

Novartis Institutes for BioMedical Research

QVM149

Clinical Trial Protocol CQVM149B2209

**A randomized, double-blind, repeat dose cross-over study
to assess the bronchodilator effects of once daily QVM149
following morning or evening dosing for 14 days compared
to placebo in patients with asthma**

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Site Operations Manual (SOM)

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

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to [Section 9.2](#) of the Clinical Trial Protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO&PS) within 24 hours after awareness of the SAE
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BMI	Body Mass Index
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulation
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	coefficient of variation
ECG	Electrocardiogram
EDC	Electronic Data Capture
eSource	Electronic Source
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	hour
HBsAg	Hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LABA	Long-acting beta adrenoceptor agonists
LAMA	Long-acting muscarinic antagonist

LFT	Liver function test
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LLN	lower limit of normal
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
NCDS	Novartis Clinical Data Standards
PA	posteroanterior
PC	personal computer
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PIP	pediatric investigation plan
p.o.	oral(ly)
PSD	Premature patient discontinuation
PT	prothrombin time
RBC	red blood cell(s)
RDC	Remote Data Capture
SABA	Short acting beta 2 agonist
SAE	serious adverse event
SAMA	Short acting muscarinic antagonist
S	Source documents
s.c.	subcutaneous
sCR	serum creatinine
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
TD	Study Treatment Discontinuation
ULN	upper limit of normal

ULQ upper limit of quantification

WBC white blood cell(s)

WHO World Health Organization

WoC Withdrawal of Consent

Glossary of terms

Assessment	A procedure used to generate data required by the study
Baseline	Period after screening and prior to the first dose of Treatment period 1
Cohort	A specific group of patients fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US Code of Federal Regulation (CFR) 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug," "Investigational Medicinal Product," or "test substance"
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an Interactive Response Technology (IRT) system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.

Patient	An individual with the condition of interest
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Run in Failure	A patient who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to patient's medications or other intervention)
Screen Failure	A patient who is screened but is not treated or randomized
Patient	A trial participant (can be a healthy volunteer or a patient)
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, <u>and</u> does not want any further visits or assessments, <u>and</u> does not want any further study related contact, <u>and</u> does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CQVM149B2209
Full Title	A randomized, double-blind, repeat dose cross-over study to assess the bronchodilator effects of once daily QVM149 following morning or evening dosing for 14 days compared to placebo in patients with asthma.
Brief title	Assess the bronchodilator effect of QVM149 dosed once daily either in the morning or in the evening compared to placebo in patients with asthma.
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	This study will provide evidence of the comparability of lung function effects of QVM149 (indacaterol acetate / glycopyrronium bromide / mometasone furoate) irrespective of the administration schedule. It is considered important for the overall QVM149 development program to demonstrate lung function benefits of QVM149 compared to placebo irrespective of time of dosing. Flexibility in dosing schedule may confer benefit to the patient by facilitating treatment compliance with subsequent lung function improvement and asthma control.
Primary Objective	To investigate the potential influence of time of dosing (morning or evening) on the bronchodilator effect of once daily orally inhaled QVM149 compared to placebo.
Secondary Objectives	<ul style="list-style-type: none">• To investigate the potential influence of time of dosing (morning or evening) on trough FEV1 of once daily orally inhaled QVM149 compared to placebo.• To investigate the potential influence of time of dosing (morning or evening), on peak expiratory flow rate (PEF) of once daily orally inhaled QVM149 compared to placebo.• To evaluate safety and tolerability of QVM149 when dosed in the morning or in the evening in patients with asthma after during two weeks of treatment in each treatment period.
Study design	This is a randomized, placebo-controlled, double-blind, six-sequence, three-period cross-over study in asthma patients. The study will consist of a 14-day screening period, followed by a 14-day run-in period, and a treatment epoch which consists of three treatment periods, with a minimum duration of 14 days each followed (for the 2 first treatment periods) by a wash-out period. The duration of each treatment period may be extended up to a duration of 18 days if needed for operational reasons. The third treatment period will be followed by a Study Completion evaluation at 1-7 days following the last dose. The treatment periods will be separated by wash-out periods of 14 to 21 days duration. The total duration of the study is approximately 13 weeks (minimum) to 19 weeks (maximum) for each patient.

Population	The study population will be comprised of male and female patients aged 18 and above with asthma. Approximately 36 adult patients will be randomized with the intention that at least 30 patients complete the study.
Key Inclusion criteria	<ul style="list-style-type: none"> Patients with a documented physician diagnosis of asthma and who additionally meet the following criteria: <ul style="list-style-type: none"> patients receiving daily treatment with an inhaled corticosteroid at a low or medium daily dose on a stable regimen for at least 4 weeks prior to screening. Pre-bronchodilator FEV1 \geq 60 % and $<$ 100% of the predicted normal value for the patient during screening. Patients who demonstrate an increase in FEV1 of \geq 12 % and \geq 200 mL after administration of 400 μg salbutamol/360 μg albuterol (or equivalent dose) at Screening. All patients must perform a reversibility test at Screening. At screening, and baseline (day 1 pre-dose time) of the first treatment period, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position and again in the standing position as outlined in the SOM. Sitting and standing vital signs should be within the following ranges: <ul style="list-style-type: none"> oral body temperature between 35.0-37.5 °C systolic blood pressure, 90-159 mmHg diastolic blood pressure, 50-99 mmHg pulse rate, 40-90 bpm Hypertensive patients must have been on stable antihypertensive therapy for at least 4 weeks prior to screening to be included in the trial. Patients must weigh at least 50 kg at screening to participate in the study, and must have a body mass index (BMI) within the range of 18 to 40 kg/m².
Key Exclusion criteria	<ul style="list-style-type: none"> Contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the drugs of a similar class Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 1 year of Screening. Patients who have had previous intubation for a severe asthma attack/exacerbation. Patients with a history of clinically relevant bronchoconstriction upon repeated forced expiratory maneuvers. History of paradoxical bronchospasm in response to inhaled medicines. Patients who during the run-in period prior to randomization require the use of \geq12 puffs / 24 hours of rescue medication for 48 hours (over two consecutive days) or who have a decline in PEF from the reference PEF of \geq 30% for 6 consecutive scheduled PEF readings Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers).
Study treatment	<ul style="list-style-type: none"> QVM149 once daily in the morning QVM149 once daily in the evening Placebo
Pharmacokinetic assessments	<ul style="list-style-type: none"> Not applicable

Efficacy/PD assessments	<ul style="list-style-type: none"> • Spirometry; FEV1 over 24 hours • Peak expiratory flow
Key safety assessments	<ul style="list-style-type: none"> • Physical examination • Vital signs • Laboratory evaluations; hematology, blood chemistry and urinalysis • Electrocardiogram (ECG) • Peak flow measures
Other assessments	<ul style="list-style-type: none"> • Patient diary to record rescue medication use, study treatment administration (am and pm), PEF measurements (am and pm)
Data analysis	<p>The primary objective is to investigate the potential influence of time of dosing (morning or evening) on the bronchodilator effect of once daily orally inhaled QVM149 compared to placebo.</p> <p>The primary variable is the weighted mean forced expiratory volume in 1 second (FEV1) over 24 hours (AUC_{0-24h}) following 14 days of treatment with QVM149 dosed in the morning, QVM149 dosed in the evening and placebo. The primary variable will be determined for each patient on day 14/15 on each treatment using the linear trapezoidal rule.</p> <p>The primary variable, FEV1 weighted mean (0- 24 h) (AUC_{0-24h}), will be analyzed using a linear mixed model. The model will include period, treatment (QVM149 morning, QVM149 evening, placebo), and sequence as fixed effect factors. The patient effect will be assumed to be random. Restricted maximum likelihood method will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. From these analyses, point estimates and their associated 90% confidence intervals will be constructed for each treatment. The difference between adjusted means and the corresponding two-sided 90% confidence interval for morning dose versus placebo, evening dose versus placebo will be presented. In addition, difference between adjusted means and the corresponding two-sided 90% confidence interval for morning versus evening doses will be presented.</p> <p>The secondary endpoints are:</p> <ul style="list-style-type: none"> • FEV1 at approximately 5 min. before last p.m. or penultimate a.m. dose obtained from spirometry data. • Daily morning and evening peak expiratory flow (PEF) rate from Day 2 to Day 14 during the three treatment periods <p>FEV1 (mL) will be analyzed by fitting the same model as described for the primary endpoint above in addition to summary statistics.</p> <p>PEF (L/min) will be analyzed separately for morning and evening values. The morning/evening PEF (L/min) will be averaged between days 2 to 14 of each treatment period for each patient. Morning and evening PEF data averaged over the days of run-in period will be used as baseline values. The change from baseline in average mean morning/evening PEF score between days 2 to 14 in each period will be analyzed using the same model as for the primary endpoint and summarized by treatment.</p>
Key words	Asthma, FEV1, spirometry, peak flow

1 Introduction

1.1 Background

Asthma is a chronic inflammatory disorder of the airways associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable bronchial airflow obstruction that is often reversible either spontaneously or with treatment. Airflow limitation occurs as a result of obstruction or narrowing of the airways, when exposed to precipitating factors ([GINA 2016](#)).

Despite existing therapies there is still significant unmet medical need in asthma, with an estimated 300 million people affected worldwide. The Global Burden of Asthma Report estimates that 15 million disability-adjusted life years (DALYs) are lost annually due to asthma, representing 1% of the total global burden. Annual worldwide deaths have been estimated at 250,000 ([Beasley 2004](#)).

Recently, tiotropium (long-acting muscarinic antagonist; LAMA) has been approved in the EU as an add-on maintenance bronchodilator treatment in adult patients (≥ 18 years) with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (ICS; $\geq 800\mu\text{g}$ budesonide/day or equivalent) and long-acting beta2-agonists (LABA), and who experienced one or more severe exacerbations in the previous year. This is reflected in the [GINA 2016](#) guideline by recommending tiotropium as an add-on option in patients requiring asthma therapy step 4 and 5 according to the GINA treatment algorithm.

There is mounting evidence that in patients who are poorly controlled on mid and high dose ICS/LABA a triple combination of LABA, LAMA and ICS can provide additional benefit in terms of lung function, symptom control and a reduction in exacerbations.

QVM149 is a fixed-dose combination of indacaterol acetate (LABA), glycopyrronium bromide (LAMA), and mometasone furoate (MF; ICS) in development for once-daily maintenance treatment of asthma GINA step ≥ 4 . QVM149 is formulated as lactose-blended inhalation powder delivered via the Concept1 inhalation device (Breezhaler[®]), a single dose dry powder inhaler (SDDPI). The three mono-components of QVM149, indacaterol, glycopyrronium bromide and MF have previously been developed as individual drugs or dual combinations (indacaterol acetate/MF called QMF149; indacaterol maleate/glycopyrronium bromide called QVA149) for treatment of either COPD or asthma as detailed below, thereby supporting the efficacy and safety of individual components and the selection of doses for their combination in QVM149.

The clinical presentation of asthma is characterized by diurnal variation: symptoms of asthma typically worsen and lung function decreases during the night ([Muers 1984](#)). The pathogenesis to diminished airway caliber during the night is not fully understood but has been linked, among other factors, to the diurnal rhythm of endogenous cortisol levels ([Barnes et al 1980](#), [Landstra et al 2007](#)). In previous studies various ICS have been administered at different times of the day. Results are not uniform but suggest that time of administration may

influence the efficacy of ICS. Fluticasone furoate at a dose of 100 µg via the Ellipta® device showed similar gains in lung function when administered in the morning (77 mL compared to placebo in 24 hours weighted means FEV1) or in the evening (105 mL) (Kempsford et al 2016). A less consistent picture has been described for Fluticasone furoate delivered with a Diskus® inhalation device (Woodcock et a. 2011).

MF formulated as Asmanex® Twisthaler® if prescribed once-daily, is recommended to be dosed in the evening (Asmanex® Twisthaler® SmPC). Clinical studies suggest that MF can also be administered once daily in the morning to convey clinical benefit to patients in terms of lung function (Noonan et al 2001) and asthma symptoms (Zetterstrom et al 2008).

Individual patients may like to choose at what time of the day they take their medication. Therefore, having the flexibility of dosing either in the morning or evening may be more convenient for the patient and may further improve treatment adherence and the management of asthma.

Indacaterol

Indacaterol maleate delivered via Concept1 (Onbrez® Breezhaler®) is approved in over 110 countries worldwide at doses of 150 µg to 300 µg once daily for maintenance bronchodilator treatment of airflow obstruction in patients with COPD.

The clinical development program of indacaterol maleate included studies in patients with asthma on background ICS therapy as recommended by GINA 2016 treatment guidelines and demonstrated that indacaterol maleate was effective and well-tolerated. A study in adolescent and adult patients with moderate to severe persistent asthma receiving concomitant ICS therapy showed that indacaterol maleate at doses of up to 600 µg o.d. over a 26-week treatment period was well-tolerated and resulted in effective bronchodilation superior to that provided by salmeterol (CQAB149B2338).

