and topical medications, such as paracetamol/acetaminophen, antihistamines, etc. may be used in line with the product labels.

	18. Patients on Prohibited medications as listed in Section 5.2 of the study protocol, and in the 'Guidance on Prohibited and Concomitant Medications' provided in the site operations manual (SOM), will be excluded from the study.
Investigational and reference therapy	QBW276 or placebo in multiple inhaled doses
Efficacy/PD assessments	• Percent predicted forced expiratory volume in 1 second (FEV_1) assessed by spirometry • Lung Clearance Index (LCI) assessed by Multiple Breath Nitrogen Washout (Cohorts 1 & 2 only) • Air trapping (RV/TLC) assessed by lung volume measurement (Cohorts Corporate Confidential Information
Safety assessments	• Vital signs • Physical exam • Safety laboratory tests • Pregnancy tests in women of child bearing potential • ECG • Metabolite screening assay • AE and SAE reporting
Other assessments	• Drug and metabolite pharmacokinetics Corporate Confidential Information
Data analysis	Cohorts 1 and 2: Adverse events will be counted within each cohort/dose-level by treatment received and corresponding percentages tabulated. Data from subjects receiving placebo may be pooled for cohorts 1 and 2 of the study. The numbers and percentages will be tabulated by system organ class, preferred term and severity. A patient with multiple adverse events within a body system is only counted once towards the total of this body system. Cohort 3: The percent of predicted FEV_1 measured on Days 7, 14, 21 and 28 of each treatment period at the study site will be analyzed using mixed effects model for repeated measurements. The model will include fixed effects for period, time (Days 7, 14, 21, 28), hypertonic saline use, treatment and treatment by time interaction term. Subject will be included as a random effect and time will be repeated within each patient by period interaction. Subject average baseline and period adjusted baseline will be fitted as covariates. The difference in adjusted means along with 80% two-sided confidence intervals together with standard error (SE) and P-value will be calculated for the contrast of QBW276 vs Placebo. These will be calculated at all time-points, and specifically at the primary time-point of interest (Day 28) using Placebo as the reference treatment.
Key words	Cystic fibrosis, inflammation, Percent of predicted FEV_1, LCI, CFQ-R

1 Introduction

1.1 Background

Cystic fibrosis (CF) is the most common lethal autosomal recessive hereditary disease of Caucasians, caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel resident on the surface of epithelial cells in several body organs such as the airways, intestine, pancreas, bile ducts, and kidney (O'Sullivan and Freedman 2009). With an incidence of 1 in 2,500 live births in Caucasians, CF is estimated to affect approximately 30,000 patients in the US and 70,000 patients worldwide (Cystic Fibrosis Foundation 2012a). Despite a consistent increase in the life expectancy of CF patients over the last three decades, predominantly due to the implementation of symptomatic therapies, the median predicted survival in the US is still only 35-40 years of age (Cystic Fibrosis Foundation 2012b). Although CF is a chronic disorder affecting the epithelial cells of multiple organs (e.g. lung, gastrointestinal tract, pancreas), >90% of morbidity and mortality in CF is currently associated with severe lung disease (Cystic Fibrosis Foundation 2012b). In the lungs, CF reduces the clearance of mucus which leads to an increased risk of bacterial and viral infections. In addition to the increased risk and therefore frequency of respiratory infections, CF airways are characterized by an exaggerated inflammatory response that eventually leads to the destruction of lung tissue and a progressive decline in lung function. There is no cure for CF. Standard of care therapies include mucolytics, antibiotics, and anti-inflammatory agents that treat the downstream disease processes that are secondary to the genetic defect. Ivacaftor, a specific CFTR potentiator, has been approved by health authorities for a small group of patients (< 10%) with one of 10 rare CF mutations. Combination therapy of Ivacaftor with Lumacaftor, a CFTR corrector, has recently been approved by some health authorities for patients with two copies of the F508del mutation (approximately 48% of all CF patients). It provides modest clinical benefit, but is ineffective in patients who carry only one copy of the F508del mutation (approximately 40% of all CF patients). Hence, there continues to be an unmet medical need for additional interventional agents to treat the majority of patients with CF.

It is now widely accepted that the defect in CFTR function leads to a dehydration of respiratory secretions (Donaldson and Boucher 2007). Normal CFTR protein function promotes anion and therefore fluid secretion into the airway lumen, a process that is balanced by the active absorption of Na^+ and therefore fluid by the epithelial sodium channel, ENaC. These ion transport processes maintain an adequate volume of airway surface liquid (ASL) in non-CF lungs to ensure the effective hydration and clearance of mucus by both mucociliary clearance (MCC) and cough clearance (CC) (Donaldson and Boucher 2007). In CF, CFTR-mediated anion secretion is impaired, thereby limiting the ability of the airway epithelium to secrete fluid into the airway lumen. Additionally, ENaC-mediated Na+ absorption is enhanced in CF, leading to an accelerated rate of fluid absorption. The net effect of the imbalance in these ion and fluid transport processes in CF is to reduce the volume of ASL available for the hydration of secreted mucus and consequently impairment in MCC (Donaldson and Boucher 2007).

A therapy designed to improve the hydration of respiratory secretions by blocking sodium reabsorption through durable attenuation of ENaC function is predicted to produce a sustained enhancement of mucociliary clearance, thereby reducing the frequency of respiratory infections

and slowing the decline in lung function (Hirsh 2002). This "rehydration" approach has been tested clinically in CF using inhaled amiloride, a direct blocker of the epithelial sodium channel (ENaC). Inhaled amiloride produced an enhancement of mucociliary clearance (App et al 1990), and initial promising reports regarding improvement in lung function (Knowles et al 1990); however with a prohibitively short duration of action in the airways and an estimated elimination half-life of around 23 minutes (Hofmann et al 1997) this compound lacked any robust clinical benefit (Pons et al 2000). Inhaled hypertonic saline, which increases ASL volume *in vitro* (Donaldson et al 2006), has been demonstrated to accelerate muco-ciliary clearance (MCC), reduce the frequency of pulmonary exacerbations, and improve lung function in CF (Elkins et al 2006 and Donaldson et al 2006) an early indication that an enhancement of MCC will be of clinical benefit in the disease. Unfortunately, hypertonic saline is often poorly tolerated in the clinic due to cough and bronchospasm, and thus there is a need for novel therapies targeting ENaC in the airway (Donaldson and Boucher 2007).

A potential consequence of an inhaled ENaC inhibitor is systemic exposure resulting in ENaC inhibition in the kidney. ENaC inhibition in the kidney can lead to hyperkalemia, hyponatremia, volume depletion, and a compensatory increase in aldosterone.

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On this basis, QBW276 represents a novel therapy with a potential for being disease-modifying in CF while avoiding the potential complications of hyperkalemia, hyponatremia, volume disturbance, and compensatory aldosterone elevation.

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1.2 Study purpose

The purpose of the study is to assess safety, tolerability, pharmacokinetics of multiple doses of inhaled QBW276 in patients with CF to support potential clinical development in this indication.

2 Study objectives

2.1 Primary objective(s)

Primary Objective: Cohorts 1 and 2	Endpoints

• To assess the safety, tolerability and PK of multiple doses of inhaled QBW276 and its metabolites over 1 or 2 weeks of treatment in patients with CF	• All safety assessments during the cohort period, including:
	  • Physical examination
	  • Hematology
	  • Blood chemistry (central and local labs)
	  • Urinalysis
	  • ECG evaluation
	  • Vital Signs
	  • AEs and SAEs
	• PK measurements

Primary Objective: Cohort 3	Endpoints
• To evaluate the pharmacodynamic response to multiple doses of inhaled QBW276 in lung function (percent of predicted FEV_1) over 4 weeks of treatment compared with placebo in patients with CF that are homozygous for the F508del mutation.	• % predicted FEV_1 (assessed by spirometry)

2.2 Secondary objective(s)

Secondary Objective: Cohorts 1 and 2	Endpoints
• To evaluate the pharmacodynamic response to multiple doses of inhaled QBW276 on change in lung function (percent of predicted FEV_1 and LCI) in patients with CF	• % predicted FEV_1 (assessed by spirometry) • $LCI_{2.5}$ (assessed by Multiple Breath Nitrogen Washout [MBNW]) if FEV_1 at screening is > 80% of predicted
Secondary Objective: Cohort 3	**Endpoints**

