

Novartis Institutes for BioMedical Research

QVM149

Clinical Trial Protocol CQVM149B2208

A randomized, double-blind, double-dummy, active-controlled, 3-period complete cross-over study to assess the bronchodilator effect and safety of two doses of QVM149 compared to a fixed dose combination of salmeterol/fluticasone 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 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 Drug Safety and Epidemiology (DS&E) 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.

Table of contents

Site Operations Manual (SOM).....	2
Notification of serious adverse events.....	2
Table of contents	3
List of tables	6
List of figures	7
List of abbreviations	8
Glossary of terms.....	11
Corporate Confidential Information	
Protocol synopsis.....	14
1 Introduction	19
1.1 Background.....	19
Corporate Confidential Information	
1.3 Clinical data	22
1.3.1 Human safety and tolerability data	22
1.3.2 Human pharmacokinetic data.....	23
1.3.3 Human pharmacodynamic data.....	23
1.4 Study purpose	24
2 Study objectives and endpoints	24
2.1 Primary objective(s).....	24
2.2 Secondary objective(s).....	24
Corporate Confidential Information	
3 Investigational plan	26
3.1 Study design.....	26
3.2 Rationale for study design	27
3.3 Rationale for dose/regimen, route of administration and duration of treatment....	28
3.4 Rationale for choice of comparator	31
Corporate Confidential Information	
3.6 Risks and benefits	31
3.6.1 Blood sample volumes	34
4 Population.....	34
4.1 Inclusion criteria	34
4.2 Exclusion criteria	35
5 Restrictions for Study Subjects	39
5.1 Contraception requirements.....	39

5.2	Prohibited treatment.....	39
5.3	Dietary restrictions and smoking.....	41
5.4	Other restrictions	41
6	Treatment.....	41
6.1	Study treatment	41
6.1.1	Investigational and control drugs	41
6.1.2	Additional study treatment.....	42
6.2	Treatment Arms	42
6.3	Treatment assignment and randomization	42
6.4	Treatment blinding.....	43
6.5	Treating the subject.....	44
6.6	Permitted dose adjustments and interruptions of study treatment.....	45
6.7	Emergency breaking of assigned treatment code	45
6.8	Treatment exposure and compliance	46
6.9	Recommended treatment of adverse events	46
6.10	Rescue medication	46
6.11	Concomitant treatment.....	47
7	Study Completion and Discontinuation.....	47
7.1	Study completion and post-study treatment	47
7.2	Discontinuation of study treatment.....	48
7.3	Withdrawal of informed consent	50
7.4	Lost to follow-up	50
7.5	Study stopping rules	50
7.6	Early study termination by the sponsor	50
8	Procedures and assessments	51
8.1	Assessment schedule	51
8.2	Informed consent procedures.....	56
8.3	Subject screening.....	56
8.4	Subject demographics/other baseline characteristics.....	57
8.4.1	Alcohol test, Drug screen, Urine cotinine.....	57
8.4.2	Reversibility	57
8.5	Efficacy / Pharmacodynamics	57
8.5.1	Spirometry.....	57
8.5.2	Peak expiratory flow	59
8.6	Safety.....	59
8.6.1	Physical examination	59

8.6.2	Vital signs.....	60
8.6.3	Height and weight	60
8.6.4	Laboratory evaluations.....	60
8.6.5	Electrocardiogram (ECG)	60
8.6.6	Pregnancy and assessments of fertility	61
8.7	Pharmacokinetics.....	61
8.8	Other assessments.....	61
8.8.1	Patient diary	61
8.8.2	Device training.....	62
Corporate Confidential Information		
9	Safety monitoring	63
9.1	Adverse events.....	63
9.2	Serious adverse event reporting.....	64
9.2.1	Definition of SAE	64
9.2.2	SAE reporting.....	65
9.3	Liver safety monitoring	66
9.4	Medication errors including misuse/abuse	67
9.5	Pregnancy reporting.....	68
9.6	Prospective suicidality assessment	68
9.7	Early phase safety monitoring	68
10	Data review and database management.....	69
10.1	Site monitoring	69
10.2	Data collection.....	69
10.3	Database management and quality control.....	70
10.4	Data Monitoring Committee.....	71
10.5	Adjudication Committee.....	71
11	Data analysis.....	71
11.1	Analysis sets	71
11.2	Subject demographics and other baseline characteristics.....	71
11.3	Treatments	71
11.4	Analysis of the primary variable(s)	71
11.4.1	Variable(s).....	71
11.4.2	Statistical model, hypothesis, and method of analysis.....	72
11.4.3	Handling of missing values/censoring/discontinuations.....	72
11.4.4	Sensitivity analyses	72