Studies comparing the indacaterol maleate salt with the acetate salt found that the acetate salt was associated with a lower incidence of post-inhalation cough (CQAB149B2102) with no impact on efficacy, safety or systemic exposure (CQAB149D2301). Indacaterol acetate bronchodilator effects, control of asthma symptoms and safety of indacaterol acetate (150 µg or 75 µg o.d.; on top of MF background medication) were further substantiated in study QMF149E2203 in patients with asthma. Therefore, the acetate salt is being used as the LABA component in the QVM149 fixed-dose combination.

Glycopyrronium bromide

Glycopyrronium bromide (50 µg once daily in a lactose-based formulation delivered via Concept1) is registered in the EU since 2012 as Seebri® Breezhaler® for the treatment of COPD.

Glycopyrronium bromide 50 µg has demonstrated clinically meaningful and statistically significant improvements in lung function in COPD patients which is sustained over 24 hours and provides significant symptomatic benefits with a favorable safety and tolerability profile. Efficacy was maintained with once-daily dosing for treatment periods of up to a year with good safety and tolerability.

The fixed dose combination of indacaterol maleate and glycopyrronium bromide (QVA149) is also registered in the EU as Ultibro® Breezhaler® with the delivered doses as proposed for QVM149.

Mometasone furoate (MF)

MF is marketed in inhalation, nasal, cream, ointment and lotion formulations. The inhalation powder formulation which may be administered once or twice daily is marketed as a multi dose dry powder inhaler (MDDPI) called Asmanex® Twisthaler® for the treatment of asthma.

Asmanex® Twisthaler® is currently approved in the United States for the treatment of asthma in adults and children \geq 4 years of age and is approved in over 55 countries world-wide for the treatment of asthma in adults and adolescents \geq 12 years of age. The recommended daily doses of Asmanex® Twisthaler® range from 200 μ g to 800 μ g.

MF delivered via Concept1 device

To deliver a matching dose of MF via Concept1 compared to Twisthaler® a dose adjustment for the MF component needed to be made. Primarily to account for differences in inhalation device performance the nominal dose of MF in Concept1 needed to be adjusted to match the MF dose delivered by the Twisthaler® device.

In a 4-week study in patients with persistent asthma (Study CQMF149E2201), MF doses of 80 μ g and 320 μ g delivered once daily via Concept1 showed comparable efficacy and systemic exposure to MF doses of 200 μ g and 800 μ g (2 x 400 μ g) delivered once daily via Twisthaler® confirming appropriate dose adjustment of the MF component in the Concept1 device. MF low (200), mid (400) and high (800) μ g doses delivered via Twisthaler® (approved doses) are considered to be comparable to 80, 160 and 320 μ g MF doses via Concept1, respectively based on the results of Study CQMF149E2101 and in vitro fine particle mass adjustment. These are the MF doses used in the LABA/ICS dual combination of indacaterol and MF (QMF149).

QVM149

An alteration in fine particle mass of MF in the QVM149 combination product compared to the corresponding MF dose in the QMF149 (LABA/ICS dual combination) combination product (matched to Asmanex® Twisthaler®) has been observed. Fine particle mass is considered as the appropriate in-vitro quality parameter to adjust the dose of the affected MF component in the QVM149 combination product to match the corresponding doses of MF in the QMF149 combination product, in order to achieve comparable aerosol performance (with respect to FPM) ([Table 3-2](#)).

Thus the mid and high nominal of MF in QVM149 are 80 μ g and 160 μ g to ensure that the fine particle mass (FPM, in-vitro aerosol performance) in the lactose blend formulation for QVM149 is similar to the nominal MF doses of 160 μ g and 320 μ g used for QMF149 ([Section 3.3](#)).

No adjustments to the doses of indacaterol or glycopyrronium in the FDC QVM149 combination are required. Additional detail is provided in [Section 3.3](#) discussing the dose rationale of this study.

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the [Investigator's Brochure](#).

Corporate Confidential Information

1.3 Clinical data

1.3.1 Human safety and tolerability data

To date no results from clinical studies being performed with QVM149 are available, however the currently available data for the monotherapy and dual combination products are considered adequate to support investigation of QVM149 in a comprehensive drug development program including phase 1 to phase 3 studies.

It is expected that the safety profile of QVM149 is comparable to that of its components since the systemic exposure to indacaterol, glycopyrronium and MF following inhalation of QVM149 is expected to be comparable to the systemic exposure following inhalation of the individual monocomponents or available dual combinations. The risks of side effects from the study medication are those known for LABAs, LAMAs and ICS. Reporting rates of adverse drug reactions have been low across the clinical studies with the monocomponents as well as the dual combinations.

For indacaterol, the characteristic adverse effects of inhaled β 2-adrenergic agonists can occur as a result of activation of systemic β -adrenergic receptors. The most common adverse effects include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in serum potassium and increases in plasma glucose.

For glycopyrronium, adverse experiences typically associated with muscarinic antagonists such as dry mouth, gastro-intestinal disturbances and urinary retention/ difficulty voiding urine were reported at low rates. The frequency of cardiovascular related adverse experiences was generally low, however a higher rate of atrial fibrillation was observed with glycopyrronium than with placebo in COPD patients. The COPD population investigated in this context, however, had a high prevalence of cardiovascular comorbidity.

For MF, the characteristic adverse effects of ICS can occur. The most prominent of these include oral candidiasis following local deposition of the steroid in the oropharynx. Systemic effects can also occur. These may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataracts, glaucoma, and yet more rarely, a range of psychological or behavioral effects.

Up to now no additional risks have been identified in completed and ongoing clinical studies with the monocomponents and the FDCs which might occur when the three components are administered concurrently or from the same inhaler.

Detailed information on the safety and tolerability profile of QVM149 can be obtained from the QVM149 Investigator's Brochure.

1.3.2 Human pharmacokinetic data

No clinical pharmacokinetic trials have been conducted with QVM149 to date.

The clinical pharmacokinetics program for QVM149 is based upon the clinical programs and post-marketing data for individual active drugs as well as the clinical programs for the dual combinations QVA149 (indacaterol maleate and glycopyrronium bromide) and QMF149 (indacaterol and mometasone furoate). Details on the pharmacokinetic data for the monotherapy and dual combinations can be found in the IB.

1.3.3 Human pharmacodynamic data

In QVM149 dual bronchodilation (LABA and LAMA) plus controller (ICS) are combined as one medication. This is expected to provide good symptom control, minimize airflow obstruction, minimize risk of exacerbations, and hospitalizations in a population of severe asthma patients. Use of multiple, often different devices represents a significant burden for these patients. Availability of three effective once- daily controller medications in a single device may offer advantages in terms of improved adherence and convenience.

The benefit of adding a muscarinic antagonist in the treatment of poorly controlled asthma is supported by two replicate studies which compared tiotropium to placebo: ([Kerstjens et al 2012](#)) showed that tiotropium on top of high dose ICS/LABA improved lung function and led to a significantly prolonged time to first severe exacerbation ([Kerstjens et al 2012](#)).

The available asthma clinical trial data suggest that a LAMA may confer bronchodilator effects in terms of improved lung function when used in addition to ICS alone or in conjunction with LABA/ICS (i.e., “free combination” or “loose” triple therapy) (Fardon et al 2007, Peters et al 2010, Bateman et al 2011, Kerstjens et al 2011, Kerstjens et al 2012, Guyer and Long 2013). A review evaluating the efficacy profile of a LAMA (tiotropium) as add-on therapy to ICS or LABA/ICS in patients with uncontrolled moderate to severe persistent asthma concluded that the addition of a LAMA resulted in significant improvements in lung function (FEV1 and peak expiratory flow) (Befekadu et al 2014).

Thus, triple therapy can provide an additional treatment option to theophylline, systemic corticosteroids or biologics for GINA Step ≥ 4 asthma patients.

No human pharmacodynamic trials have been conducted with QVM149 to date.

Details on the pharmacodynamic data of the monotherapy and dual combinations can be found in the QVM149 IB.

1.4 Study purpose

The purpose of this study is to assess the bronchodilator effects of QVM149 dosed once daily either in the morning or in the evening for 2 weeks compared to placebo. It will provide evidence of the comparability of lung function effects of QVM149 irrespective of the administration schedule. It is considered important for the overall QVM149 development program to demonstrate lung function benefits of QVM149 compared to placebo irrespective of time of dosing because in all other planned and ongoing studies QVM149 is dosed in the evening. Flexibility in dosing schedule may confer benefit to the patient by facilitating treatment compliance with subsequent lung function improvement and asthma control.

2 Objectives and endpoints

2.1 Primary objective(s)

Objective	Endpoint
<ul style="list-style-type: none">To investigate the potential influence of time of dosing (morning or evening) on the bronchodilator effect of once daily orally inhaled QVM149 compared to placebo	<ul style="list-style-type: none">Weighted mean forced expiratory volume in 1 second (FEV1) over 24 h (AUC_{0-24h}) following 14 days of treatment with QVM149 dosed in the morning, QVM149 dosed in the evening and placebo.

2.2 Secondary objective(s)

Objective	Endpoint
<ul style="list-style-type: none">To investigate the potential influence of time of dosing (morning or evening) on trough FEV1 of once daily orally inhaled QVM149 compared to placebo.To investigate the potential influence of time of dosing (morning or evening), on	<ul style="list-style-type: none">FEV1 at approximately 24 h after the last p.m. or penultimate a.m. dose.Daily morning and evening peak expiratory flow rate from Day 2 to Day

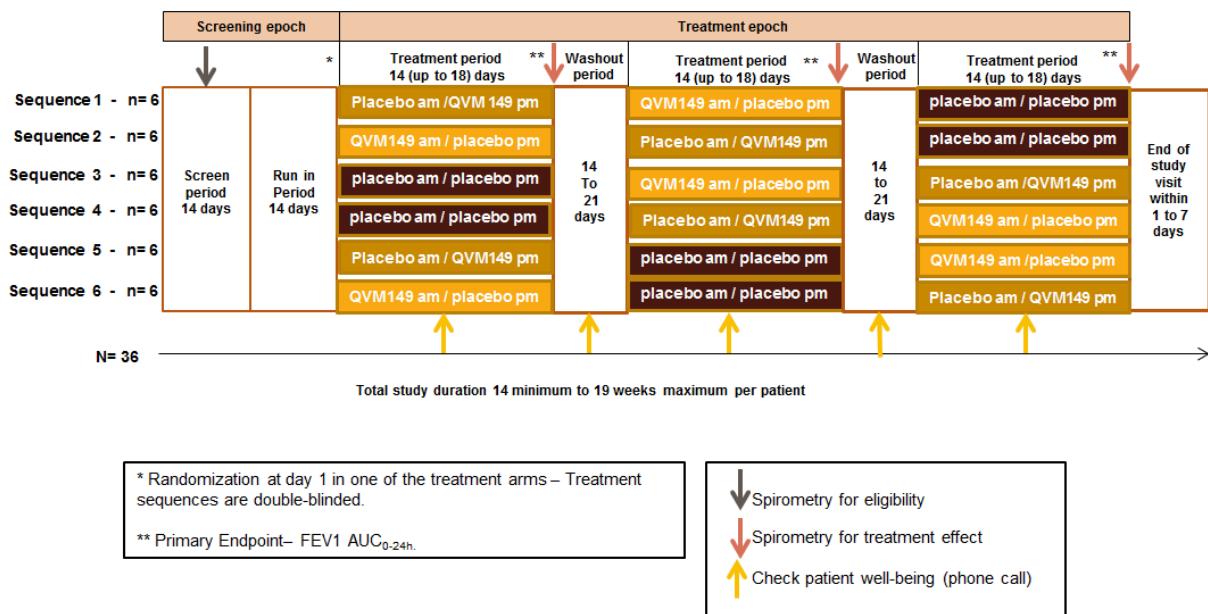
Objective	Endpoint
peak expiratory flow rate (PEF) of once daily orally inhaled QVM149 compared to placebo (all administered via the Concept1 inhalation device).	14 during the three treatment periods
<ul style="list-style-type: none">• To evaluate safety and tolerability of QVM149 when dosed in the morning or in the evening in patients with asthma during two weeks of treatment in each treatment period.	<ul style="list-style-type: none">• Adverse events• Hematology• Blood chemistry• Urinalysis• Vital signs• ECG

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3 Investigational plan

3.1 Study design

Figure 3-1 Study design



This is a randomized, placebo-controlled, double-blind, six-sequence, three-period cross-over study in asthma patients. The study will consist of a 14-day screening period, followed by a 14-day run-in period, and a treatment epoch which consists of three treatment periods, with a minimum duration of 14 days each followed (for the 2 first treatment periods) by a wash-out period. The duration of each treatment period may be extended up to a duration of 18 days if needed for operational reasons. The third treatment period will be followed by a Study Completion evaluation at 1-7 days following the last dose. The treatment periods will be separated by wash-out periods of 14 to 21 days duration.

The total duration of the study is approximately 13 weeks (minimum) to 19 weeks (maximum) for each patient.

Screening

Before any screening assessment and asthma drug cessation, patient has to agree to the study and complete informed consent process and provide written informed consent.