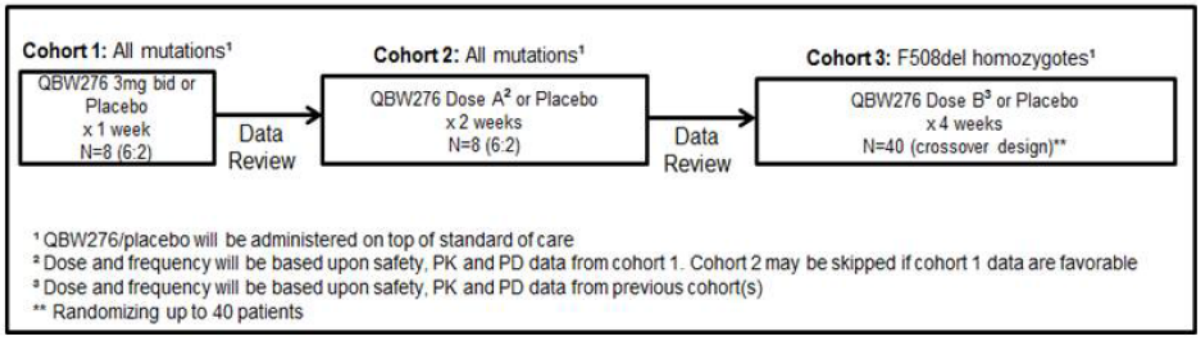
• To assess the safety, tolerability, PK and PD of multiple doses of inhaled QBW276 and its metabolites over 4 weeks of treatment in patients with CF who are homozygous for the F508del mutation	• All safety assessments during the cohort period, including:
	  • Physical examination
	  • Hematology
	  • Blood chemistry
	  • Urinalysis
	  • ECG evaluation
	  • Vital Signs
	  • AEs and SAEs
	• PK measurements

3 Investigational plan

3.1 Study design

This is a study of multiple doses of inhaled QBW276 in patients with CF on top of Standard of Care, including hypertonic saline, CFTR potentiators and correctors, if applicable. The study will be divided into three cohorts. Cohorts 1 and 2 are designed to be a randomized, double-blind, placebo−controlled, parallel arm multiple ascending dose study of the safety, tolerability, PK and preliminary efficacy of inhaled QBW276 over 1 week (cohort 1) and 2 weeks (cohort 2) in patients with CF regardless of their genotype. The primary rationale for cohorts 1 and 2 will be to assess PK, safety and tolerability in CF. Cohort 3 is a randomized, double-blind, placebo-controlled, cross-over design multiple dose study of the efficacy, safety, tolerability, and PK of inhaled QBW276 over 4 weeks in patients with CF who are homozygous for the F508del mutation. The primary rationale for cohort 3 will be to assess efficacy in a high unmet need CF patient population.

Figure 3-1 Schematic for study design



Cohort 1 will receive 3 mg bid dose (6 mg/day) or placebo over 1 week. This dose selection is based on safety and tolerability data obtained from healthy volunteers in the first-in-human CQBW276X2101 study. Upward, downward, or repeat dosing will continue in cohorts 2 and 3,

as long as the systemic exposure cap based on pre-clinical data or a clinical maximum tolerated dose (MTD) is not exceeded. Cohorts 1 and 2 will enroll 8 patients each, with 6 patients randomized to receive active drug and 2 patients randomized to receive matching placebo. Cohort 1 will be dosed for 1 week while cohort 2 will be dosed for 2 weeks. Cohort 2 will be initiated only after cohort 1 has completed dosing. Cohort 2 may be skipped if safety, tolerability, PK and PD data from cohort 1 are found favorable to proceed directly to cohort 3. In cohorts 1 and 2, patients may be replaced if they do not complete the study duration for reasons other than safety to obtain 8 completers in each cohort. If a patient has participated in cohort 1, he/she may qualify to participate in cohort 2 contingent upon approval from the sponsor, as long as he/she has been through a 4 week wash-out between dosing in the two cohorts, and has not experienced any significant AEs since enrollment in cohort 1. This will ensure that no patient receives more than 4 weeks of the investigational drug QBW276 in his/her lifetime until further supportive toxicology studies are conducted in the drug's development program.

NOTE: No patient randomized to cohort 1 or 2 will be eligible for cohort 3.

Cohort 1 and 2

Cohorts 1 and 2 will consist of a 21 day screening period followed by a baseline visit and a 7 or 14 day Treatment Period in cohort 1 and 2, respectively Adequate windows will be provided for patient's convenience. QBW276 will be administered on top of the patient's usual standard of care medications.

Study inclusion/exclusion criteria as well as medication use will be assessed at screening. Patients who meet the inclusion/exclusion criteria at screening will report to the study site on Day -1 at a time specified by the investigator, for the baseline assessments. All baseline safety evaluation results must be available prior to dosing on Day 1, hence, Day -1 assessments can be carried out up to 72 hours prior to Day 1 dosing.

Patients who meet all of the inclusion and none of the exclusion criteria at baseline will then report to the study site on Day 1 and will remain in the clinic until at least 6 hours after the first dose in the morning.

On Day 1, pre-dose safety, biomarker, PK blood draw, and urine collection will be performed. Following the pre-dose procedures, subjects will be randomized. Post-dose evaluations will include routine safety evaluations and blood for PK assessments. The patients will be asked to return to the study site for follow-up visits as specified on the respective assessment schedules (Section 8).

Safety will be monitored by assessment of vital signs, physical examination, ECG, clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), urine electrolytes, aldosterone in plasma, lung function, and monitoring of adverse events (AEs) throughout the study. PK (drug and metabolites) and safety biomarkers (blood and urine electrolytes and plasma aldosterone) measured in cohorts 1 and 2 will be compared with data from the healthy volunteer study.

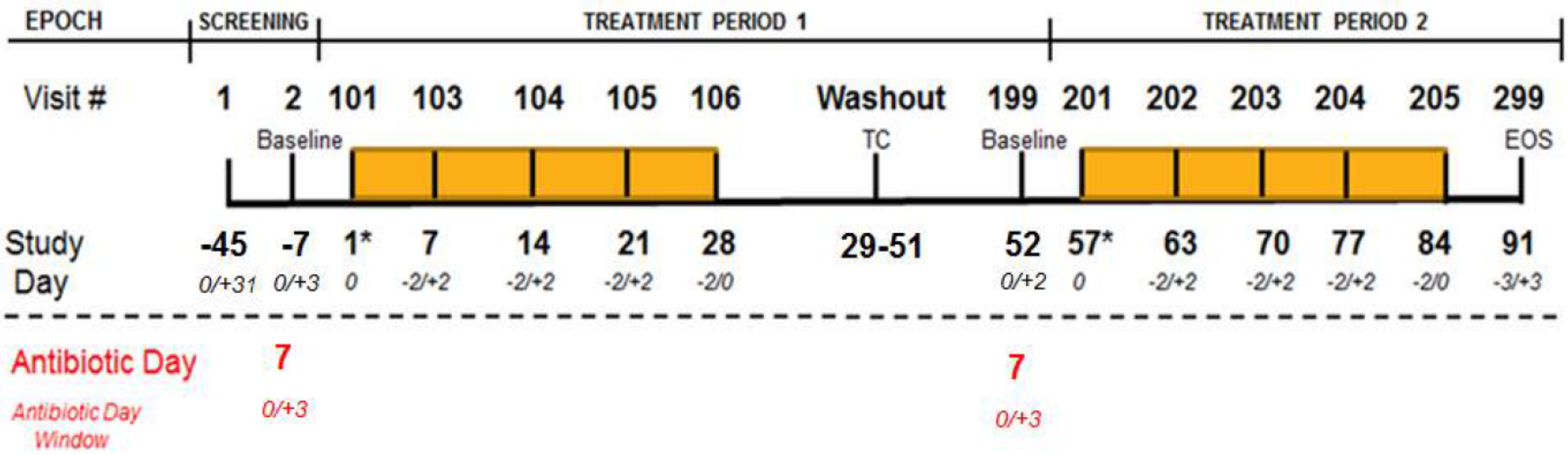
A blinded review of data will be conducted after completion of each cohort prior to initiation of the next cohort. The Sponsor (medically qualified representative) in conjunction with the designated site Investigator(s) will review blinded data (including lung function, AEs, vital

signs, safety laboratory parameters including aldosterone values, and PK). An external data monitoring committee (DMC) will also be assembled to monitor study safety data as per an approved charter. After the first 4 patients in Cohort 1 have completed the Day 7 study assessments, the PK data may be reviewed by the study pharmacokineticist to compare exposure levels with previously observed data in healthy patients.

Cohort 3

Dosing in cohort 3 will not commence until the Sponsor (medically qualified representative) in conjunction with the designated site Investigator(s) have reviewed all available safety, tolerability, PK, and PD data from cohorts 1 and/or 2. Endorsement for the dose selected for cohort 3 will also be sought from the DMC members per the DMC charter.