11.5	Analysis of secondary variable(s).....	72
11.5.1	Efficacy / Pharmacodynamics.....	72
11.5.2	Safety.....	73
11.5.3	Other assessments	73
	Corporate Confidential Information	
11.7	Sample size calculation.....	74
11.8	Power for analysis of key secondary variables.....	75
	Corporate Confidential Information	
12	Ethical considerations.....	76
12.1	Regulatory and ethical compliance.....	76
12.2	Responsibilities of the investigator and IRB/IEC.....	76
12.3	Publication of study protocol and results.....	76
13	Protocol adherence	76
13.1	Protocol Amendments	77
14	References	78
15	Appendix 1: Liver Event Definitions and Follow-up Requirements.....	79
16	Appendix 2: Instruction for Use of Concept1	81
17	Appendix 3: How to Use salmeterol xinafoate/ fluticasone propionate and its inhaler ...	86

List of tables

Table 3-1	Comparison of the comparable nominal MF component doses between Asmanex Twisthaler, QMF149 and QVM149	30
Table 5-1	Withholding period of bronchodilators prior to any spirometry assessment during the trial	39
Table 5-2	Prohibited asthma medication during treatment period	39
Table 5-3	Prohibited treatment, cessation periods.....	40
Table 5-4	Medication allowed under certain conditions if taken as follows.....	40
Table 6-1	Overview of study medication	41
Table 6-2	Definition of treatment sequences.....	42
Table 6-3	Blinding and unblinding plan.....	44
Table 8-1	Assessment Schedule	51
Table 8-2	Spirometry – Assessments	55
Table 9-1	Summary of reporting requirements for medication errors.....	68
Table 15-1	Liver Event Definitions.....	79
Table 15-2	Actions required for Liver Events.....	79
Table 15-3	Exclusion of underlying liver disease	80

List of figures

Figure 3-1 Study design27

List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	atrioventricular
b.i.d.	twice a day
BA	Bioanalytical
BMI	Body Mass Index
BP	blood pressure
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CK	creatinine kinase
CO ₂	carbon dioxide
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report/Record Form (paper or electronic)
CSR	clinical study report
CV	coefficient of variation
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEF _{25-75%}	Forced Expiratory Flow (25-75%)
FEV ₁	Forced Expiratory Volume in 1 second
FPM	fine particle mass
FVC	forced vital capacity
GCP	Good Clinical Practice
h	Hour
HbA1C	hemoglobin a1c

HBsAG	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
i.v.	Intravenous
IB	Investigator's Brochure
IBD	International birthdate
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	inhaled corticosteroid
IEC	Independent Ethics Committee
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
kg	Kilogram
LABA	Long-acting β_2 agonist
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
MDDPI	Multi-dose dry powder inhaler
mg	milligram(s)
ml	milliliter(s)
o.d.	once a day
OTC	over-the-counter
p.o.	Oral
PD	pharmacodynamic(s)
PEF	peak expiratory flow
PI	post-inhalation
PK	pharmacokinetic(s)
pMDI	pressurized metered-dose inhaler

RBC	red blood cell(s)
REB	Research Ethics Board
SABA	Short-acting β_2 agonist
SAE	serious adverse event
SD	standard deviation
SDDPI	single-dose dry powder inhaler
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TBL	total bilirubin
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)
γ -GT	gamma-glutamyl transferase
μ g	Microgram

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 subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
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.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
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
Screen Failure	A subject who is screened but is not treated or randomized
Subject	A trial participant (can be a healthy volunteer or a patient)

Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject 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 subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

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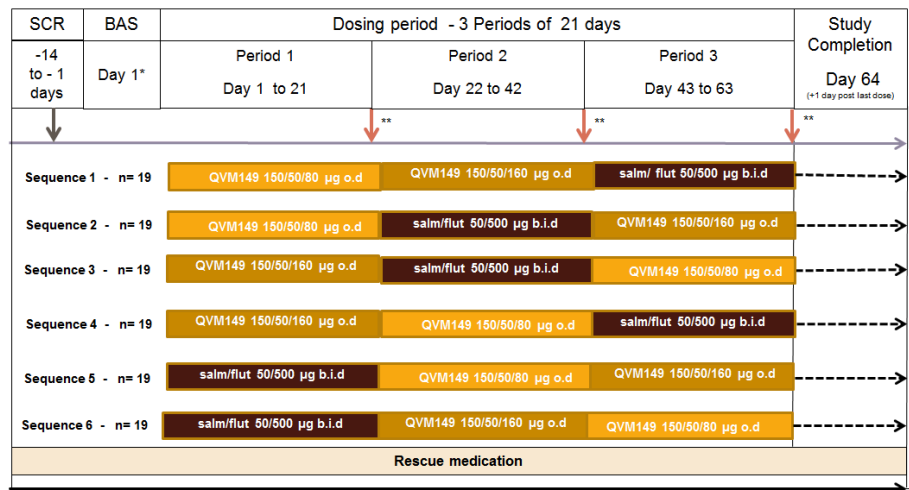
Protocol synopsis