Screening assessments can be performed over a 2-week period maximum. Inclusion and exclusion criteria will be checked to confirm patient's eligibility.

At beginning of screening period, patient will be provided with a PEF-meter and a patient-diary for recording the measurements. At screening, only PEF need to be recorded with the device. A minimum of 5 days screening is required to allow for PEF reference calculation.

Patients who meet the eligibility criteria at screening will undergo run-in period.

Run-in

On Day 1 of the run-in period, patients will discontinue their previous asthma medication and remain off this medication throughout the run-in period. Patients will be provided with the short-acting β 2-agonist (SABA) salbutamol (dose strength of 100 μ g/puff; an equivalent SABA may be dispensed based on local availability) at the beginning of the run-in period.

Patients should use this provided SABA as rescue medication throughout the trial. Patients are required to measure their PEF twice per day (morning and evening) during the all run-in period.

Patient will also record their use of rescue medication during the run-in phase (SABA during run-in and wash-out; SABA and study medication during treatment periods) as well as asthma symptoms if any. This will allow for continuous monitoring of PEF, rescue medication use and asthma symptoms from the start of the run-in period to completion of the treatment epoch (end of treatment period three).

After approximately 7 days into the 14-day run-in period, patients will attend to the site for an outpatient visit. Site staff will control patient's PEF measurements and rescue medications use records as well as collect blood safety which will support patient eligibility for randomization.

Baseline is defined by the assessments to be performed at pre-dose treatment period 1 Day 1 only.

These assessments will confirm patient eligibility before randomization.

All run-in and baseline (day 1 pre-dose, treatment period 1) safety evaluation results must be available prior to randomization.

Randomization

At the end of the run-in period, patients will be randomized to one of 6 possible treatment sequences ([Figure 3-1](#)), each consisting of 3 double-blind treatment periods. Each treatment sequence will have approximately 6 patients. . Randomization will take place only if the patient tolerated withdrawal of controller medication (as judged by use of SABA, rescue medication use and PEF; details provided in [Section 4](#), exclusion criteria)

Details of study drug administration procedures are provided in [Section 6](#) of the protocol and in the Study Operations manual.

Study treatments

The treatments are:

1. QVM149 150/50/80 µg o.d. (indacaterol acetate 150 µg/ glycopyrronium bromide 50 µg/ MF 80 µg once daily) administered in the morning (plus matching placebo in the evening)
2. QVM149 150/50/80 µg o.d. (indacaterol acetate 150 µg/ glycopyrronium bromide 50 µg/ MF 80 µg once daily) administered in the evening (plus matching placebo in the morning)
3. placebo administered in the morning and in the evening.

To facilitate double-blind administration of study medication all patients will be dosed twice daily in all treatment periods as detailed in [Table 3-1](#) below:

Table 3-1 Study Treatments

Dosing time Treatment options	a.m. dosing	p.m. dosing
QVM149 morning dose	QVM149	Placebo
QVM149 evening dose	Placebo	QVM149
Placebo	Placebo	Placebo

Treatment period Day 1

On Day 1 of each treatment period patients will attend the site for an outpatient visit in the afternoon (approximately 1 to 2 hours before the first scheduled evening dose). Only the evening dose will be administered on Day 1.

Day 1 pre-dose assessments will be performed. Patient will be evaluated for randomization eligibility (but only at treatment period 1), trained /re-trained on the use of the Concept1 inhalation device and will administer the study drug or placebo under the guidance and supervision of site personnel at approximately 19:00 hours

Treatment period Day 2 to Day 13

The first morning dose of each treatment period will be administered on Day 2 of each treatment period. Patients will self-administer study drug on Days 2 to 13 of each treatment period at home.

Patients will be instructed to take the study medication in the morning (at approximately 07:00 hours) and in the evening (at approximately 19:00 hours) and to record their pre-treatment morning and evening PEF throughout the study in a diary.

Site staff will call the patient once a week during the treatment and during washout periods to verify patient well-being and to ensure none of the study discontinuation criteria ([Section 7.2](#)) are met.

Treatment period Day 14 and Day 15

Patients will attend to the site in the morning of Day 14 of each treatment period to inhale the morning dose of study medication or placebo under the guidance and supervision of site staff.

Site personnel will also review PEF measures and rescue medication intake as well as study drug compliance. Patients can stay on site for the remainder of Day 14.

Patient will be re-trained on the use of the Concept1 inhalation device under the guidance of site personnel.

Patients will then be admitted in the afternoon of Day 14 of each treatment period approximately 4 hours prior to Day 14 assessments in each treatment period. This time is required to ensure that patient will not take any rescue medication within 4 hours prior spirometry starts.

The last evening and morning dose of study drug or placebo will be administered under the guidance and supervision of site personnel at approx. 19:00 hours on Day 14 and approx. 07:00 hours on Day 15. For 24 hour repeated spirometric assessments, patients will remain domiciled (1 night). Spirometry will be performed from Day 14 starting before the evening dose (at approximately -5 min in relation to planned evening dosing time, i.e. at approximately 19:00 h) and then every 3 hours after administration of the evening dose until 24 hours after the Day 14 evening dose, i.e. until approximately 19:00 hours on Day 15.

After spirometry ended and last Day 15 visit assessment performed, the patient will be discharged and will start the wash-out period.

Wash-out (duration 14 to 21 days)

During the wash-out period, patient will continue to measure PEF and register rescue medication intake. Site personnel will call the patient weekly to check patient's well-being.

Procedures in treatment periods two and three are identical to the procedures of treatment period one apart from:

- Check of eligibility which occurs only prior to randomization on Day 1 of treatment period 1.
- At the end of treatment period three, the patient will complete end of study visit assessments instead of entering into a wash-out period.

Study completion

At the end of the last treatment period, patients will then undergo Study Completion evaluations and will be discharged from the study. The study design is shown in [Figure 3-1](#).

3.2 Rationale for study design

This short-term treatment cross-over design is chosen to characterize the bronchodilator effects of once daily QVM149 (indacaterol/glycopyrronium/MF 150/50/80 µg) either dosed in the morning or in the evening compared to placebo in asthma patients.

A 2-week screening period will allow for sufficient flexibility for patients and at the site to schedule all required assessments to ensure patient selection based on the inclusion and exclusion criteria. Screening procedures may be performed over more than one day within the defined 2-week screening period.

The 2-week run-in period will allow for an assessment of likely study adherence in the population of asthma patients since patients will be using short-acting rescue medication only. The run-in period will thereby help to ensure that patients who cannot tolerate withdrawal from ICS for a short period of time will not be randomized. The maximum duration that patients are on SABA only and off ICS (and other asthma medication) is 6 to 8.5 weeks (2 to 3 weeks of wash-out, 2 to 2.5 weeks during the placebo treatment period and 2 to 3 weeks during washout). This is in-line with previous studies conducted in comparable patient populations that showed that such duration of time off controller medication is tolerable for patients with the investigated severity of asthma ([Kempsford et al 2013](#), [Kempsford et al 2016](#)). If a patient's condition should deteriorate during the study the comprehensive rules on "Discontinuation of study treatment" ([Section 7.2](#)) will help ensure patient safety throughout the trial. Patients with more severe asthma are excluded from this study.

The run-in period of 2 weeks before the first treatment period as well as the washout periods of 2 to 3 weeks between the treatment periods will allow for pharmacodynamic assessments on Day 14/15 of each treatment period without any carry-over effect from previous medications present. Run-in and washout periods of approximately two-week duration have been successfully used in similar trials with a LABA/ICS combination ([Kempsford et al 2013](#)) or with an ICS ([Kempsford et al 2016](#)). For glycopyrronium, based on 24 hour spirometry data, the half-life of the bronchodilatory effect is estimated to be \leq 80 hours. Therefore the bronchodilatory effect is expected to be washed-out at the very latest following 17 days after last dose administration. Consequently, the proposed minimum 2 weeks washout plus 2 weeks of treatment in the next following treatment period are sufficient to avoid a carry-over pharmacodynamic effect between treatment periods for glycopyrronium as well. The duration of the washout periods of 2 to maximally 3 weeks is considered adequate to not put patients at undue risk for deterioration of their disease.

The crossover design (rather than a parallel group design) was chosen because within patient variability is expected to be less than between-patient variability for the assessed parameters. This allows for greater precision to be achieved whilst exposing a smaller number of patients to study treatment and assessments.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The components of QVM149 at the daily dose investigated in this trial are approved for COPD or asthma. QVM149 is delivered via the Concept 1 inhalation device, called Breezhaler® for approved products. QVM149 is formulated in a similar lactose-based formulation as in Onbrez Breezhaler® (indacaterol maleate) and Seebri Breezhaler® (glycopyrronium bromide) which are approved for use in COPD. In this formulation mometasone furoate is integrated as the third component. MF delivered with the Twisthaler® inhalation device is approved for asthma at matching doses.

In order to allow for placebo to be used in this trial patients with relatively mild asthma (low to mid-dose ICS use before enrollment, pre-bronchodilator FEV1 $\geq 60\%$ and $\leq 100\%$ of the predicted normal value for the patient, no systemic corticosteroids for asthma over the year preceding the study; further details available in [Section 4](#)) will be enrolled (please compare section on definition of patient population below). It is expected that patients generally can tolerate being off any controller medication and use SABA only for the short periods of time as required under this study protocol. Similar study designs have been employed in comparable patient populations in the past ([Kempsford et al 2013](#); [Kempsford et al 2016](#)). Furthermore, given the good tolerability profile of the components of QVM149, it is deemed acceptable to administer the triple fixed-dose combinations to the relatively mild asthmatics enrolled for the duration of 2 weeks each in the respective treatment periods.

Details justifying the dose of each component of QVM149 are given below:

Indacaterol acetate

Indacaterol maleate at a dose of 150 µg o.d. is marketed for the maintenance treatment of COPD. In a dose ranging study with indacaterol maleate in asthma patients (CQVA149A2210) which investigated single doses of indacaterol of 150 µg, 75 µg, and 37.5 µg o.d. with serial spirometry over 24 hours a clear dose-response profile was established for FEV1 over the entire dosing interval of 1 day with no discernible differences in the safety and tolerability profile between the doses. Another dose-ranging study of indacaterol maleate in asthmatic patients also demonstrated that a dose of 150 µg o.d. was safe and effective following 14 days of treatment (Study CQAB149B2357). In study CQAB149D2301, the acetate salt of indacaterol was found to result in a lower incidence of the post-inhalation cough compared to indacaterol maleate, without impact on efficacy or safety. The dose of indacaterol acetate 150 µg was also confirmed in Study CQMF149E2203 in adult asthma patients where indacaterol acetate 150 µg and 75 µg delivered via Concept1 and placebo were investigated following 12 weeks of treatment. Indacaterol acetate 150 µg showed positive trends in terms of trough FEV1, PEF and rescue medication use compared with indacaterol acetate 75 µg and significantly improved lung function compared to placebo. Therefore, a dose of indacaterol acetate 150 µg o.d. has been selected for use in the QVM149 program.

Glycopyrronium bromide

Glycopyrronium bromide (NVA237: 50 µg once daily in a lactose-based formulation) has been registered in the EU since 2012 as Seebri® Breezhaler® for the treatment of COPD.

Although no data exists for glycopyrronium bromide in asthma, extensive data from the Phase III development program in COPD supports the efficacy and safety of glycopyrronium bromide 50 µg once daily. It has demonstrated clinically meaningful and statistically significant improvements in lung function in COPD patients which were sustained over 24 hours and provided significant symptomatic benefits with a favorable safety and tolerability profile. Lung function improvements were comparable to tiotropium 18 µg administered via HandiHaler®.

The two LAMAs, glycopyrronium and tiotropium both demonstrate similar kinetic selectivity for M3 over M2 receptors, which is important for their similar long and sustained bronchodilator effects (Testi 2014). In phase 2 and phase 3 studies in COPD patients glycopyrronium bromide 50 µg o.d. and tiotropium (HandiHaler®) 18 µg o.d. show similar bronchodilator effects (CNVA237A2205, CNVA237A2303). It is therefore expected that glycopyrronium bromide 50 µg once-daily will provide similar efficacy in an asthma population as Triotropium Respimat® 5 µg once-daily (considered equivalent to tiotropium 18 µg administered via HandiHaler® and has recently been approved in Europe for treatment of asthma).

Based on the available data glycopyrronium bromide 50 µg is considered an appropriate dose for further development in asthma as part of triple FDC QVM149 (LABA/LAMA/ICS) used in this study.

Mometasone furoate

Mometasone furoate (MF) is approved for the treatment of asthma in doses of up to 800 µg per day as Asmanex Twisthaler® in many countries of the EU, Japan, the US, Canada, and other countries world-wide. Since available data for the MF component exists in the Twisthaler® device, we conducted a 3 step bridging approach to determine the MF dose (to be delivered with the Concept 1 inhalation device) which is comparable to each of the registered daily doses of Asmanex Twisthaler® (MF, inhalation powder). This was necessary due to differences in device performance characteristics between the Twisthaler® and Concept1 devices.