Figure 3-2 Schematic for Cohort 3 study design



For Cohort 3, patients will be randomized to one of two treatment sequences: QBW276 in Period 1 and Placebo in Period 2 or Placebo in Period 1 and QBW276 in Period 2. Based on drop-out rates observed during conduct of the study, up to 40 patients will be randomized to ensure that at least 24 patients complete the study. After a 45 day screening period, patients who meet all inclusion and exclusion criteria will receive drug for 4 weeks and placebo for 4 weeks, separated by a washout period of approximately 3 to 4 weeks in patients who cycle inhaled antibiotics. Washout period may be shortened to 2 weeks in patients who do not cycle inhaled antibiotics. QBW276 will be administered on top of the patient's usual standard of care medications. For patients on cyclic inhaled antibiotics, baseline for periods 1 and 2 will commence on approximately day 7 (0/+3) of the patient's standard of care cyclic inhaled antibiotic regimen. Patients who use the same inhaled antibiotic throughout the year may start the study on any antibiotic day.

Screening and baseline visits for cohort 3 will be similar to the respective visits in cohorts 1 and 2. On Day 1 of cohort 3, pre-dose safety, efficacy Corporate Confidential Information will be performed. Following the pre-dose procedures eligible patients will be dosed for up to 28 days. Post-dose evaluations will include routine safety evaluations and blood for PK assessments. The patients will be asked to return to the study site for follow-up visits on Days 7, 14, 21, and 28 after which they will undergo an approximately 3 to 4 week wash-out period (may be shortened to 2 weeks in patients who do not cycle inhaled antibiotics) prior to cross-over to the opposite arm, and follow a similar visit schedule until End of Study assessment approximately 7 days after the last visit in the second period. All patients will undergo the same assessments regardless of their dose.

Efficacy will be evaluated by spirometry and responses to the respiratory domain of the CFQ-R. Safety will be monitored by assessment of vital signs, physical examination, ECG, clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), urine electrolytes, aldosterone in plasma, and monitoring of adverse events (AEs) throughout the study.

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If a maximum tolerated dose for patients with CF (MTD) is identified in cohorts 1 or 2 on the basis of dose-limiting toxicity, the predicted exposure at the maximum planned dose in cohort 3 shall not exceed the exposure at the MTD. If an MTD is not defined in cohorts 1 and 2, the maximum planned dose in cohort 3 shall not exceed the systemic exposure cap based on pre-clinical data.

3.2 Rationale for study design

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Cohort 3 is designed as a cross-over study which is a more powerful design requiring fewer patients than a parallel group design. Parallel group designs have significant between patient variability in percent of predicted FEV_1 (primary outcome); hence, a cross-over design will allow for each patient to be his/her own control.

The use of a placebo arm in both parts of the study is to provide a comparison group for an unbiased collection of safety, tolerability, PK/ , and efficacy data in a blinded manner.

The rationale to allow CFTR modulators (correctors, potentiators, etc), chronic inhaled and systemic antibiotics Corporate Confidential Information during the study is related to the fact that many patients are/will be treated with these drugs as routine standard of care. Some CF patient's standard of care regimen may include treatment with systemic antibiotics on a chronic basis. Some CF patients with chronic respiratory infections are prescribed inhaled antibiotics (for instance Tobramycin or vancomycin) which are alternately cycled after 4 weeks of therapy, or patients may have a 4 week antibiotic holiday between two 4 week antibiotic cycles.

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3.3 Rationale of dose/regimen, duration of treatment

Cohorts 1 and 2: Up to 16 patients with CF (8 patients in each cohort, regardless of genotype) will complete 7 to 14 days of inhaled QBW276 or placebo via the concept 1 inhaler. Cohort 1 will receive 3 mg bid dose, which is based on safety, tolerability, PK and adverse event data obtained from the CQBW276X2101 healthy volunteer study.

Cohort 3: Cohort 3 will be restricted to CF patients who are homozygous for the F508del mutation, Corporate Confidential Information
This may also help reduce variability in baseline characteristics of patients in this small study. Patients will receive 4 weeks of drug and 4 weeks of placebo, separated by a washout period of approximately 3 to 4 weeks in patients who cycle inhaled antibiotics. Washout period may be shortened to 2 weeks in patients who do not cycle inhaled antibiotics. For patients on cyclic inhaled antibiotics, the baseline visit will be on approximately the 7^{th} day (0/+3 days) of inhaled antibiotic use during their 28 day antibiotic cycle. Patients who use the same inhaled antibiotic throughout the year may start the study on any antibiotic day. Patients will take their inhaled antibiotic therapy at approximately the same time during the study as they would usually at home Corporate Confidential Information

Cohort 1 - The first cohort will be dosed at 3 mg bid to begin assessment of safety and tolerability in CF because this dose has been Corporate Confidential Information and found to be safe and well tolerated. Corporate Confidential Information

The dose and frequency will be proposed by the sponsor at the data review, and will require approval from the designated site Investigator(s) and endorsement from the independent DMC. The maximum dose in cohort 3 will be expected to not exceed 6 mg bid. Corporate Confidential Information

PK data will be assessed after each dose cohort completes the study to confirm that an appropriate exposure margin exists before escalating to the next dose level.

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Cohort 3 –The dose selected for cohort 3 will be one that is expected to be safe and well-tolerated over 4 weeks of treatment based on blinded data obtained from cohorts 1 and 2 after 7 to 14 days of treatment. If a maximum tolerated dose for patients with CF (MTD) is identified in cohorts 1 or 2 on the basis of dose-limiting toxicity, the predicted exposure at the maximum planned dose in cohort 3 shall not exceed the exposure at the MTD. If an MTD is not defined

in cohorts 1 or 2, the maximum planned dose in cohort 3 shall not exceed the systemic exposure cap based on pre-clinical data. The efficacy of the proposed dose will be justified by the lung function measurements which will be conducted during cohorts 1 and 2. Corporate Confidential Information

3.4 Rationale for choice of comparator

This is a placebo controlled study. The use of a double blind placebo arm as a comparator is to provide a comparison group for an unbiased collection of safety and tolerability data.

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3.6 Risks and benefits

While patients who participate in the study may notice an improvement in their symptoms and/or lung function, this is not expected because of the exploratory nature of this study. QBW276 has been safe and well tolerated at doses examined and the risk/benefit assessment remains supportive for examination in patients with CF.

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The risk to patients in this trial will be minimized by adherence to the eligibility criteria, close clinical and laboratory monitoring, stopping rules and dosing well within the safety margins of the systemic exposure cap determined from pre-clinical toxicity studies. Patients will be closely monitored for changes in vital signs, serum electrolytes, ECG intervals and lung function. Plasma aldosterone will be monitored between cohorts during the study.

A maximum of 333 mL and 371 mL of blood is planned to be collected for Cohorts 1 and 2 over a period of 18 (+21) and 25(+21) days, respectively. A maximum of 421 mL of blood is planned to be collected over a period of 105 (+16) days in cohort 3. Additional samples for clinical monitoring of any abnormal laboratory values may be collected. This is not considered to be a risk for this population.

Women of child bearing potential should be informed that taking the study drug 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 pre-specified contraception requirement for the duration of the study and for at least 3 days after the last dose of the study drug or until the end-of-study visit, whichever occurs later. If there is any question that the patient will not reliably comply, they should not be randomized in the study.

Refer to exclusion criteria for further details in Section 4.2.

There may be unknown risks of QBW276 which may be serious and unforeseen.

4 Population

The study population will be comprised of male and female patients aged 18 and above with a diagnosis of CF. Patients in cohort 3 will be restricted to those who are homozygous for the F508del mutation.

The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible patients.

Patient selection is to be established by checking through all eligibility criteria at screening and baseline. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a patient from enrollment into the study.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients of age 18 and above with a confirmed diagnosis of CF, all mutations as per the Cystic Fibrosis Foundation consensus guidelines (Farrell et al 2008).
3. For Cohort 3, male and female patients of age 18 and above with a confirmed diagnosis of CF, who are homozygous for the F508del mutation.
4. Should be on stable medical regimen in the 4 weeks prior to screening and baseline visits (Cohorts 1 & 2: Screening; Cohort 3: Screening (v1) and Baseline (v2)).
5. Should be established as "clinically stable to participate in the study" in the judgment of a site investigator at the screening and baseline visit.
6. FEV_1 must be between 40 and 100% predicted (inclusive) by NHANES/Hankinson standards at screening and baseline visits (may be repeated once at screening and once at baseline) (Cohorts 1 & 2: Screening; Cohort 3: Screening (v1) and Baseline (v2)).
7. $LCI_{2.5} \geq 8$ at screening if $FEV_1 > 80\%$ (Cohorts 1 & 2 only).

8. Must pass the metabolite screening assay prior to baseline visit.
9. Must demonstrate ability to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

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. The only exception to this is QBW276. If a patient has participated in cohort 1 of CQBW276X2201, he or she will qualify to participate in cohort 2 contingent up on approval from the sponsor, as long as he/she has been though a 4 week wash-out between dosing in the two cohorts, and has not experienced any significant AEs since enrollment in cohort 1. This will ensure that no patient receives more than 4 weeks of the investigational drug QBW276 in his lifetime until further supportive toxicology studies are conducted in the drug's development program. Note that patients who participate in cohorts 1 or 2 cannot participate in cohort 3.
2. History of significantly uncontrolled or untreated cardiovascular, adrenal or electrolyte abnormalities.
3. History of 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.
4. History of lung transplant.
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation.
6. A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening or baseline visits:
    - PR > 200 msec
    - QRS complex > 120 msec
    - QTcF > 450 msec (males)
    - QTcF > 460 msec (females).
7. History of adverse reaction or hypersensitivity to any of the study drugs, excipients (e.g. lactose) or to drugs of similar chemical classes, such as amiloride.
8. Any upper respiratory tract infection (e.g. common cold, influenza, sinusitis) or signs or symptoms thereof within 4 weeks prior to dosing that, in the opinion of the investigator, may jeopardize the patient or the study data in case of the patient's participation in the study.
9. Clinical evidence of liver disease or liver injury as indicated by clinically significant abnormal liver function tests as judged by the investigator, such as SGOT, SGPT, GGT, alkaline phosphatase, or serum bilirubin at screening or baseline visits.

10. Clinical evidence of significantly impaired renal function (i.e., CLr <30 mL/min) as indicated by abnormal creatinine or BUN values or clinically significant abnormal urinary constituents (e.g., albuminuria) at screening or baseline visits.
11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception for the duration of the study and for at least 3 days after the last dose of the study drug or until the end-of-study visit, whichever occurs later.

    Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. 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 m prior to screening). For female patients in the study, the vasectomized male partner should be the sole partner for that patient.
    - Use of oral, injected or implanted combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

    In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

    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) or tubal ligation at least six weeks prior to enrollment. 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.
12. Smokers (use of inhaled tobacco products in the previous 3 months). Urine cotinine levels will be measured during screening and at baseline for all patients. Smokers will be defined as any patient who reports inhaled tobacco use in the previous 3 months and/or who has a urine cotinine $\geq$ 500 ng/mL. (E-cigarettes and nicotine patches are considered permitted concomitant medications).
13. Sexually active males unless they agree to use a condom during intercourse for the duration of the study and for at least 3 days after the last dose of the study drug or until the end-of-study visit, whichever occurs later, and agree to not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of drug via seminal fluid.
14. Recent (within the last one year) and/or recurrent history of autonomic dysfunction (e.g., recurrent episodes of fainting, palpitations, etc.).

15. A positive HIV, Hepatitis B Ag or Hepatitis C Ab test result (Unless previously treated and confirmed Hepatitis C cleared).
16. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening and baseline visits.
17. Any changes in concomitant medications during the 4-week prior to screening and baseline visits. Over-the-counter oral and topical medications, such as paracetamol/acetaminophen, antihistamines, etc may be used in line with the product labels.
18. Patients on Prohibited medications as listed in Section 5.2 of the study protocol and in the 'Guidance for Prohibited and Concomitant Medications' provided in the SOM, will be excluded from the study.

Note: In the case where a safety laboratory assessment at screening and/or initial baseline is outside of the normal range and considered clinically significant, the assessment may be repeated once prior to randomization. Non-clinically significant abnormal values need not be repeated if this is deemed appropriate by the investigator.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for Study Patients

During recruitment, screening/informed consent review, and baseline visit, the patients must be informed and reminded of the following restrictions:

5.1 Contraception requirements

Please refer to exclusion criteria (Section 4) for details of contraception requirements for the study.

5.2 Prohibited treatment and rescreening

If a patient experiences a respiratory infection or exacerbation which requires systemic antibiotics and/or systemic glucocorticoids at any time, he/she will be discontinued from the study. He/she may be rescreened if he/she subsequently fulfills the required inclusion/exclusion criteria for the study. Note that chronic inhaled and/or systemic antibiotics are permitted as concomitant medications during the study, if they are considered the patient's standard of care at screening and baseline visits.

If a patient is deemed a screened failure, he/she maybe rescreened once based on the investigator's judgement.

Patients who have failed to meet ATS requirements for acceptability/reproducibility for Spirometry or MBNW (Cohorts 1 & 2), will be allowed one additional repeat testing session at Screening and/or Baseline in order to meet inclusion criteria. For additional details on rescreening and retesting, please refer to the site operations manual (SOM).

Patients should refrain from using their short and long acting bronchodilators for 6, 12 or 24 hours as described in the site operations manual (SOM) to enable measurement of trough

lung function. If the patient is not able to withhold rescue medications due to bothersome symptoms, the patient may be rescheduled if deemed appropriate by the investigative site.

Butylcholinesterase and acetylcholinesterase inhibitors are prohibited because QBW276 is hydrolyzed mainly by butylcholinesterase and acetylcholinesterase enzymes. Patients who are either on these inhibitors or patients who fail the butylcholinesterase screening assay will be excluded from the study. The following butylcholinesterase and acetylcholinesterase inhibitors are prohibited:

- Aclidinium bromide
- Amitriptyline
- Citalopram
- Donepezil
- Ecothiopate
- Galantamine
- Lovastatin
- Neostigmine
- Rivastigmine
- Simvastatin
- Sertraline
- Tacrine

Patients who are prescribed these medications during the course of the study should be immediately discontinued from the study and the Sponsor must be informed. The list of prohibited medications is not inclusive and subjects may be exposed to non-medicinal butyrylcholinesterase inhibitors, such as insecticides, which should be monitored.

5.3 Dietary restrictions and smoking

- Smokers (use of inhaled tobacco products in the previous 3 months) will be excluded from participating in the study. Urine cotinine levels will be measured during screening and at baseline for all patients. Smokers will be defined as any patient who reports inhaled tobacco use in the previous 3 months and/or who has a urine cotinine $\geq$ 500 ng/mL. (E-cigarettes and nicotine patches are permitted concomitant medications).
- No alcohol for 48 hours prior to all clinic visits and while in the clinic. During the treatment phase of the study, alcohol consumption is restricted to no more than 2 regular drinks/day.
- Caffeine restriction should apply for 4 hours prior to the start of lung function testing. Patients should refrain from drinking caffeine for 4 hours prior to the start of these tests.

6 Treatment

6.1 Study treatment

Details on the storage and management of study medication, randomization, and instructions for prescribing and taking study treatment are outlined in the SOM.

6.1.1 Investigational treatment

The investigational drug QBW276 1.5 mg strengths and matching placebo capsules, and if required, 0.3 mg strengths and matching placebo capsules) will be prepared by Novartis and supplied to the Investigator in blister packs. Novartis will also supply the Concept1 inhalation devices to the Investigator.

6.1.2 Additional study treatment

The patient or the Investigational site is responsible for sourcing all additional study treatments listed in the protocol, including but not limited to:

- Hypertonic Saline
- Inhaled antibiotics
- Rescue inhalers

6.2 Treatment arms

Cohort 1 and 2:

Patients will be assigned to one of the following 2 treatment arms in a ratio of 3:1. In each cohort (n=8), there will be 6 patients randomized to receive QBW276 and 2 patients randomized to receive Placebo.

Study treatments are defined as:

Cohort 1:

- QBW276 3mg bid
- Placebo to QBW276 3mg bid

Cohort 2:

- QBW276 Dose 6 mg bid
- Placebo to QBW276 Dose 6 mg bid

Cohort 3:

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Patients will be randomly assigned to one of the following 2 treatment sequences.

Study treatments are defined as:

- A: QBW276 Dose B (no more than 6 mg bid)
- B: Placebo to QBW276 Dose B (no more than 6 mg bid)

6.3 Permitted dose adjustments and interruptions of study treatment

In case of notable adverse events, safety concerns and/or based on pharmacokinetic data during review of data at the end of a cohort, the following changes to the next planned dose level may be considered:

- Administration of a dose below the starting dose
- Administration of an intermediate dose between the current and preceding dose
- Administration of an intermediate dose between the current and next planned dose
- Repeated administration of the current dose
- Termination of any further doses

These changes must be recorded on the Dosage Administration Record CRF.

6.4 Treatment assignment

If a patient is deemed eligible for enrollment into the study, they will be randomized and treatment will be assigned via the IRT system

6.5 Treatment blinding

This is a double blind study: Patients, investigator staff, and persons performing the assessments will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: PK bioanalyst, clinical pharmacologist, and persons involved in the interim analyses as specified in the SOM and (2) The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, schedule of administration, appearance, taste and odor.

Unblinding will only occur in the case of patient emergencies (see Section 6.6), at the time of the interim analysis and at the conclusion of the study.