Step 1: pharmacokinetic bridging utilizing pharmacokinetic characterization in study CQMF149E2101 followed by in-vitro fine particle mass adjustment (step 2) and finally pharmacodynamic evaluation of efficacy in asthma patients in study CQMF149E2201 (step 3).

For Step 1 and 2, the data of study CQMF149E2101, along with in-vitro fine particle mass adjustments have led to the selection of 80, 160 and 320 µg as doses of MF in Concept1 device that are comparable to the approved doses 200 µg, 400 µg and 800 µg (2x400 µg) MF in Twisthaler®.

For Step 3, two of the MF doses in Twisthaler® and Concept1 were further evaluated for pharmacodynamic and clinical comparability in a 4-week study (CQMF149E2201) in patients with persistent asthma. MF doses of 80 µg and 320 µg delivered once daily via Concept1

showed comparable efficacy in trough FEV1 and slightly lower systemic exposure compared to MF doses of 200 µg and 800 µg (2 x 400 µg) delivered once daily via Twisthaler® confirming the selected doses for MF Concept1 are appropriate for further QMF149 Concept1 development.

In summary, MF doses of 200 µg o.d., 400 µg o.d. and 400 µg b.i.d. delivered by Twisthaler® are comparable with MF doses of 80 µg o.d., 160 µg o.d. and 320 µg o.d., respectively in QMF149 delivered by Concept1.

For QVM149, as a result of a component interaction in the pharmaceutical formulation, an increase in the MF fine particle mass (FPM) in the QVM149 combination product compared to the corresponding same nominal MF dose in QMF149 (matched to Asmanex® Twisthaler®) was observed. To adjust for this, the nominal doses of MF have been reduced to 80 µg o.d. and 160 µg o.d. to ensure that the fine particle mass (FPM, in-vitro aerosol performance) in the lactose blend formulation for the triple FDC is comparable to the nominal MF doses of 160 µg o.d. and 320 µg o.d. for QMF149 program, respectively. Therefore 400 µg MF via Twisthaler® is comparable with 160 µg MF in QMF in Concept 1 and with 80 µg QVM149 via Concept1 (Table 3-1); all provide similar fine particle mass and thereby are expected to provide similar lung and systemic exposure, since oral bioavailability of MF is low.

QVM149 is available in two formulations that differ by MF dose strength only. The indacaterol and glycopyrronium dose is constant. In this study the dose containing 80 µg MF is investigated. This is the lower of the two MF doses within the available formulations of the QVM149 FDC that is investigated in the ongoing phase III program. It is expected that a potential differential effect of morning and evening dosing of QVM149 on lung function compared to placebo would be less easily detectable with the high MF dose. This is based on earlier study results using MF (in a different formulation and delivered with the Twisthaler® inhalation device) in asthma patients in which there was a trend toward some separation in lung function effect following morning and evening dosing of MF which seemed to be more visible at lower MF doses ([Noonan et al 2001](#)).

Table 3-2 Comparison of the comparable MF component doses between Asmanex® Twisthaler®, QMF149 and QVM149 drug products

MF dose level	Asmanex® Twisthaler®	MF in QMF149	MF in QVM149
Low	200 µg	80 µg	not applicable
Mid	400 µg	160 µg	80 µg
High	800 µg	320 µg	160 µg

Duration of treatment

The entire treatment epoch consists of 3 treatment periods of 14 days each (up to 18 days if required for operational reasons; this added flexibility is not expected to impact on lung function read-outs as evidenced by earlier studies investigating lung function effects of ICS or ICS/LABA).

A 2-week treatment per period is considered sufficient to investigate the effect of a.m. and p.m. dosing of QVM149 in comparison to placebo. Based on available data for indacaterol in COPD patients it is not expected that indacaterol exerts a differential effect on lung function by time of dosing (study QAB149B2305). Since the bronchodilator effects of indacaterol are largely evident after the first few days of dosing the treatment duration of 2 weeks is considered sufficient. These aspects hold true for glycopyrronium as well, however, a study investigating both, morning and evening dosing has not been conducted. Data on time to maximal effect is available from studies in COPD patients but not asthma (NVA237A2205, NVA237A2208). Supportive evidence is available from a study that investigated effect of time of dosing of tiotropium, another LAMA, on lung function parameters. This study suggests that once-daily LAMAs can be administered any time of the day ([Calverley et al 2003](#)). For ICS a plateau in lung function effect may be achieved only later than after two weeks ([Corren et al 2003](#)). However, in study QMF149E2201 which investigated MF delivered via the Concept1 and the Twisthaler® inhalation devices the majority of the increase in FEV1 from baseline was already evident after 2 weeks of treatment with only small incremental additional lung-function benefit until the end of week 4. This confirmed an earlier study in which different doses of mometasone furoate (delivered by the Twisthaler® inhalation device) were given over 12 weeks. The change from baseline FEV1 after 2 weeks of treatment was approximately 71% to 83% of the effect seen after 12 weeks of treatment ([D'Urzo et al 2005](#)). Similarly, [Karpel et al 2005](#) described approximately 76% and 80% of maximal lung function effect of MF delivered by the TH after 12 weeks as either b.i.d. or o.d. dose. In addition, the approach to assess ICS treatments in comparison to placebo over two week treatment periods has been used successfully with clear differentiation of lung function profiles compared to placebo ([Kempsford et al 2016](#), [Kempsford et al 2013](#)).

3.4 Rationale for choice of comparator

This is a placebo-controlled trial to establish assay sensitivity and to allow for an unbiased assessment of the lung function effect of a.m. and p.m. dosing of QVM149. Without the placebo control an assessment of the overall absolute effect of morning and evening dosing of QVM149 could not be established. Precedence in the literature and in regulatory documents substantiates this approach ([Kempsford et al 2013](#), [Kempsford et al 2016](#), [European Public Assessment Report on Relvar Ellipta 2013](#)).

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3.6 Risks and benefits

The risks to which patients participating in this study will be exposed may be divided into those associated with the conduct of the study itself, and those associated with the investigational treatment (QVM149).

Risks associated with study conduct

Patients will be required to perform repetitive lung function measurements during the study, and these can lead to cough, shortness of breath, dizziness, or exhaustion. Since patients only carry out full forced maneuvers during clinic visits (not at home), these will be performed under medical supervision to ensure availability of immediate aid if required. Considering the 2 week treatment duration per period, the number of assessments is small and these are part of the regular medical assessments of this patient population. Other procedural risks are related to blood sampling for safety laboratory. Puncturing of the veins can cause discomfort, pain, hematoma, or in rare cases lead to an infection.

Risks associated with investigational treatment (QVM149)

In light of their underlying asthma disease and the inclusion requirements in this study, patients have been exposed to ICS and likely β 2-agonist bronchodilators (e.g. SABA) before entering the trial.

MF, the ICS component of QVM149 is approved for the treatment of asthma.

The safety and tolerability profile of indacaterol, the LABA component in QVM149 is comparable to that of other medications of the same classes (e.g. formoterol, salmeterol).

The third component of QVM149, glycopyrronium bromide 50 μ g is approved for the maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Evidence for the efficacy and safety of glycopyrronium bromide has been extensively provided via studies in approximately 6,028 healthy patients and COPD patients across 34 completed studies. Addition of LAMA (Spiriva[®] Respimat[®]) to ICS/LABA is now a recommended treatment option in [GINA 2016](#) guideline for step 4 onwards. As glycopyrronium and tiotropium (HandiHaler[®]) demonstrated comparable efficacy and safety in COPD, it is reasonable to expect that both drugs would show similar risk-benefit profiles in asthma. The risk-benefit profile of glycopyrronium bromide has been shown to be positive in COPD patients. Overall there is less comorbidity in asthma patient populations; therefore the safety profile in an asthma population is also expected to be positive.

With any inhaled drug allergic reaction to the drug or to formulation excipients cannot be fully ruled out. Also, reflex bronchoconstriction can occur as an unspecific intolerance reaction to inhaled drugs. Patients are under clinical observation at the site when inhaling the drugs for the first time so that the emergence of allergic or other intolerance reactions can be detected. When indacaterol is inhaled patients may react with short-lasting cough immediately after inhalation; this post-inhalational cough was not associated with other symptoms or bronchial obstruction in previous studies.

The characteristic adverse effects, contraindications, warnings and interactions with other medications of the components of QVM149 are provided in [Section 1.3.1](#) and in more detail in the QVM149 investigator brochure as well as SmPCs for indacaterol (Onbrez[®] Breezhaler[®]), mometasone (Asmanex[®] Twisthaler[®]) and glycopyrronium (Seebri[®] Breezhaler[®]). Patients participating in this trial may experience these adverse effects.

In addition, there is extensive evidence of the efficacy and safety of the two dual combinations indacaterol acetate/mometasone furoate (QMF149) and indacaterol maleate/glycopyrronium bromide (QVA149, marketed as Ultibro® Breezhaler®) which are part of the FDC triple QVM149. Up to now no additional risks have been identified in completed and ongoing clinical studies with the FDCs which might occur when two or three of the components are administered concurrently or from the same inhaler.

During the run-in period, the washout period between treatment periods as well as the treatment period in which the patient will receive placebo the patient will be without asthma controller medication (no background ICS, only SABA as rescue medication is available throughout the trial). This change in asthma treatment may lead to worsening of lung function and/or asthma symptoms.

Management and mitigation of risks

Frequent and regular contacts between patients and study staff will occur in terms of clinic visits and intermittent telephone calls throughout the treatment periods. The site will contact the patient approximately once per week to ensure adequate clinical monitoring of participating patients. In addition, safety monitoring (e.g. collection of symptoms and rescue medication use via the combined device PEF-patient electronic diary), assessment of compliance with study medication regimen, and twice daily PEF measurements throughout the study will help assess a patient's health status. Therefore, investigators may have an early indication of worsening symptoms and will be able to monitor the patient closely throughout the study. Furthermore, comprehensive stopping criteria have been defined ([Section 7.2](#)) to ensure a patient safety.

Guidance to manage potential worsening of asthma symptoms will be provided to investigators consistent with guideline recommendations ([GINA 2016](#)). Patients will receive well written instructions as to how to contact the investigator in the event of worsening of their asthma symptoms. The investigator should discontinue study treatment for a given patient and/or withdraw the patient from the study if, on balance, he/she believes that continuation would be detrimental to the patient's well-being. Patients are also instructed that they can withdraw from the study at any time, and for any reason ([Section 7.2](#)).

In this clinical study all patients will receive the glucocorticosteroid MF (ICS component of QVM149). Since glucocorticosteroids are teratogenic in rodents and rabbits, only women of childbearing potential (WOCBP) who agree to use highly effective methods of contraception (see [Section 4.2](#) eligibility criteria) will be permitted to participate in the study. Women of child bearing potential will be informed that taking the investigational 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 ***highly effective contraception*** requirement for the duration of the study ([Section 4.2](#)). If there is any question that the patient will not reliably comply, they will not be entered in the study.

QVM149 is under development and therefore it is possible that unexpected safety issues may be identified. Risks will be minimized by compliance with the eligibility criteria and close clinical monitoring of patients.

There may be unknown risks of QVM149 which may be serious.

Benefits

There is no intended benefit for the patients in this study and the study is not designed to provide substantial benefit for the patient. Benefits may, however, include an improvement in pulmonary function and a potential translation into better asthma control such as reductions in symptoms and rescue medication use during the QVM149 treatment periods. A thorough medical evaluation of the patient's disease and close clinical monitoring for the duration of the study may provide additional patient benefit.

Conclusion

In conclusion, the risk-benefit assessment for this study suggests that the patients are not exposed to any undue risk, that adequate safety measures are in place to protect study participants, and that the study according to this protocol is conducted in accordance with ethical and regulatory requirements.

3.6.1 Blood sample volumes

A maximum of 100 mL of blood is planned to be collected over a period of 13 to 19 weeks from each patient as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule ([Section 8.1](#)).

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

See [Section 8.9](#) regarding the potential use of residual samples.

4 Population

The study population will be comprised of male and female patients aged 18 and above with asthma. Approximately **36** adult patients will be randomized with the intention that at least **30** patients complete the study.

The investigator must ensure that all patients being considered for the study meet eligibility criteria. No additional exclusions should be applied by the investigator.

Patient selection is to be established by checking through all inclusion and exclusion criteria at screening and at the first baseline visit. Source documentation relating to eligibility must be stored at the study site.