Further information regarding blinding (and unblinding) is presented in the SOM.

6.6 Emergency breaking of assigned treatment code

Emergency unblinding should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code break can be performed via the IRT system. The investigator must also immediately inform the Novartis local monitor that emergency unblinding has occurred via IRT.

It is the investigator's responsibility to ensure that there is a procedure in place to allow unblinding via the IRT system in case of emergency. If appropriate, the investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable.

The appropriate site personnel and the sponsor will do an assessment after an emergency unblinding to assess whether or not study drug should be discontinued for a given patient.

6.7 Treatment exposure and compliance

As dose administration will occur in the research clinic and at home, compliance will be confirmed as fully as possible by site staff checking medication as it is returned by the patient (any doses administered in the clinic will be checked by site staff). The patient will inhale the first dose at the research clinic and receive training at the research clinic on the use of the inhaler and study medication.

Patients will also document their study drug administration time in the clinic and at home on a paper diary.

The correct allocation of study drug and number of doses taken by the patient will be confirmed via drug accountability procedures.

Site staff will enter drug administration information (at least date/time/dose) into the eCRF to ensure a complete record of dosing for each patient.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients treated with QBW276, as detailed in Section 8.5.

6.8 Recommended treatment of adverse events

There is no specific anti-dote for the compound. In case of an overdose or other adverse events such as hyperkalemia, the patient should be monitored and managed at the discretion of the treating physician. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.9 Rescue and bronchodilator medication

Patients should refrain from using their short and long acting bronchodilators for 6, 8, 12 or 24 hours as described in the SOM to enable measurement of trough lung function. If the patient is not able to withhold rescue medications due to bothersome symptoms, the patient may be rescheduled if deemed appropriate by the investigative site. If rescheduling the patient is not feasible, the visit may continue but the use of a bronchodilator during the restricted time prior to PFT assessments must be noted in the CRF, and captured in the nDD EasyOne Pro Lab device.

If this use occurs after the start of study treatment (i.e. after Visit 101), it also must be documented in the Concomitant medications/Significant non-drug therapies CRF.

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Hence, patients are permitted to use their short or long-acting bronchodilator immediately prior to administration of the study drug if they wish to, as long as pre-dose lung function measurements have been completed during study visits. The study staff will have the opportunity to perform unscheduled spirometry maneuvers if they wish to evaluate the patient for post-drug bronchospasm based on the patient's signs and symptoms, and administer additional bronchodilator if needed. These events may be captured as adverse events if appropriate.

Patients who take multiple inhaled medications as part of their standard of care may continue to do so

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6.10 Concomitant treatment

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Please refer to Section 5.2 and the SOM for permitted and prohibited concomitant medications for study participants.

7 Discontinuation and study completion

7.1 Discontinuation of study treatment

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

Study treatment **must** be discontinued under the following circumstances:

- Patient withdraws consent.
- Pregnancy.
- A serious adverse event that is suspected of being related to study drug.
- The site investigator judges that continuation would be detrimental to the patient's well-being.

- Emergence of the following adverse events:
  - On-treatment increase in QTcF > 60 ms from baseline
  - Clinically significant and/or persistent serum electrolyte or other laboratory abnormalities.
- If a patient has an exacerbation during the study, the patient should be discontinued and may be replaced.
- Use of prohibited treatment as per Section 5.2 and the Prohibited and Concomitant Medication Guidance provided in the SOM.
- Any other protocol deviation that results in a significant risk to the patient's safety.
- Investigator's discretion if the physician perceives a significant risk to the patient's safety or study data integrity.
- Cohorts 1 and 2: if a patient misses ≥ 4 doses, either between visits or consecutive doses overall.
- Cohort 3: if a patient misses ≥ 8 doses, either between visits or consecutive doses overall.

The appropriate personnel from the site and Novartis will assess whether treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

The appropriate personnel from the site and Novartis will assess whether treatment should be discontinued for a patient who has been prescribed a new standard of care treatment or concomitant medication which may impact the integrity of study data.

Patients 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 7.4). Where possible, patients should return for the End of Study assessments listed in the assessment table. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact them as specified in Section 7.3.

7.2 Study completion and post-study treatment

Each patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion is defined as when the last patient completes their End of Study 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.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

7.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone

calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.4 Withdrawal of consent

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

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

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

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

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

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

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

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

For EU and 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.

7.5 Study Stopping rules

The study will be placed on clinical hold, no dose escalation will occur in any subsequent cohorts and the current dose level will not be repeated if any one of the following occur:

(a) One SAE occurs in a cohort that is suspected of being related to study drug by the Sponsor, pending full safety review.

(b) Two similar AEs which are severe (Grade 3 or greater) occur in two patients in the same cohort and are suspected of being related to study drug by the Sponsor, pending full safety review.

(c) If the mean systemic exposure for the parent drug or metabolites at the current or next dose level (using either non-compartmental or PK modeling methods) is observed or predicted to exceed the exposure at the AUC0-24 at steady state at the NOAEL of 5.04 mg/kg/day in the rat preclinical toxicology study.

7.6 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, patients should be seen as soon as possible and treated as a prematurely withdrawn patient. End of study visit should be completed as soon as possible. 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 patient's interests.

The Health Authorities and IRBs/IECs will be informed in case early termination of the trial.

8 Procedures and assessments

Table 8-1 Assessment schedules

Cohort 1 - 7 Days

EPOCH	SCREENING		TREATMENT			
Visit Name	Screening	Baseline	Day 1	Day 2	Day 7	ET/EOS[2]
Visit Numbers[1]	1	2	101	102	103	199
Study Day(s)	-28 to -7	-1 -2 +0	1	2 -0 +1	7 -2 +2	11 -2 +2
Informed consent	X					
Inclusion / Exclusion criteria	X	X				
Metabolite Screening Assay	X					
Corporate Confidential Information	X					
Randomization			X[4]			
Study Drug Administration in Clinic in the Morning			X	X	X	
Medical history/current medical conditions	X	X				
Concomitant therapies	X	X	X	X	X	X
Demography	X					
Vital Signs	See table below					
Body height	X					
Body weight	X	X			X[3]	X
Physical examination	X	X			X[3]	X
Spirometry	X	X	X[3]	X[3]	X[3]	X
Lung Volumes	X[9]	X			X[3]	X
Multiple Breath Nitrogen Washout (MBNW)	X[9]	X			X[3]	X
ECG evaluation	X	X	X[3]		X[3]	X

EPOCH	SCREENING		TREATMENT			
Visit Name	Screening	Baseline	Day 1	Day 2	Day 7	ET/EOS[2]
Visit Numbers[1]	1	2	101	102	103	199
Study Day(s)	-28 to -7	-1 -2 +0	1	2 -0 +1	7 -2 +2	11 -2 +2
Corporate Confidential Information		X			X	X
	See table below					
PK blood collection[6]	See table below					
Central Lab Blood Chemistry[7]	X	X	X[3]	X[3]	X[3]	X
Central Lab Hematology	X	X	X[3]		X[3]	X
Hepatitis screen	X					
Corporate Confidential Information			X			
Local Lab Blood Chemistry[8]	See table below					
Alcohol Test, Drug Screen, and Cotinine Test	X	X				X
HIV screen	X					
Pregnancy test	X[10]	X[11]			X[3,11]	X[11]
Urinalysis	X	X	X[3]		X[3]	X
Adverse Events	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X
Study Drug Questionnaire						X
Phase / Study completion information		X[12]				X

[1] Visit structure given for internal programming purpose only
[2] Early Termination/End of Study completion (study/treatment discontinuation and premature subject withdrawal should complete all these assessments)
[3] Pre-dose
[4] May be completed any time between visit 2 and 101 after eligibility is confirmed

0m sample is taken pre-dose; all post-dose samples (15 minutes – 6 hours) are timed from the start of inhalation
[7] Central lab collection: Sodium, potassium, bicarbonate, creatinine, BUN, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, PT/INR, amylase, lipase, CK, glucose, total cholesterol, and triglycerides
[8] Local lab collection: sodium, potassium, chloride, bicarbonate
[9] Only to be performed if subject's FEV1 is >80% of predicted at Screening
[10] Serum pregnancy test
[11] Urine pregnancy test/dipstick
[12] Screening phase completion

Cohort 1 - Details for highly repetitive assessments

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EPOCH	Visit Name	Visit Number	Day	Time (post-dose)	Vital Signs	PK blood collection	Local Lab Blood Chemistry
SCREENING	Screening	1	-28 to -7	-	X		
	Baseline	2	-1 -2 +0	-	X		
TREATMENT	Day 1	101	1	0m[1]	X	X	X
				15m		X	
				30m		X	X
				1h	X	X	X
				2h		X	X
				4h		X	X
				6h	X	X	X
	Day 2	102	2 -0 +1	0m[1]	X	X	
	Day 7	103	7 -2 +2	0m[1]	X	X	X
				15m		X	
				30m		X	X
				1h	X	X	X
				2h		X	X
				4h		X	X
				6h	X	X	X
	ET / EOS[2]	199	11 -2 +2	-	X	X	

[1] 0 minute (0m) sample is taken pre-dose; all post-dose samples (15 minutes – 6 hours nhalation of the morning dose

[2] Early termination/Study completion (study/treatment discontinuation and premature subject withdrawal should complete all these assessments)

Cohort 2 - 14 Days

EPOCH	SCREENING		TREATMENT				
Visit Name	Screening	Baseline	Day 1	Day 2	Day 7	Day 14	ET/EOS[2]
Visit Numbers[1]	1	2	101	102	103	104	199
Study Day(s)	-28 to -7	-1 -2 +0	1	2 -0 +1	7 -2 +2	14 -2 +2	18 -2 +2
Informed consent	X						
Inclusion / Exclusion criteria	X	X					
Metabolite Screening Assay	X						
Corporate Confidential Information	X						
Randomization			X[3]				
Study Drug Administration in Clinic in the Morning			X	X	X	X	
Medical history/current medical conditions	X	X					
Concomitant therapies	X	X	X	X	X	X	X
Demography	X						
Vital Signs	See table below						
Body height	X						
Body weight	X	X			X[4]	X[4]	X
Physical examination	X	X			X[4]	X[4]	X
Spirometry	X	X	X[4]	X[4]	X[4]	X[4]	X
Lung Volumes	X[6]	X			X[4]	X[4]	X
Multiple Breath Nitrogen Washout (MBNW)	X[6]	X			X[4]	X[4]	X
ECG evaluation	X	X	X[4]		X[4]	X[4]	X
Corporate Confidential Information		X			X	X	X
	See table below						
PK blood collection[7]	See table below						
Central Lab Blood Chemistry[8]	X	X	X[4]	X[4]	X[4]	X[4]	X
Central Lab Hematology	X	X	X[4]		X[4]	X[4]	X

EPOCH	SCREENING		TREATMENT				
Visit Name	Screening	Baseline	Day 1	Day 2	Day 7	Day 14	ET/EOS[2]
Visit Numbers[1]	1	2	101	102	103	104	199
Study Day(s)	-28 to -7	-1 -2 +0	1	2 -0 +1	7 -2 +2	14 -2 +2	18 -2 +2
Hepatitis screen	X						
Corporate Confidential Information			X				
Local Lab Blood Chemistry[9]	See table below						
Alcohol Test, Drug Screen, and Cotinine Test	X	X					X
HIV screen	X						
Pregnancy test	X[10]	X[11]			X[4,11]	X[4,11]	X[11]
Urinalysis	X	X	X[4]		X[4]	X[4]	X
Adverse events	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X
Study Drug Questionnaire							X
Phase / Study completion information		X[12]					X

[1] Visit structure given for internal programming purpose only
[2] Early termination/Study completion (study/treatment discontinuation and premature subject withdrawal should complete all these assessments)
[3] May be completed any time between visit 2 and 101 after eligibility is confirmed
[4] Corporate Confidential Information

Only to be performed is subject's FEV1 is >80% of predicted at Screening
[7] 0m sample is taken pre-dose; all post-dose samples (15 minutes – 6 hours) are timed from the start of inhalation
[8] Central lab collection: Sodium, potassium, bicarbonate, creatinine, BUN, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, PT/INR, amylase, lipase, CK, glucose, total cholesterol, and triglycerides
[9] Local lab collection: Sodium, potassium, chloride, bicarbonate
[10] Serum pregnancy test
[11] Urine pregnancy test/dipstick
[12] Screening phase completion

Cohort 2 - Details for highly repetitive assessments

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EPOCH	Visit Name	Visit Number	Day	Time (post-dose)	Vital Signs	PK blood collection	Local Lab Blood Chemistry
SCREENING	Screening	1	-28 to -7	-	X		
	Baseline	2	-1 -2 +0	-	X		
TREATMENT	Day 1	101	1	0m[2]	X	X	X
				15m		X	
				30m		X	X
				1h	X	X	X
				2h		X	X
				4h		X	X
				6h	X	X	X
	Day 2	102	2 -0 +1	0m[2]	X	X	
	Day 7	103	7 -2 +2	0m[2]	X	X	
	Day 14	104	14 -2 +2	0m[2]	X	X	X
				15m		X	
				30m		X	X
				1h	X	X	X
				2h		X	X
				4h		X	X
				6h	X	X	X
	ET/EOS[1]	199	18 -2 +2	-	X	X	

[1] Early termination/Study completion (study/treatment discontinuation and premature subject withdrawal should complete all these assessments)
[2] 0 minute (0m) sample is taken pre-dose; all post-dose samples (15 minutes – 6 hours) are timed from the start of inhalation of the morning dose

Cohort 3 - Total Duration is up to 4 Months

EPOCH	SCREENING		TREATMENT PERIOD 1							TREATMENT PERIOD 2					
Visit Name	Screening	Baseline	Day 1	Day 7	Day 14	Day 21	Day 28	Washout	Baseline/ET/EOS[2]	Day 57	Day 63	Day 70	Day 77	Day 84	ET/EOS
Visit Numbers[1]	1	2	101	103	104	105	106	TC	199	201	202	203	204	205	299
Study Day(s)	-45 to -14	-7 to - 4	1	7 -2 +2	14 -2 +2	21 -2 +2	28 -2 +0	29-51	52 -0 +2	57	63 -2 +2	70 -2 +2	77 -2 +2	84 -2 +0	91 -3 +3
Informed consent	X														
Inclusion / Exclusion criteria	X	X							X[12]						
Metabolite Screening Assay	X														
Corporate Confidential Information	X														
Randomization			X[10]												
Contact IRT	X	X	X	X	X	X	X			X	X	X	X	X	
Study drug dispensation and administration in clinic in the morning			X	X	X	X	X			X	X	X	X	X	
Medical history/current medical conditions	X	X							X						
Concomitant therapies	X														
Demography	X														
Vital Signs	X	X	X[4]	X[4]	X[4]	X[4]	X[4]		X	X[4]	X[4]	X[4]	X[4]	X[4]	X
Body height	X														
Body weight	X	X			X[4]		X[4]		X			X[4]		X[4]	X
Physical examination	X	X			X[4]		X[4]		X			X[4]		X[4]	X

EPOCH	SCREENING		TREATMENT PERIOD 1							TREATMENT PERIOD 2					
Visit Name	Screening	Baseline	Day 1	Day 7	Day 14	Day 21	Day 28	Washout	Baseline/ET/EOS[2]	Day 57	Day 63	Day 70	Day 77	Day 84	ET/EOS
Visit Numbers[1]	1	2	101	103	104	105	106		199	201	202	203	204	205	299
Study Day(s)	-45 to -14	-7 to - 4	1	7 -2 +2	14 -2 +2	21 -2 +2	28 -2 +0	29-51	52 -0 +2	57	63 -2 +2	70 -2 +2	77 -2 +2	84 -2 +0	91 -3 +3
Spirometry	X	X		X[4]	X[4]	X[4]	X[4]		X		X[4]	X[4]	X[4]	X[4]	X
ECG evaluation	X	X			X[4]		X[4]		X			X[4]		X[4]	X
Corporate Confidential Information		X			X		X		X			X		X	X
		X	X[4]	X[4]	X[4]	X[4]	X[4]		X	X[4]	X[4]	X[4]	X[4]	X[4]	X
PK blood collection			X[9]	X[9]	X[9]	X[9]	X[9]		X[13]	X[9]	X[9]	X[9]	X[9]	X[9]	X
Central Lab Blood Chemistry[6]	X	X	X[4]	X[4]	X[4]	X[4]	X[4]		X	X[4]	X[4]	X[4]	X[4]	X[4]	X
Central Lab Hematology	X	X			X[4]		X[4]		X			X[4]		X[4]	X
Hepatitis screen	X														
Corporate Confidential			X												
Alcohol Test, Drug Screen, and Cotinine Test	X	X							X						X
HIV screen	X														
Pregnancy test	X[7]	X[8]			X[4,8]		X[4,8]		X[8]			X[4,8]		X[4,8]	X[8]
Urinalysis	X	X	X[4]	X[4]	X[4]	X[4]	X[4]		X	X[4]	X[4]	X[4]	X[4]	X[4]	X
Telephone follow-up								X[3]							
AEs and SAEs	X														

EPOCH	SCREENING		TREATMENT PERIOD 1							TREATMENT PERIOD 2					
Visit Name	Screening	Baseline	Day 1	Day 7	Day 14	Day 21	Day 28	Washout	Baseline/ET/EOS[2]	Day 57	Day 63	Day 70	Day 77	Day 84	ET/EOS
Visit Numbers[1]	1	2	101	103	104	105	106		199	201	202	203	204	205	299
Study Day(s)	-45 to -14	-7 to - 4	1	7 -2 +2	14 -2 +2	21 -2 +2	28 -2 +0	29-51	52 -0 +2	57	63 -2 +2	70 -2 +2	77 -2 +2	84 -2 +0	91 -3 +3
Study Drug Questionnaire									X[13]						X
Phase / Study completion information		X[11]							X[13]						X

[1] Visit structure given for internal programming purpose only
[2] Baseline: For patients continuing onto study treatment period 2.