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

Patients who are prematurely withdrawn from the study for any reasons will not be replaced.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients aged ≥ 18 and above
3. Patients with a documented physician diagnosis of asthma and who additionally meet the following criteria:
 - patients receiving daily treatment with an inhaled corticosteroid at a low or medium daily dose as defined by GINA guidance ([GINA 2016](#), Box 3-6),
 - on a stable regimen (dose unchanged) for at least 4 weeks prior to screening.
4. Pre-bronchodilator FEV1 $\geq 60\%$ and $< 100\%$ of the predicted normal value for the patient (after withholding bronchodilators) during screening.
 - Withholding period of bronchodilators prior to spirometry (also applicable for Reversibility testing) are given in [Table 5-1](#).
 - Re-testing is allowed once. Re-assessment of percentage predicted FEV1 should be done in an ad-hoc visit to be scheduled on a date that would provide sufficient time to receive confirmation from the spirometry data central reviewer of the validity of the assessment before randomization
5. Patients who demonstrate an increase in FEV1 of $\geq 12\%$ and ≥ 200 mL after administration of 400 μg salbutamol/360 μg albuterol (or equivalent dose) at Visit 1 (Screening). All patients must perform a reversibility test at Visit 1.
If reversibility is not demonstrated at Screening, then, reversibility testing may be repeated once during the screening epoch on a date that would provide sufficient time to receive confirmation from the spirometry data central reviewer of the validity of the assessment before randomization.
If reversibility is not demonstrated after repeated assessment, patients must be screen failed.
6. At screening, and baseline (day 1 pre-dose time) of the first treatment period, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position and again in the standing position as outlined in the SOM.

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7. Hypertensive patients must have been on stable antihypertensive therapy for at least 4 weeks prior to screening to be included in the trial.

8. Patients must weigh at least 50 kg at screening to participate in the study, and must have a body mass index (BMI) within the range of 18 to 40 kg/m².
9. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

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

1. Contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class, or any component thereof.
 - Sympathomimetic amines / adrenoreceptor agonist agents
 - Antimuscarinic agents
 - Lactose or any of the other excipients of the study drug (including patients with history of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption)
2. Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 1 year of Screening.
3. Patients who have had a respiratory tract infection or asthma worsening within 4 weeks prior to Screening. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening.
4. Patients who have had previous intubation for a severe asthma attack/exacerbation.
5. Patients with a history of chronic lung diseases other than asthma, including (but not limited to) COPD, sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis and active tuberculosis.
6. Patients with a history of clinically relevant bronchoconstriction upon repeated forced expiratory maneuvers.
7. History of paradoxical bronchospasm in response to inhaled medicines.
8. Patients with any chronic conditions affecting the upper respiratory tract (e.g. chronic sinusitis) which in the opinion of the investigator may interfere with the study evaluation or optimal participation in the study.
9. Patients who during the run-in period require the use of ≥ 12 puffs / 24 hours of rescue medication for 48 hours (over two consecutive days) or who have a decline in PEF from the reference PEF (PEF reference during screening period defined in [Section 8.5.2](#)) of $\geq 30\%$ for 6 consecutive scheduled PEF readings (including readings taken in the morning and evening).

10. History or current diagnosis (at Screening and prior to randomization) of any the following ECG abnormalities:
 - Clinically significant cardiac arrhythmias (for example sustained ventricular tachycardia, and second or third degree AV block)
 - History of familial long QT syndrome or known family history of Torsades de Pointes
 - Paroxysmal (e.g., intermittent) atrial fibrillation.
 - Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., cardioselective beta blockers, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be considered for inclusion. In such patients, atrial fibrillation must be present at screening with a resting ventricular rate < 100/min.
 - Any other clinically significant ECG abnormality
11. Concomitant use of an agent known to prolong the QT interval unless it can be discontinued for the duration of study.
12. Patients with a history of long QT syndrome or whose QTc measured at Screening (Fridericia method) is prolonged (> 450 msec for males and > 460 msec for females).
13. Patients with a history of myocardial infarction within the previous 12 months.
14. Patients who in the judgment of the investigator have a clinically significant condition such as (but not limited to) unstable ischemic heart disease, New York Heart Association (NYHA) Class III/IV left ventricular failure arrhythmia, uncontrolled hypertension, cerebrovascular disease, psychiatric disease, neurodegenerative diseases, or other neurological disease, uncontrolled hypo- and hyperthyroidism and other autoimmune diseases, hypokalemia, hyperadrenergic state, or ophthalmologic disorder or patients with a medical condition that might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study
15. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
16. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
17. In this study QVM149 which contains an ICS is administered during two of the three treatment periods. Therefore, women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 4 weeks after stopping of investigational drug are excluded. ***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), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

- Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected or implanted 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 be 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), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. Refer to [Section 8.6.6](#) (Pregnancy and Assessments of Fertility).

A pregnancy test will be performed for all female patients regardless of reported reproductive status at specified time points throughout the study.

If requested by local authorities, additional and more frequent pregnancy testing might be performed.

18. Patients with Type I diabetes or uncontrolled Type II diabetes (HbA1c > 9%) at screening.
19. Plasma donation > 150 mL within 7 days prior to first dosing.
20. Donation or loss of 400 mL or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation.
21. Other significant illness which has not resolved within two (2) weeks prior to initial dosing. Patients may be re-screened 4 weeks after recovery from their illness.
22. Recent (within the last three years) and/or recurrent history of autonomic dysfunction (e.g., recurrent episodes of fainting, palpitations, etc.).
23. Patients receiving medications in the classes listed in [Section 5.2](#) (Prohibited treatment) should be excluded.
24. Use of other investigational drugs at screening, or within 30 days or 5 half-lives of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations.
25. Current smokers and patients who have smoked or inhaled tobacco products within the 6 month period prior to Screening, or who have a smoking history of greater than 10 pack years (*Note: 1 pack is equivalent to 20 cigarettes. 10 pack years = 1 pack /day x 10 yrs., or ½ pack/day x 20 yrs.*).
26. 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.

27. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the patient in case of participation in the study. The Investigator should make this determination in consideration of the patient's medical history and/or clinical or laboratory evidence of any of the following:

- Inflammatory bowel disease, peptic ulcers, gastrointestinal including rectal bleeding;
- Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection;
- Pancreatic injury or pancreatitis;
- Liver disease or liver injury as indicated by abnormal liver function tests. ALT (SGPT), AST (SGOT), γ -GT, alkaline phosphatase and serum bilirubin will be tested during screening epoch.

28. Patients with seasonal allergy whose asthma is likely to deteriorate during the study period.

29. Patients on Maintenance Immunotherapy (desensitization) for allergies for less than 3 months prior to randomization or patients on Maintenance Immunotherapy for more than 3 months prior to randomization but expected to change throughout the course of the study.

30. Patients with evidence upon visual inspection (laboratory culture is not required) of clinically significant (in the opinion of investigator) oropharyngeal candidiasis during Screening, with or without treatment. Patients may be re-screened once their candidiasis has been treated and has resolved.

31. Patients who have a clinically significant laboratory abnormality at Screening epoch in the opinion of the investigator (one re-test is allowed before the randomization).

32. Patients with a serum potassium or magnesium level below the laboratory limit of normal at screening.

33. History of being immunocompromised; immunodeficiency diseases.

34. No person who is considered vulnerable or person who is in detention may participate in this study.

35. Patients with a known history of non-compliance to medication or who were unable or unwilling to complete a patient diary or who are unable or unwilling to use Electronic Peak Flow with e-diary device.

36. Patients unable to use the Concept1 dry powder inhaler or a metered dose inhaler.

37. Patients with narcolepsy and/or insomnia.

38. Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers).

39. Patients who are directly associated with any members of the study team or their family members

40. Patients incapable of understanding the nature, significance and implications of the clinical trial and therefore incapable of giving consent personally

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

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

5.1 Contraception requirements

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement outlined in the [Section 4.2](#) (Exclusion Criteria). If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

5.2 Prohibited treatment

Restrictions for medications other than study drug apply according to below tables:

Table 5-1 Withholding period of bronchodilators prior to spirometry

Class of Medication	Minimum cessation prior spirometry
SABA	≥ 6 h
SAMA	≥ 8 h (only applicable at screening)
LABA or fixed dose combination of ICS/LABA b.i.d.	≥ 24 h (only applicable at screening)
LABA or fixed dose combination of ICS/LABA o.d. or tiotropium	≥ 48 h (only applicable at screening)
Xanthines	≥ 7 days (only applicable at screening)

Table 5-2 Prohibited asthma medication during treatment period

Medication	Action to be taken
Long-acting anti-cholinergic agents (other than study drug)	<i>patient to be withdrawn</i>
Short-acting anti-cholinergics	<i>patient to be withdrawn</i>
Fixed-combinations of long-acting β_2 -agonists and inhaled corticosteroids	<i>patient to be withdrawn</i>
Long-acting β_2 -agonists (other than study drug)	<i>patient to be withdrawn</i>
Short acting β_2 -agonists (other than those prescribed in the study)	<i>patient to be withdrawn</i>
Theophylline and other xanthines	<i>patient to be withdrawn</i>
Inhaled (other than study drug), parenteral or oral corticosteroids	<i>patient to be withdrawn</i>
Newly introduced or increased dose leukotriene antagonists, ketotifen, inhaled nasal cromolyn, nedocromil, inhaled nasal corticosteroid	<i>patient to be withdrawn*</i>

*Leukotriene antagonists, ketotifen, inhaled nasal cromolyn, nedocromil, inhaled nasal corticosteroid are allowed for the treatment of asthma or allergic conditions during the study if taken regularly every day as part of the patient's treatment regime, and if treatment has been stable for 4 weeks prior to screening.

Table 5-3 Prohibited treatments, cessation periods

Medication*	Minimum cessation period prior to Day 1 or as indicated
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug)	7 days prior to Day 1
Non-selective systemic β -blocking agents	7 days prior to Day 1
Cardiac anti-arrhythmics Class Ia	7 days prior to Day 1
Cardiac anti-arrhythmics Class III	7 days, amiodarone 3 months prior to Day 1
All antipsychotic agents (first, second and third generation, inclusive of atypical antipsychotics). Combinations of antipsychotic agents with antidepressants are prohibited	14 days prior to Day 1
Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)	14 days prior to Day 1
Monoamine-oxidase inhibitors	14 days prior to Day 1
Systemic anticholinergics	7 days prior to Day 1
Mizolastine or terfenadine (H1 antagonists)	5 days prior to Day 1
Strong inhibitors of cytochrome P4503A e.g.ketoconazole	7 days prior to Day 1
Tricyclic antidepressants (Please note that tetracyclics which are similar in class with regards to drug interaction are also to be excluded)	14 days prior to Day 1
Other investigational drugs	30 days or 5 half-lives, whichever is longer prior to Day 1
Parenteral or oral corticosteroids	Within 30 days prior to Day 1
Noradrenaline reuptake inhibitors	7 days prior to Day 1
Live attenuated vaccine	30 days prior to Day 1

* Informed consent needs to be signed before to cessation period starts.

Table 5-4 Medication allowed under certain conditions if taken as follows

Class of Medication	Condition under which medication is permitted
Selective Serotonin Reuptake Inhibitors	Stable dose for at least 30 days prior to the Screening and during the trial.
Topical corticosteroids for skin disease	Stable dose for at least 30 days prior to Screening.
H ₁ -antagonists except mizolastine or, terfenadine	Stable dose/regimen for at least 5 days prior to Screening
Inactivated influenza, pneumococcal or any other inactivated vaccine	Not administered 48 hours prior to the 1st dose in treatment period 1 and anytime thereafter during the trial. Vaccinations within 48 hours and afterward are not allowed.

5.3 Dietary restrictions and smoking

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

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

5.4 Other restrictions

No unusual (for individual patients) strenuous physical exercise (e.g. weight training, aerobics, football) for 7 days before first dosing of Treatment period 1 until after Study Completion evaluation.

6 Treatment

6.1 Study treatment

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

6.1.1 Investigational and control drugs

Table 6-1 Overview of study medication

Study drug name	Formulation	Appearance	Unit dose	Packaging	Provided by
QVM149 and Concept1 Inhaler	Capsules with powder for Inhalation	Hard capsules	150/50/80µg	Provided as single blind supplies including Concept1 devices	Novartis Drug Supply Management
Placebo to QVM149 and Concept1 Inhaler	Capsules with powder for Inhalation	Hard capsules	0µg	Provided as single blind supplies including Concept1 devices	Novartis Drug Supply Management
Placebo to QVM149 and Concept 1 Inhaler as training kit	Capsules with powder for Inhalation	Hard capsules	0µg	Blister +Inhaler	Novartis Drug Supply Management
Concept1 device	NA	Single-dose dry powder inhaler	NA	Inhaler	Novartis Drug Supply Management

6.1.2 Additional study treatment

No additional treatment beyond investigational drug and control drug are included in this trial. Rescue medications are described in [Section 6.10](#).

6.2 Treatment arms

Study treatments are defined as:

- A: Matching placebo (am); QVM149 150/50/80 µg (pm)
- B: QVM149 150/50/80 µg (am); Matching placebo (pm)
- C: Placebo (am); Placebo (pm)

Patients will be randomized to one of the following 6 treatment sequences (defined according to a Williams design for 3 treatments and 3 periods) in the ratio of 1:1:1:1:1:1.

Table 6-2 Definition of treatment sequences

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	A	C
3	C	B	A
4	C	A	B
5	A	C	B
6	B	C	A

6.3 Treatment assignment and randomization

Randomized treatment will be assigned to individual patients by way of a randomization number, which will be in the range of 5101-5136.