ET/EOS: Early Termination/End of Study: For subjects who undergo study/treatment discontinuation and subjects who withdraw prematurely
[3] Telephone Contact on Day 42 (-5/+5) of Washout
[4] Pre-dose

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[6] Central lab collection: Sodium, potassium, bicarbonate, creatinine, BUN, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, PT/INR, amylase, lipase, CK, glucose, total cholesterol, and triglycerides
[7] Serum pregnancy test
[8] Urine pregnancy test. If positive, drug must be withheld and a confirmatory serum pregnancy test must be sent
[9] PK blood sample to be collected at 15 minutes after the start of inhalation of the morning dose
[10] Randomization can occur any time between visits 2 and 101 after eligibility is confirmed
[11] Screening phase completion
[12] To be completed only for Baseline visit
[13] To be completed only for ET/EOS (Early Termination/End of Study) visit

8.1 Informed consent procedures

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

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

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

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

Novartis will review the Investigators proposed informed consent form to ensure it complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any further changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

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

8.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses and not symptoms will be recorded.

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

8.3.1 Lung Clearance Index (LCI)

LCI will be determined using MBNW according to ATS guidelines (Robinson et al 2013) in Cohorts 1 and 2 only.

LCI represents the cumulative expired volume required to wash out nitrogen to 2.5% of the starting concentration, normalized to the function residual capacity (FRC) of the lungs. With heterogeneous small airway obstruction, a greater expired volume is required for nitrogen washout and the LCI is increased. Additional measurements provided by MBNW include Scond and Sacin, which reflect ventilation heterogeneity in the conducting and acinar airways. Detailed procedures for the LCI acquisition are provided in the SOM.

8.3.2 Lung volumes

Lung volumes will be determined according to ATS guidelines (Wanger et al 2005) in Cohorts 1 and 2 only.

Measurements will include IC, FRC, TLC and RV. Additional information for conduct of lung volume testing is provided in the SOM.

8.3.3 Spirometry

All spirometry evaluations should follow the recommendations of the ATS/ERS 2005 Task Force: Standardization of Spirometry (Miller et al 2005). The spirometry equipment used during the trial must meet or exceed the minimal ATS/ERS recommendations for diagnostic spirometry equipment as defined in the guideline. All patient spirometry reports should be stored as source data. Spirometric parameters for screening, baseline and subsequent assessments are pre bronchodilator, including % predicted FEV1, FVC, difference between SVC and FVC, FEV1/FEV6, FEV1/FVC ratio, FEF_{25-75}, FEV3, 1-FEV3, FEV3/FVC ratio, 1-FEV3/FVC, FEV6, FEV3/FEV6 ratio, 1-FEV3/FEV6 ratio (Hansen et al 2006). Additional information for conduct of spirometry evaluations is provided in the SOM.

8.4 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the Assessment schedule detailing when each assessment is to be performed.

8.4.1 Physical examination

- Physical examination

8.4.2 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse
- Respiratory rate
- Pulse oximetry

8.4.3 Height and weight

- Height
- Body weight
- Body mass index (BMI) will be calculated (Body weight (kg) / [Height (m)]^2)

8.4.4 Laboratory evaluations

Clinically significant deviations of laboratory test results occurring at screening or baseline visits, or during or at completion of the study must be repeated, reported and/or discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count will be measured.

Clinical chemistry

Sodium, potassium, bicarbonate, creatinine, blood urea nitrogen, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, PT/INR, amylase, lipase CK, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Local blood chemistry (Cohorts 1 &2 only)

Sodium, potassium, chloride, bicarbonate collection to monitor for hyperkalemia.

Urinalysis

Routine urinalysis and Sodium/potassium ratio measurement will be provided by the central lab

8.4.5 Electrocardiogram (ECG)

A standard ECG will be performed. Interpretation of the tracing must be made by a qualified physician within 72 hours and documented on the ECG section of the e(CRF).

The following will be recorded in the e(CRF):

- date and time of ECG
- heart rate
- PR interval
- QT interval
- QTcF interval
- QRS duration

Each ECG tracing should be labeled with the

- study number
- patient initials
- patient number
- Date of assessment

and kept in the source documents at the study site. Photocopies of the ECG tracings should be made to preserve the integrity of ECG data. Only clinically significant abnormalities should be reported on this page. Clinically significant abnormalities should also be recorded on the Relevant medical history/Current medical conditions e(CRF) page. Clinically significant findings must be discussed with the sponsor.

The overall interpretation will be collected with a Yes/No statement to confirm if any clinically significant abnormalities are present which need to be specified further.
Original ECG tracings, appropriately signed, will be archived at study site.

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

8.4.6 Spirometry

Besides the spirometry measurements required for the study as per the assessment table, additional pre- or post-dose spirometry may be conducted by the sites for safety reasons.

8.4.7 Pregnancy and assessments of fertility

Serum and urine pregnancy tests will be conducted per the assessment tables. All pre-menopausal women who are not surgically sterile will have regular pregnancy tests during the study per protocol. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

8.5 Pharmacokinetics

Pharmacokinetic blood samples will be collected at the time points defined in the Assessment schedule. In Cohorts 1 and 2 this consists of multiple samplesthrough 6 hours after inhalation on Days 1 and either 7 or 14 and predose concentrations on selected days. In Cohort 3 this consists of a 15-minute sample after the start of inhalation of the morning dose on selected days. Details on sample collection, numbering, processing and shipment are in the SOM. The customized tubes used for collection of PK blood samples are not sterile and must NOT be filled by direct phlebotomy; the specific instructions on the use of these tubes, provided in the SOM, must be followed.

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Concentrations below the quantification limit will be reported as 0 ng/mL. Blood remaining after completion of the bioanalytics described above may be used for exploratory assessment of metabolites or other bioanalytical purposes (e.g. cross check between different sites, stability assessment).

Pharmacokinetic abbreviations and definitions are in the list at the beginning of this protocol. The following pharmacokinetic parameters for all three analytes will be determined for Day 1 and Day 7 or 14 in Cohorts 1 and 2 using the actual recorded sampling times and noncompartmental methods: Cmax, Tmax, and AUCtau on Day 1 and Cmax,ss, Tmax,ss, and AUCtau,ss on Day 7 for cohort 1 and Day 14 for cohort 2. Half-lives will be calculated by log-linear regression on the terminal portion of the concentration-time profile if enough concentrations are available (minimum 3). Racc will be derived as the ratio of AUCtau,ss from Day 14 divided by the AUCtau from Day 1. In cohort 3, exposure from 15-minute sample after start of inhalation of the morning dose on selected days will be monitored. Other PK parameters maybe calculated in all cohorts if deemed necessary.

In order to avoid long clinical stays for patients in this study, the blood sampling for AUC's is terminated at 6 hours after inhalation.

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No formal statistical comparison is foreseen as the intent of this comparison is to determine if exposure is similar in the two groups.

9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient *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 occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

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 should 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 patients with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for liver related events are included in Section 9.3.

Adverse events must be recorded on the Adverse Events CRF for patients that pass screening and enter into the study. The adverse events should be reported according to the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. The Common Toxicity Criteria (CTC) AE grade (version 4.03)] CTCAE 4.03 can be found at the following Internet site: http://evs.nci.nih.gov/ftp1/CTCAE/About.html
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities

If CTC-AE grading does not exist for an adverse event, use:

- 1=mild,
- 2=moderate,
- 3=severe
- 4=life threatening.

CTC-AE grade 5 (death) is not used, but is collected in other CRFs (e.g. Study Completion, Death/Survival).

2. its relationship to the study treatment (no/yes)

3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
4. whether it constitutes a serious adverse event (SAE) See Section 9.2 for definition of SAE
5. action taken regarding [study/investigational] treatment(select as appropriate).
   All adverse events should be treated appropriately. Treatment may include one or more of the following:
   - no action taken (i.e. further observation only)
   - study treatment dosage adjusted/temporarily interrupted
   - study treatment permanently discontinued due to this adverse event
   - concomitant medication given
   - non-drug therapy given
   - patient hospitalized/patient's hospitalization prolonged
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or Core Data Sheet (for marketed drugs) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

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:

- is fatal or life-threatening
- 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 the start of study drug
  - 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
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

Life-threatening in the context of a SAE refers to a reaction in which the patient 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 more severe.

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.

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 patient or might require intervention to prevent one of the other outcomes listed above. 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.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per Section 9.2.2.

9.2.2 SAE reporting

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

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to each specific component of study treatment (if study treatment consists of several drugs) complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis CMO & PS Department, notifying the Clinical Trial Leader. Contact information is listed in the SOM.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the source documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

SAEs (initial and follow-up) that are recorded electronically in the Electronic Data Capture system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis CMO & PS immediately after investigator signature or 24 hours after entry, whichever occurs first. Study site personnel must also inform the Clinical Trial Leader.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

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 investigational 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 investigational 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.

9.3 Liver safety monitoring

To ensure patient 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:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 9-1 and Table 9-2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in in Table 9-2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

Repeat laboratory tests should be entered on the appropriate unscheduled local laboratory CRF page.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug (refer to Section 7.1, if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded as appropriate in the CRF, including the liver event overview CRF pages.

Table 9-1 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 *

Table 9-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for *more than 2 weeks*, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver 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 • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT 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 drug immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study drug interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

*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

[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.

9.4 Renal safety monitoring

Renal events are defined as one of the following:

- confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared with baseline during normal hydration status
- new onset (≥1+) proteinuria, hematuria or glucosuria; or as a
- doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable).

The following two categories of abnormalities/adverse events have to be considered during the course of the study:

- Serum creatinine triggers that will require follow up and repeat assessments of the abnormal laboratory parameter

- Urine dipstick triggers that will require follow up and repeat assessments of the abnormal laboratory parameter

Table 9-3 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Serum creatinine increase 25 – 49% compared with baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Serum creatinine increase ≥ 50 % compared with baseline	Follow up within 24-48h if possible Consider drug interruption Consider patient hospitalization /specialized treatment
Albumin- or Protein-creatinine ratio increase ≥ 2-fold Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; New dipstick proteinuria ≥ 1+ Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider drug interruption / discontinuation
New dipstick glucosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
Document contributing factors: co-medication, other co-morbid conditions, and additional diagnostic procedures performed in the CRF	
Monitor patient regularly (frequency at investigator's discretion) until one of the following: Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) 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.	

9.5 Pregnancy reporting

To ensure patient safety, each pregnancy in a patient on study drug 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. The study drug must be discontinued, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments. Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis CMO & PS Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on an SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.6 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs 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 monitor will visit the site to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each patient 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 patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety 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 patients will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the SOM and assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

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

Novartis staff review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database.

Concomitant medications entered into the database will be coded using the 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.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data in reference to dispensing of study drug(s) to the patient and all IRT recorded dosage changes will be tracked using Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

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.

11 Data analysis

Analysis of the data will be conducted under the direction of Novartis personnel in compliance with internal guidance documents and standards.

11.1 Analysis sets

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

The safety analysis set will include all patients that received any study drug.

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

11.2 Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by cohort, treatment and patient. Summary statistics will be provided for all patients, as well as for each treatment. Data from patients receiving placebo may be pooled only for cohort 1 and 2 of the study.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment (treatment sequence for cohort 3) and patient.

11.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Use of rescue and/or concomitant medications and data on administration of study drug will be listed by cohort, treatment (treatment sequence for cohort 3), and patient.

11.4 Analysis of the primary variable(s)

11.4.1 Variable(s)

The primary variable is occurrence of an adverse event for cohort 1 and cohort 2 and evaluate the pharmacodynamic response as reflected in percent of predicted FEV1 for cohort 3 of multiple doses of inhaled QBW276 in CF patients.

11.4.2 Statistical model, hypothesis, and method of analysis

Cohort 1 and Cohort 2: All information obtained on adverse events will be listed by cohort, treatment and patient. For each cohort, adverse events will be counted within each cohort/dose-level, by treatment received and corresponding percentages will be tabulated.

Data from subjects receiving placebo may be pooled for cohorts 1 and 2 of the study. The numbers and percentages will be tabulated by body system, preferred term and severity. A patient with multiple adverse events within a body system is only counted once towards the total of this body system.

All other safety assessments including ECG, vital signs and laboratory data will be listed by cohort, treatment, patient, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

Drug concentrations will be listed by treatment, patient and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below the LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters in Cohorts 1 and 2 will be calculated as described in Section 8.5 and will be listed by treatment and patient. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Individual concentration-time profiles and mean profiles with SD bars will be presented for Day 1 and Day 7 or 14 in Cohorts 1 and 2.

Cohort 3:

The percent of predicted FEV1 may be put into a mixed effects model. Percent of predicted FEV1 values measured on Day 7, 14, 21 and 28 of each treatment period at the study site will be analyzed using a mixed effects model for repeated measurements. The model will include fixed effects for period, time (Days 7, 14, 21, 28), Corporate Confidential Information treatment and treatment by time. Subject will be included as a random effect and time will be repeated within each patient by period interaction term. Subject-average baseline and period-adjusted baseline will be fitted as covariates. An unstructured covariance matrix will be applied. Kenward Roger options will be used to calculate the degrees of freedom in all Proc Mixed analysis.

The subject average baseline will be derived as the average of their pre-dose assessments from each period. Period adjusted baseline will be calculated for each subject and for each period, as the difference between the period baseline and the subject average baseline, i.e. value of period baseline – value of average baseline (Kenward and Roger 1997).

The final model estimates will include the LSmean for each treatment together with standard error (SE), the adjusted mean difference between treatments, and 80% two-sided confidence intervals and P-value for the differences. These will be calculated at all time points, and specifically at the primary time point of interest (Day 28) using Placebo as the reference treatment.

The results of analysis will also be presented in a graphical representation showing the estimated mean differences to placebo and their confidence intervals per time point.

Summary statistics and graphical representations of percent of predicted FEV1 will be presented by treatment group and time.

No adjustments for multiplicity will be applied for this exploratory study.

Additional exploratory analyses such as responder analyses and analysis by gender may be performed. Detailed statistical methods will be discussed in the Statistical Analysis Plan.

11.4.3 Handling of missing values/censoring/discontinuations

Cohorts 1 and 2: Patients withdrawn for reasons other than safety and tolerability prior to completion of the Day 7 or 14 assessments may be replaced to gather sufficient data to perform an informed decision on dose selected for the subsequent cohort.

Cohort 3: The repeated measures analysis includes all available information in terms of measurements at all times. If missing measurements are missing at random, an analysis of the available data provides consistent estimates of model parameters. Alternative assumptions may be explored to investigate the robustness of the results under plausible non-Missing at Random situations. Reasons for dropouts will be explored.

Where data has values below and above limits of quantification then the following rule will apply.

In the summary tables, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be included.

Any values below the limit of quantification will be analyzed as 0.5*the lower limit, both in the descriptive and the model analysis. Any values above the limit of quantification will be analyzed as 1.0*the upper limit, both in the descriptive and the model analysis.

No other imputation of missing data is allowed.

11.5 Analysis of secondary and exploratory variables

11.5.2 Safety

Vital signs

All vital signs data will be listed by cohort, treatment (treatment sequence for cohort 3), patient, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by cohort, treatment (treatment sequence for cohort 3), patient 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 cohort, treatment (treatment sequence for cohort 3), patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

For cohort 3, all information obtained on adverse events will be displayed by cohort, treatment sequence and patient.

The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A patient with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

11.5.3 Pharmacokinetics

The 15 minute post-dose concentrations in Cohort 3 will be listed by treatment, patient and visit/sampling time point. Descriptive statistics will be provided by treatment and visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. Concentrations below the LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

11.6 Sample size calculation

Cohort 1 and 2: The first and second cohort will include 8 patients each, randomized 3:1 to drug: placebo. The sample size of 8 patients per cohort was based on practical considerations and clinical judgment that the numbers of patients are appropriate for the assessment of overall safety and tolerability and for providing adequate confidence for dose escalation. In cohort 1, for instance, an adverse event with an incidence of 23.5% will have a probability of 80% of occurring in at least one patient and a probability of 43% of occurring in two or more patients.

Cohort 3: Based on drop-out rate during the study, up to 40 patients may be randomized to cohort 3 to ensure that at least 24 complete both periods.

11.7 Power for analysis of key secondary variables

Not Applicable

12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should 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, patient recruitment procedures (e.g. advertisements) and any other written information to be provided to patients. 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.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 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 patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. If the 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/REB/regulatory authority it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

13.1 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 intended to eliminate an apparent immediate hazard to patients may be implemented, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the CTL should be informed and (serious) adverse event reporting requirements (Section 9) followed as appropriate.

14 References

Available upon request.

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