The randomization number is only used to identify which treatment the patients have been randomized to receive. The Patient number assigned to a patient at screening remains the unique identifier for the patient throughout the study. For information on patient numbering, please see 'Patient numbering' section in the SOM.

The table below details the general details of the numbering of the patients once randomized to treatment:

Table 6-3 Randomization assignment numbering

Cohort	Randomization numbers
I (n=36)	5101 – 5136

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers.

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

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

The investigator will enter the screening number and medication number in the eCRF. IRT will assign to the patient a unique patient identification number at screening. This unique patient number will be used throughout all the study and no randomization will be entered in the eCRF.

6.4 Treatment blinding

This is a patient, investigator and sponsor-blinded study. Patients, investigators and sponsor will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single patient at site for safety reasons (necessary for patient management) will occur via an emergency system in place at the site (see [Section 6.7](#)).

Drug product will be supplied in single-blind patient packs, so an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist will receive a randomization list or treatment allocation cards from Drug Supply Management with the appropriate treatment allocation numbers. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor staff

The following unblinded sponsor roles are required for this study:

Unblinded clinical staff managing drug re-supply to site

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual patients.

Sponsor clinical staffs are required to assist in the management and re-supply of investigational drug product. These individuals are not provided with randomization lists directly, but may be unblinded through communication of drug re-supply needs via the unblinded site pharmacists.

For interim analysis purpose, the Independent Statistician / Programmer / Modeler will receive unblinded sample data from the sample analysts to report results for review.

All other sponsor staff (study statistician, study programmer, biomarker expert, clinical trial team, decision boards etc) will stay blinded to treatment assignments (except in the case of a safety event necessitating unblinding) until database lock.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure until clinical database lock.

Following final database lock all roles may be considered unblinded. See [Table 6-4](#) for an overview of the blinding/unblinding plan.

Table 6-4 Blinding and unblinding plan

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single patient unblinded)	Interim Analysis
Patients/Patients	B	B	UI	B
Site staff	B	B	UI	B
Unblinded site staff e.g. unblinded pharmacist or designee	B	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff e.g. for drug re-supply, unblinded monitor(s)	B	UI	UI	UI
Statistician/statistical programmer	B	B	UI	B
All other sponsor staff not identified above (trial team, project team, management & decision boards, support functions)	B	B	UI	B

UI: Allowed to be unblinded on individual patient level

B: Remains blinded

NA: Not applicable to this study

6.5 Treating the patient

QVM149 and placebo will be administered to the patient orally via inhalation. Administration will occur at the clinical site under supervision of study personnel at Day 1, Day 14 and Day 15 of each treatment period. On other days (Day 2 to Day 13), study drug will be taken at home. See the Site Operations Manual and [Section 16-Appendix 2: Instruction for Use of Concept1](#) for further details.

Patients will be instructed to take both morning and evening doses of study medication at approximately the same time of day (both in the morning and evening). Patients will be instructed to rinse their mouth after inhalation of study drug (2 times with approximately 30 mL water). Water used for mouth rinsing should be spat out and should NOT be swallowed.

From Day 2 to Day 13

In each treatment period, from Day 2 to Day 13, administration of study medication should occur within \pm 1h of the time of dosing on Day 1 (for evening dose) and Day 2 (for morning dose) in Treatment period 1. Morning and evening dosing should be approximately 12 hours apart.

On Day 14 and Day 15

On Days 14 and 15 study drug must be administered at 07:00h and 19:00h with a time window of \pm 30 min. There must be 12 hours in between morning and evening doses on Days 14 and 15. A deviation of \pm 15 min is acceptable.

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

6.6 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and/or interruptions are not permitted.

6.7 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. 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 treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the Study Team that the code has been broken.

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

- protocol number
- study drug name (if available)
- patient number.

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

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given patient.

6.8 Treatment exposure and compliance

For treatment administration at the site, compliance will be ensured by administration under the guidance and direct supervision of the investigator/designee. The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Compliance will be assessed by the Investigator and/or study personnel at each visit using capsule counts and information provided by the patient. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Furthermore, compliance with the intake of rescue medication and study drug treatment at home will be monitored closely by a review of electronic patient diary in which all patients will record administration each day on morning and evening.

6.9 Recommended treatment of adverse events

Medication used to treat adverse events (AEs) must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.10 Rescue medication

At Day 1 of the run-in period, all patients will be provided with a short acting β 2-agonist (100 μ g salbutamol/90 μ g albuterol or equivalent dose). Patients will be instructed to use it throughout the study as rescue medication on an 'as needed basis'. Patients will be advised that between visits they can take their rescue medication for symptoms of intercurrent bronchospasm. No other rescue treatment is permitted. Also refer to [Section 3.1](#) (Study design), [Section 4.2](#) (Exclusion criteria), [Section 5.2](#) and [Section 7.2](#) (Discontinuation of study treatment) for details.

6.11 Concomitant treatment

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study.

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 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.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before randomizing a patient or, if the patient is already enrolled, to determine if the patient should continue participation in the study.

7 Study completion and discontinuation

7.1 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 Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All randomized and/or treated patients should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in [Section 9.2](#) and the Site Operations Manual. Documentation of attempts to contact the patient should be recorded in the source documentation.

7.2 Discontinuation of study treatment

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

Study treatment must be discontinued and the patient withdrawn from the study under the following circumstances:

- Patient decision - patients may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the patient or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the patient's safety
- Any severe or serious adverse event considered at least possibly related to the study medications
- Pregnancy (see [Section 8.6](#) (Safety) and [Section 9.5](#) (Pregnancy reporting))
- Use of prohibited treatment as outlined in [Section 5.2](#) (Prohibited treatment)
- For liver event occurs, refer to [Appendix 1](#): Liver Event Definitions and Follow-up Requirements
- ≥ 3 consecutive days in any one treatment period in which ≥ 12 inhalations/day of SABA rescue medication were used
- Patients who have a decline in PEF from the reference PEF (during screening period) of $\geq 30\%$ for 6 consecutive scheduled PEF readings (including readings taken in the morning and evening) at any point during the study.

Emergence of the following adverse events:

- Paradoxical bronchospasm as evidenced either by a significant increase in wheeze and dyspnea shortly after the administration of study drug or a fall in FEV₁ of $>20\%$ within 30 minutes of administration of study drug

- Reflex bronchoconstriction or other severe intolerance reaction to study drug inhalation
- If the absolute QTcF is >500 msec or an increase from pre-dose Treatment Period 1 of >60 msec on two adequate ECGs at least a minute apart, second (if Mobitz Type 2) or third degree AV block, atrial or ventricular arrhythmias (as judged clinically significant by the investigator).
- Clinical asthma worsening which required additional asthma treatment other than study medication or study-defined rescue medication in any one treatment or washout period.

Any of the following laboratory abnormalities:

- Random (non-fasting) plasma glucose greater than 15 mmol/L
- Serum potassium below the lower limit of the laboratory reference range if confirmed by a repeat test to exclude laboratory error
- Urine cotinine > than the laboratory's lowest level of quantification (LoQ of 500 ng/mL or lower) after randomization (a positive test at screening would preclude inclusion into the study)

Discontinuation of study treatment and patient withdrawal will be at the discretion of the Investigator, under the following circumstances:

- Clinically significant abnormal laboratory value(s) (as judged clinically significant by the investigator).
- The Investigator deems discontinuation is necessary for the safety of the patient.

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

If discontinuation of study treatment occurs, investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

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 7.3](#), Withdraw of Informed Consent). Where possible, they should return for the assessments indicated by an asterisk (*) 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 the patient/pre-designated contact as specified in [Section 7.4](#) (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

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

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

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

Patients who are prematurely withdrawn from the study for any reasons will not be replaced.

7.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore and
- Does not want any further visits or assessments and
- Does not want any further study related contacts and
- Does not allow analysis of already obtained biologic material.

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient'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 patient are not allowed unless safety findings require communicating or follow-up.

7.4 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 cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study stopping rules

The study will be halted with no further recruitment and dosing suspended for all study participants pending a safety review if two or more study-drug related SAEs are reported or if the aggregate of severity, frequency, and/or drug relatedness of AEs, in the opinion of the investigator or Novartis, merit halting the study. Further dosing may only commence if deemed safe after a full safety review by the Novartis Translational Medical Expert (TME) and investigator.

7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, patients must be seen as soon as possible and treated as a prematurely discontinued patient. 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 investigator will be responsible for informing Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

Table 8-1 Assessment schedule

Epoch	Screening			Treatment Epoch 1 / Treatment Epoch 2 / Treatment Epoch 3 ²				
Visit Name	Screening	Run in		Treatment periods ³			Washout ⁵	Day 1 next Epoch or EOS
Visit Numbers ¹	1	2	3	101		102	103	
				201		202	203	
				301		302	303	
Study Day(s)	-28 to -15	-14	-8 to -5	1	2 to 13	14	15	199
				30	31 to 42	43	44	299
				59	60 to 71	72	73	399
Time (post-dose)	-	-	-	-	-5 min	12h	24h	-
Informed consent	X							
Corporate Confidential Information	X							
Inclusion / Exclusion criteria	X			X ⁷				
Randomization				X ⁸				
Medical history/current medical conditions	X							
Demography	X							
Physical Examination	X			X				X ⁹

Epoch	Screening			Treatment Epoch 1 / Treatment Epoch 2 / Treatment Epoch 3 ²				Washout ⁵	Day 1 next Epoch or EOS	
	Visit Name	Screening	Run in		Treatment periods ³					
Visit Numbers ¹	1	2	3	101	102	103	199			
				201	202	203	299			
				301	302	303	399			
Study Day(s)	-28 to -15	-14	-8 to -5	1	2 to 13	14	15	16 to 29	30	
				30	31 to 42	43	44	45 to 58	59	
				59	60 to 71	72	73	73	73	
Time (post-dose)	-	-	-	-	-	-5 min	12h	24h	-	
Pregnancy test ¹⁰	X		X	X					X	
Alcohol Test, Drug Screen, and Cotinine Test	S		S	S						
Urinalysis	X		X	X ¹¹					X	
Body Height	X									
Body Weight	X			X					X	
Blood Pressure	X ¹²			X ^{12,13}		X ¹³			X ¹³	
Pulse rate	X ¹²			X ^{12,13}		X ¹³			X ¹³	
Body Temperature	X			X ¹³					X ¹³	
Electrocardiogram (ECG)	X			X ¹⁴					X ¹⁴	
Hematology	X		X	X ¹⁵					X	
Clinical Chemistry	X		X	X ¹⁶					X	
Corporate Confidential Information			X ¹⁷							
Inhaler device training	X	X	X	X ¹⁸		X ¹⁸			X ¹⁸	
Drug administration record				X ¹⁹	X ²⁰	X ²¹	X ²²	X ^{23,24}	X ¹⁹	
Patient domiciled							X			
Rescue medication use (e-Diary)						X				
Spirometry	X					X (see table below)				
Peak expiratory flow / e-Diary						X ²⁷				
Patient check well-being (phone call)					X ⁴			X ⁶		

Epoch	Screening			Treatment Epoch 1 / Treatment Epoch 2 / Treatment Epoch 3 ²									
	Visit Name	Screening	Run in		Treatment periods ³			Washout ⁵	Day 1 next Epoch or EOS				
Visit Numbers ¹			1	2	3	101		102	103		199		
						201		202	203		299		
						301		302	303		399		
Study Day(s)	-28 to -15	-14	-8 to -5	1	2 to 13		14	15	16 to 29		30		
				30	31 to 42		43	44	45 to 58		59		
				59	60 to 71		72	73			73		
Time (post-dose)	-	-	-	-	-	-5 min	12h	24h	-	-	-		
Adverse Events							X						
Serious Adverse Events							X						
Concomitant medications							X						
Study completion information											X ²⁵		
Safety Follow up Call											X ²⁶		
Comments							X						

X = assessment to be recorded on clinical database

S = assessment to be recorded on source documentation only and will not be entered into the CRF

¹ Visit structure given for internal programming purpose only

² This is a six-sequence, three period cross-over design.

³ Treatment periods are consisting in a minimum of 14 days up to 18 days.

⁴ During treatment period, site will call the patient once a week to collect information on safety and ensure there is no asthma exacerbation.

⁵ A washout (minimum of 14 days and maximum of 21 days from last dose on Day 15) must occur after completion of treatment period 1 and after completion of treatment period 2. Study days are based on a 14 days wash-out period. Visit days may be adapted if the wash-out period is up to 21 days as allowed per protocol.

⁶ During washout period, site will call the patient once a week to collect information of safety and ensure there is no asthma exacerbation.

⁷ Eligibility to be confirmed before randomization (only at Day 1 of treatment period 1).

⁸ Patient will be randomized at Day 1 treatment period 1 after inclusion and exclusion criteria have been checked.

⁹ Physical examination to be performed if patient early discontinued or completed the study.

¹⁰ Pregnancy test: in serum at screening and run-in, in urine at other visits. Pregnancy assessments may be performed at a greater frequency if required by local regulation.

¹¹ If urinalysis at run-in is done within 7 days prior to Day 1 treatment period 1, Day 1 treatment period 1 urine analysis doesn't need to be repeated.

¹² Both standing and supine/sitting blood pressure measurements are required at Screening and Baseline of the first treatment period. Only sitting or supine blood pressure measurements are required at the other visits. Patients' positions during measurement collections should be consistent between visits (sitting or supine throughout the study).

¹³ Vital signs will be measured before study drug intake.

¹⁴ ECG to be done before study drug intake.

¹⁵ If hematology at run-in is done within 7 days prior to Day 1 treatment period 1, Day 1 treatment period 1 hematology doesn't need to be repeated.

¹⁶ If clinical chemistry at run-in is done within 7 days prior to Day 1 treatment period 1, Day 1 treatment period 1 clinical chemistry analysis doesn't need to be repeated.

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¹⁸ Patient will be re-trained to inhalation technique to Concept 1 device at the beginning and at the end of each treatment period (Day 1 and Day 14).

¹⁹ Patient will be admitted in the afternoon in order to have assessments performed before randomization. Day 1 first dose will be administered on site around 7 pm.

²⁰ Drug will be taken at home from Day 2 am to Day 13 pm.

²¹ Study drug morning dose intake on site at Day 14. Patient can be discharged or stay on site up to evening dosing.

²² At Day 14, evening dose will be taken at 7 pm - The first spirometry assessment will be - 5 minutes before evening dose.

²³ Study drug morning intake on site at Day 15. There is no drug intake on the evening of Day 15, washout starts from Day 15 evening.

²⁴ Morning dose will be around 7 am.

²⁵ Patient status information will be collected at the end of each epoch (early discontinuation or Study completion), completed in Summary eCRF page.

²⁶ A call to follow-up on patient safety will be performed at least 30 days after last study treatment administration.

²⁷ From the start of the screening period to completion of the treatment epoch (end of 3rd treatment period).

Note: If several assessments are scheduled at the same time point, please see the SOM for guidance on recommended sequence of assessments.

Table 8-2 Spirometry

For each treatment period	Spirometry (timing in relation to study drug administration)
Day 14 (Visit 102) (Visit 202) (Visit 302)	Timing prior to study drug administration -5 min
	Study drug - evening dose Day 14 – 19:00
	Timing post evening dose + 3 h (Day 14 – 22:00)
Day 15 (Visit 103) (Visit 203) (Visit 303)	+ 6 h (Day 15 – 01:00) + 9 h (Day 15 – 04:00) + 12 h (Day 15 – 06:55) – before Day 15 am dose
	Study drug morning dose Day 15 – 07:00
	+ 15 h (Day 15 – 10:00) + 18 h (Day 15 – 13:00) + 21 h (Day 15 – 16:00) + 23h55min (Day 15 – 18:55)- before Day 15 am dose
Post Day 15 morning dose	Study drug – morning dose Day 15 – 07:00
	After Day 15 morning dose intake, wash-out start.

8.2 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.

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

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

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the patient agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

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

Ensure patients are informed of the contraception requirements outlined in the [Section 4.2](#) (Exclusion criteria) and in [Section 5.1](#) (Contraception requirements).

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

Refer to the Site Operations Manual for a complete list of Informed Consent Forms included in this study.

8.3 Patient screening

Re-screening is allowed under certain circumstances. Please refer to [Section 4.2](#) (Exclusion criteria) for details.

Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

8.4 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the Site Operations Manual.

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

8.4.1 Alcohol test, Drug screen, Urine cotinine

All patients will be screened for substances of abuse and cotinine. See the Site Operations Manual for details.

8.4.2 Reversibility

Reversibility is to be measured at Visit 1 (Screening). Refer to [Section 4.1](#) (Inclusion criteria) for details. Respective washout period of bronchodilators must be fulfilled prior to reversibility testing. Please refer to [Table 5-1](#) and Study Operations manual for details.

8.5 Efficacy / Pharmacodynamics

Pharmacodynamic assessments (spirometry) will be collected at the timepoints defined in the [Assessment schedule](#).

Pharmacodynamic (PD) assessments will be performed and evaluated in all patients at all dose levels, including the placebo group.

8.5.1 Spirometry

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Refer to [Section 2.1](#) (Primary objectives), [Section 2.2](#) (Secondary objectives), [Section 2.3](#) (Exploratory objectives), [Table 8-2](#) (Spirometry) and Study Operations Manual for details.

8.5.2 Peak expiratory flow

PEF will be measured on **all** days from Screening to completion of the treatment epoch (end of 3rd treatment period).

The screening reference PEF will be determined by calculating the average of PEF values over the screening period (minimum of 5 days required).

Please refer to [Section 3.1](#) (Study design) and Study Operations Manual for details.

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment schedule ([Section 8.1](#)) detailing when each assessment is to be performed.

8.6.1 Physical examination

See the Site Operations Manual for details.

8.6.2 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse

8.6.3 Height and weight

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

8.6.4 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and 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 be contacted.

8.6.4.1 Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count will be measured. Coagulation testing including prothrombin time (PT) also reported as International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT) will be measured.

8.6.4.2 Clinical chemistry

Sodium, potassium, creatinine, blood urea nitrogen (BUN)/urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, bicarbonate/HCO₃, LDH, G-GT, AST, ALT, CK, glucose, total cholesterol, triglycerides. HbA1c will be included in the *screening panel only*.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

8.6.4.3 Urinalysis

Dipstick measurements for protein, blood, and WBC/leukocytes, nitrite, pH, glucose, ketones, urobilinogen, bilirubin will be performed.

If dipstick measurement results are positive (abnormal), results will be captured in the CRF. Microscopy must be assessed following an abnormal dipstick test with results captured in the CRF.

8.6.5 Electrocardiogram (ECG)

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

The CRF will contain: PR interval, QRS duration, heart rate, RR interval, QT interval, QTc

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

As applicable, QTcF and QTcB may be calculated in-house. Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility. See the Site Operations Manual for additional details.

Clinically significant abnormalities must be reported in the AE CRF.

8.6.6 Pregnancy and assessments of fertility

Pregnancy Testing

All pre-menopausal women who are not surgically sterile will have pregnancy testing. See the Assessment schedule ([Section 8.1](#)), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements*. A positive urine pregnancy test requires immediate interruption of study treatment until serum β -hCG is performed and found to be negative.

*Additional pregnancy testing might be performed if requested per local requirements.

Refer to [Section 9.6](#) for details on Reporting Pregnancy.

Assessments of Fertility

Refer to [Section 4.2](#) for criteria to determine women that are not of child bearing potential.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

- surgical bilateral oophorectomy without a hysterectomy
- reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female patient, regardless of reported reproductive/menopausal status at Screening/Baseline.

8.6.7 Patient Diary (e-Diary)

Each patient will be provided with an electronic diary to record study assessments while at home from Run in to completion of the treatment epoch (end of 3rd treatment period). Please refer to [Section 3.1](#) (Study design) and Study Operations Manual for details.

8.7 Pharmacokinetics

Not applicable.

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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 after *providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See [Section 9.5](#) for an overview of the reporting requirements.

The occurrence of adverse events must 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 finding, laboratory test finding, 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 [Appendix 1](#).

Adverse events should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. The severity grade
 - mild: usually transient in nature and generally not interfering with normal activities
 - moderate: sufficiently discomforting to interfere with normal activities
 - severe: prevents normal activities
2. its relationship to the study treatment
 - Yes or
 - No
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see [Section 9.2](#) for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.

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

- no action taken (e.g. further observation only)
- investigational treatment dosage increased/reduced
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- hospitalization/prolonged hospitalization (see [Section 9.2](#) for definition of SAE)

6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. Once an adverse event is detected, it must 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 investigational drug, the interventions required to treat it, and the outcome.

The investigator must 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 must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

*Refer to the Site Operations Manual for data capture methodology regarding AE collection for patients that fail screening.

9.2 Serious adverse event reporting

9.2.1 Definition of Serious Adverse Event (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, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

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 it were more severe (please refer to [ICH-E2D Guideline 2004](#)).

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 (please refer to [ICH-E2D Guideline 2004](#)).

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

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO&PS) as per [Section 9.2.2](#).

9.2.2 SAE reporting

Screen Failures & Run-In Failures

Note the following requirement for Screen Failures: SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis.

For patients considered Run-In Failures, SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Run-In Failure must be reported to Novartis.

Randomized Patients

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence as described below.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must 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 study treatment a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information

from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

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

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.

Please refer to [Table 15-1-Appendix 1](#) for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in [Table 15-1-Appendix 1](#) should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in [Table 15-2-Appendix 1](#).

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation within 48-72 hours.

These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the patient. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.

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

- Discontinuation of the investigational drug (refer to [Section 7.2](#) (Discontinuation of study treatment), if appropriate
- Hospitalization of the patient if appropriate
- Causality assessment of the liver event

- Thorough follow-up of the liver event should include
 - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and Gamma-glutamyl transferase (GGT). If total bilirubin is elevated $> 2 \times$ ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic. Retesting should be continued up to resolution.
 - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
 - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
 - Exclusion of underlying liver disease, as specified in [Table 15-3](#).
 - Imaging such as abdominal US, CT or MRI, as appropriate
 - Obtaining a history of exposure to environmental chemical agents.
 - Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.4 Reporting of study treatment errors including misuse/abuse

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

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

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

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Chief Medical Office and Patient Safety (CMO&PS) department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO&PS). As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. [Table 9-1](#) summarizes the reporting requirements.

Table 9-1 Guidance for capturing study treatment errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in Adverse Event CRF	Complete Serious Adverse Event form/CRF
Unintentional study treatment error	Yes	Only if associated with an Adverse Event	Only if associated with a Serious Adverse Event
Misuse/Abuse	Yes	Yes	Yes, even if not associated with an Serious Adverse Event

For more information on AE and SAE definition and reporting requirements, please see [Section 9.1](#) and [Section 9.2](#), respectively.

9.5 Pregnancy reporting

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

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO&PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on an SAE form.

9.6 Prospective suicidality assessment

Not required.

9.7 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 data capture requirements (i.e. eSource or eCRFs) with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and 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 eCRFs 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 data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and 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 eCRFs 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 (eCRF) 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 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 copies of the patient data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment schedule ([Section 8.1](#)) and can be recorded directly on the eCRFs. All other data captured for this study will have an external originating source (either written or electronic) with the eCRF not being considered as source.

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

10.3 Database management and quality control

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. The signed copy of the Data Query Form is kept at the investigator site.

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.

Diary data will be entered into an electronic diary by the patient. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis.

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis.

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.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

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10.4 Data Monitoring Committee

Not required.

10.5 Adjudication committee

Not required.

11 Data analysis

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

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 PD analysis set will include all patients with available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

11.2 Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence and patient. Summary statistics will be provided for all patients, as well as for each treatment sequence.

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

11.3 Treatments

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment sequence and patient.

11.4 Analysis of the primary variable(s)

The primary objective is to investigate the potential influence of time of dosing (morning or evening) on the bronchodilator effect of once daily orally inhaled QVM149 (150 µg indacaterol / 50 µg glycopyrronium / 80 µg MF) compared to placebo (all administered via the Concept1 inhalation device).

11.4.1 Primary Variable(s)

The primary variable is the weighted mean forced expiratory volume in 1 second (FEV1) over 24 hours (AUC_{0-24h}) following 14 days of treatment with QVM149 dosed in the morning, QVM149 dosed in the evening and placebo. The primary variable will be determined for each patient on day 14 on each treatment using the linear trapezoidal rule.

11.4.2 Statistical model, hypothesis, and method of analysis

The primary variable, FEV1 weighted mean (0- 24 h) (AUC_{0-24h}), will be analyzed using a linear mixed model. The model will include period, treatment (QVM149 morning, QVM149 evening, placebo), and sequence as fixed effect factors. The patient effect will be assumed to be random. Restricted maximum likelihood method will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. From these analyses, point estimates and their associated 90% confidence intervals will be constructed for each treatment. The difference between adjusted means and the corresponding two-sided 90% confidence interval for morning dose versus placebo, evening dose versus placebo will be presented. In addition, difference between adjusted means and the corresponding two-sided 90% confidence interval for morning versus evening doses will be presented.

11.4.3 Handling of missing values/censoring/discontinuations

If a patient takes rescue medication within 6 hours prior to the spirometry assessments and the visit is not rescheduled to the next day then all spirometry assessment data from this visit and the following visits in this treatment period will be set to missing.

11.4.4 Sensitivity analyses

Sensitivity analyses will be performed on a subset of patients where patients having drug administered outside of the allowed time window on day 14 or 15 will be excluded. Spirometry data assessed outside of the allowed time window will also be excluded.

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

The secondary endpoints are:

- FEV1 at approximately 5 min. before last p.m. or penultimate a.m. dose obtained from spirometry data.
- Daily morning and evening peak expiratory flow (PEF) rate from Day 2 to Day 14 during the three treatment periods

FEV1 (mL) will be analyzed by fitting the same model as described for the primary endpoint above in addition to summary statistics.

PEF (L/min) will be analyzed separately for morning and evening values. The morning/evening PEF (L/min) will be averaged between days 2 to 14 of each treatment period for each patient. The average morning/evening PEF score between days 2 to 14 in each period will be analyzed using the same model as for the primary endpoint and summarized by treatment.

11.5.2 Safety

All safety parameters will be summarized on the safety set.

Vital signs

All vital signs data will be listed by treatment sequence, 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 treatment sequence, 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 treatment sequence, patient, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a patient with any abnormal values. Summary statistics will be provided by treatment and visit/time.

Adverse events

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

All study emergent adverse events will be summarized and listed. Adverse events starting on or after the time of the first inhalation of study drug will be classified as a treatment emergent adverse event. Any adverse events that started during the study before the time of the first inhalation of study drug of the first period will be classified as a prior adverse event.

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

11.5.3 Other assessments

Not Applicable.

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11.7 Sample size calculation

With a sample size of 30 completers (5 patients per sequence), a two-sided 90% confidence interval for the difference between QVM149 pm/am and placebo in weighted mean FEV1 over 24 hours (AUC_{0-24h}) after 2 weeks of treatment will have an interval that extends no more than 88ml from the observed difference in means. This calculation assumes a within-patient standard deviation of 200 ml in weighted mean FEV1 over 24 hours (AUC_{0-24h}) (historical study HZA114624 - Fluticasone furoate and vilanterol ([Kempsford et al 2013](#))).

To ensure at least 30 patients complete the study, 36 patients will be enrolled assuming a drop-out rate of up to 20% and assuming equal assignment to the 6 sequences.

11.8 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, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US 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 must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, 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 by 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

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.

12.4 Quality control and quality assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

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

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 is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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

13.1 Protocol amendments

Any change 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.

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

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in [Section 9](#) (Safety Monitoring) must be followed and the Study Lead informed.

14 References

References are available upon request

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15 Appendix 1: Liver event definitions and follow-up requirements

Table 15-1 Liver event definitions

Definition	Thresholds
Potential Hy's law cases	<ul style="list-style-type: none"> ALT or AST $> 3 \times \text{ULN}$ and TBL $> 2 \times \text{ULN}$ without initial increase in ALP to $> 2 \times \text{ULN}$
ALT or AST elevation with coagulopathy	<ul style="list-style-type: none"> ALT or AST $> 3 \times \text{ULN}$ and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	<ul style="list-style-type: none"> ALT or AST $> 3 \times \text{ULN}$ accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	<ul style="list-style-type: none"> ALT or AST $> 8 \times \text{ULN}$ $5 \times \text{ULN} < \text{ALT/AST} \leq 8 \times \text{ULN}$ $3 \times \text{ULN} < \text{ALT/AST} \leq 5 \times \text{ULN}$
Isolated ALP elevation	<ul style="list-style-type: none"> ALP $> 2 \times \text{ULN}$ (in the absence of known bone pathology)
Others	<ul style="list-style-type: none"> Any clinical event of jaundice (or equivalent term) Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for liver events

Criteria	Actions required
Potential Hy's Law case	
ALT or AST elevation with coagulopathy	<ul style="list-style-type: none"> Discontinue the study treatment immediately
ALT or AST elevation accompanied by symptoms	<ul style="list-style-type: none"> Hospitalize, if clinically appropriate Establish causality
Isolated ALT or AST elevation $> 8 \times \text{ULN}$	<ul style="list-style-type: none"> Complete CRFs per liver event guidance*
Jaundice	
Isolated ALT or AST elevation $> 5 \text{ to } \leq 8 \times \text{ULN}$	<ul style="list-style-type: none"> If confirmed, consider interruption or discontinuation of study drug If elevation persists for more than 2 weeks, discontinue the study drug Establish causality Complete CRFs per liver event guidance*
Isolated ALT or AST elevation $> 3 \text{ to } \leq 5 \times \text{ULN}$ (patient is asymptomatic)	<ul style="list-style-type: none"> Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	<ul style="list-style-type: none"> Repeat liver chemistry tests within 48-72 hours If elevation is confirmed, measure fractionated ALP; if $>50\%$ is of liver origin, establish hepatic causality Complete CRFs per liver event guidance*

Criteria	Actions required
Any AE potentially indicative of liver toxicity	<ul style="list-style-type: none"> Consider study treatment interruption or discontinuation Hospitalize if clinically appropriate Complete CRFs per liver event guidance*

*Liver event guidance for CRF completion is available in the Site Operations Manual

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	<ul style="list-style-type: none"> IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	<ul style="list-style-type: none"> IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	<ul style="list-style-type: none"> ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	<ul style="list-style-type: none"> Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	<ul style="list-style-type: none"> Ultrasound or MRI
Hypoxic/ischemic hepatopathy	<ul style="list-style-type: none"> Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	<ul style="list-style-type: none"> Ultrasound or MRI, ERCP as appropriate.
Wilson disease	<ul style="list-style-type: none"> Caeruloplasmin
Hemochromatosis	<ul style="list-style-type: none"> Ferritin, transferrin
Alpha-1-antitrypsin deficiency	<ul style="list-style-type: none"> Alpha-1-antitrypsin

16 Appendix 2: Instruction for Use of Concept1

Instructions for using inhaler and capsules

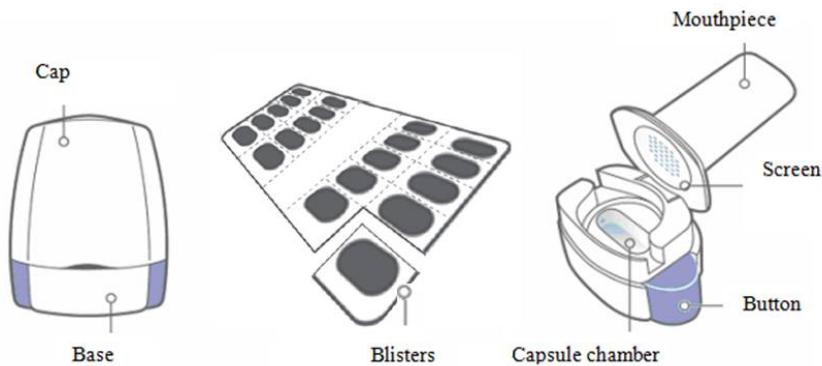
Do not swallow capsules.

Follow the instructions below for using your inhaler. You will take the study drug contained within the capsules by inhalation using the inhaler. If you have any questions, please ask the doctor or nurse at the study center.

Your inhaler and capsules

The study drug package consists of both the inhaler and one or more blister-packaged capsules.

- Capsules are supplied in blisters.
- Inhaler consists of a cap, mouthpiece and a base.



Your inhaler is designed to deliver the medicine contained within the capsules.

Do not use the study medication capsules with any other capsule inhaler, and do not use the inhaler to take any other capsule medicine.

How to use your inhaler

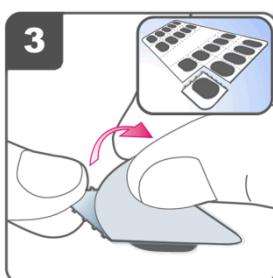


Pull off cap.



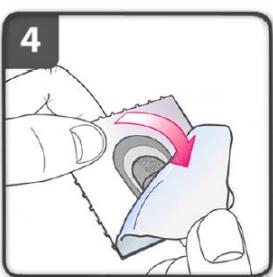
Open inhaler:

Hold the base of the inhaler firmly and tilt back the mouthpiece. This opens the inhaler.



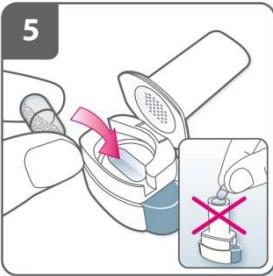
Prepare capsule:

Immediately before use, with dry hands, separate one of the blisters from the blister card by tearing along the perforations and lift the corner of the foil.



Remove a capsule:

Peel away the foil and remove the capsule from the blister.



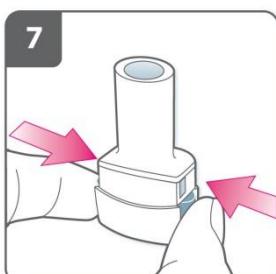
Insert capsule:

Place the capsule into the capsule chamber.

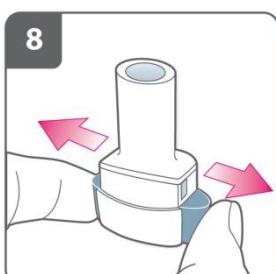
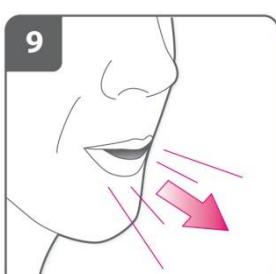
Never place a capsule directly into the mouthpiece.

**Close the inhaler:**

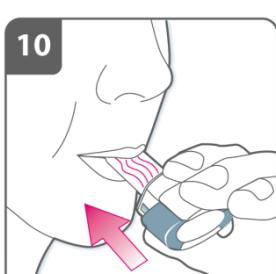
You should hear a “click” as the mouthpiece closes onto the inhaler base.

**Pierce the capsule:**

- Hold the inhaler upright with the mouthpiece pointing up.
- Pierce the capsule by firmly pressing together both side buttons at the same time. **Do this only once.**
- You should hear a “click” as the capsule is being pierced.

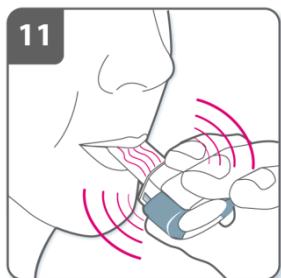
**Release the side buttons fully.****Breathe out:**

Before placing the mouthpiece in your mouth, breathe out fully.

Do not blow into the mouthpiece.**Inhale the medicine**

To breathe the medicine deeply into your airways:

- Hold the inhaler as shown in the picture. The side buttons should be facing left and right. Do not press the side buttons.
- Place the mouthpiece in your mouth and close your lips firmly around it.
- Breathe in rapidly but steadily and as deeply as you can.

**Note:**

As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. You will experience a sweet flavor as the medicine goes into your lungs.

Additional information

Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed. The chances of the capsule breakage will be increased if the capsule is accidentally pierced more than once (step 7). Therefore it is recommended that you follow the storage directions, remove the capsule from the blister immediately before use and pierce each capsule only once.

If you do not hear a whirring noise:

The capsule may be stuck in the capsule chamber. If this happens:

- Open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. Do not press the side buttons.
- Inhale the medicine again by repeating steps 9 to 11.

Hold breath:

After you have inhaled the medicine:

- Hold your breath for at least 5-10 seconds or as long as you comfortably can while taking the inhaler out of your mouth.
- Then breathe out.
- Open the inhaler to see if any powder is left in the capsule.

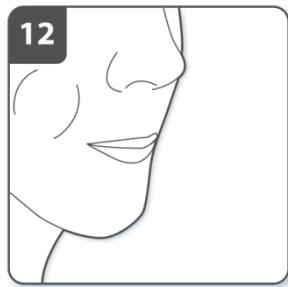
If there is powder left in the capsule:

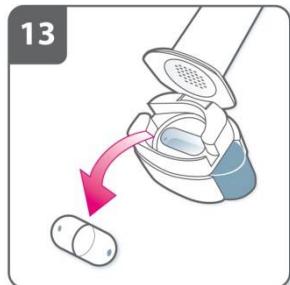
- Close the inhaler.
- Repeat steps 9, 10, 11 and 12.

Most people are able to empty the capsule with one or two inhalations.

Additional information

Some people may occasionally cough briefly soon after inhaling the medicine. If you do, don't worry. As long as the capsule is empty, you have received your medicine.



**After you have finished taking your medicine:**

- You may be directed by your physician to rinse mouth with water and spit it out; do not swallow the water.
- Open the mouthpiece again, and remove the empty capsule by tipping it out of the capsule chamber. Put the empty capsule in your household waste.
- Close the inhaler and replace the cap.

Do not store the capsules in the inhaler.

REMEMBER:

- **Do not swallow capsules.**
- Only use the inhaler contained in this pack.
- Capsules must always be stored in the blister, and only removed immediately before use.
- Never place a capsule directly into the mouthpiece of the inhaler.
- Do not press the side buttons more than once.
- Never blow into the mouthpiece of the inhaler.
- Always release the push buttons before inhalation.
- Never wash the inhaler with water. Keep it dry. See “How to clean your inhaler”.
- Never take the inhaler apart.
- Always use the new inhaler that comes with your new medication pack. Use the same inhaler throughout a treatment period of 14 (up to 18) days. Dispose of each inhaler after the end of a treatment period of 14 (up to 18) days.
- Do not store the capsules in the inhaler.
- Always keep the inhaler and capsules in a dry place, and avoid very hot or cold temperatures.

How to clean your inhaler

- Clean your inhaler once a week.
- Wipe the mouthpiece inside and outside to remove any powder with a clean, dry lint-free cloth.
- Do not wash your inhaler with water. Keep it dry.
- Do not take the inhaler apart.