Protocol number	CQVM149B2208
Title	A randomized, double-blind, double-dummy, active-controlled, 3-period complete cross-over study to assess the bronchodilator effect and safety of two doses of QVM149 compared to a fixed dose combination of salmeterol/fluticasone in patients with asthma
Brief title	Assess the bronchodilator effect and safety of QVM149 compared to salmeterol/fluticasone in patients with asthma
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	To assess peak FEV1 of two doses QVM149 compared to a fixed-dose combination of salmeterol/fluticasone (50/500µg b.i.d.) and to characterize the respective 24 hour bronchodilator effect profiles in patients with asthma. Data from this study will complement lung function data obtained in the pivotal QVM149 phase 3 program by assessing the bronchodilatory effect of QVM149 at multiple time-points over an entire dosing interval of 24 hours.
Primary Objective(s)	To demonstrate superiority in peak bronchodilator effect of QVM149 at a dose of 150/50/160 µg o.d. and 150/50/80 µg o.d. compared to a FDC of salmeterol/fluticasone at a dose of 50/500 µg b.i.d. after 3 weeks of treatment in patients with asthma
Secondary Objectives	To evaluate the bronchodilator effect of each dose of QVM149 compared to salmeterol/fluticasone FDC after 3 weeks of treatment. To evaluate the bronchodilator effect of each dose of QVM149 compared to salmeterol/ fluticasone FDC by measuring standardized FEV1 AUCs after 3 weeks of treatment respective period. To evaluate post-dose trough bronchodilator effect of each dose of QVM149 compared to salmeterol/fluticasone FDC after 3 weeks of treatment in the respective treatment period. To evaluate safety and tolerability of each dose of QVM149 and salmeterol/ fluticasone FDC when administered for 3 weeks.
Study design	This is a confirmatory, randomized, double-blind, double-dummy, active-controlled, 3-period complete cross-over study. During the 2-week screening period, patients will be required to abstain from using any asthma medication before screening lung function assessments in line with cessation periods. Patients are allowed to use their previous asthma medication between screening spirometry and randomization but need to stop at randomization when study drug administration commences. Short-acting beta-2-agonist bronchodilators will be provided to each patient to be used as rescue medication throughout the trial. Rescue medication use will be recorded in the patient diary. The 2-week screening period may be divided into more than one visit for operational reasons with the informed consent being obtained prior to any study related activities.

Eligible subjects may be re-screened once if they are not included in the study within the allowed 2 week screening period. Subjects may also be re-screened at the discretion of the Investigator, and following discussion with the Medical Monitor and/or Sponsor, if the reason for screen failure was considered temporary in nature. All screening data must be obtained within 2 weeks prior to administration of study medication, as stipulated above. Subjects who are re-screened will re-consented and will be allocated a new screening number.

At the end of the screening period, patients will be randomized to one of 6 possible treatment sequences), each consisting of 3 double-blind, double-dummy treatment periods of 21 days (cross-over design).

There is no washout period between treatments periods since drug effects from the previous period are not expected to be present after 3 weeks with current treatment in each period.



* Randomization at day 1 in one of the 6 treatment arms – Treatment sequences are double-blinded.
 ** Primary Endpoint – Peak FEV1 after the last dose of the preceding 3 week treatment period.

↓ Spirometry for eligibility
 ↓ Spirometry for treatment effect

Each treatment sequence will have approximately 19 subjects.

Procedures in treatment periods two and three are identical to the procedures of treatment period one. At the end of the last treatment period, subjects will then undergo Study Completion evaluations and will be discharged from the study site.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry and urinalysis), adverse event and serious adverse event monitoring.

Population	Male and female patients aged between 18 and 75 years with asthma and who have been treated with ICS and LABA for at least 12 months prior to screening
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<p>Key Inclusion criteria</p>	<ul style="list-style-type: none"> • Male and female adult patients ≥ 18 years old and ≤ 75 years. • Patients with a documented physician diagnosis of asthma for a period of at least 12 months prior to Visit 1 (Screening). • Patients who have used ICS and LABA combinations for asthma for at least 3 months and at a stable medium or high dose of ICS for at least 1 month prior to Visit 1 (Screening). • Pre-bronchodilator FEV1 of < 80 % of the predicted normal value at screening Visit 1 (spirometry will not be repeated at baseline prior to randomization). • Patients who demonstrate an increase in FEV1 of ≥ 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 (Screening). If reversibility is not demonstrated at Visit 1 (Screening), then, reversibility testing may be repeated once during the screening period. • If reversibility is not demonstrated at Visit 1 (retesting allowed once), patients must be screen failed. Spacer devices are not permitted during reversibility testing.
<p>Key Exclusion criteria</p>	<ul style="list-style-type: none"> • Patients who have smoked or inhaled tobacco products within the 6 month period prior to Visit 1 • Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of Visit 1 • Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia (BPH) or bladder-neck obstruction or severe renal impairment or urinary retention • Patients who have had a respiratory tract infection or asthma worsening within 4 weeks prior to Visit 1 • Patients with any chronic conditions affecting the upper respiratory tract • 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. • Patients with Type I diabetes or uncontrolled Type II diabetes (HbA1c $>9\%$ at screening). • Patients who have a clinically significant ECG abnormality at Visit 1 • Patients with a history of hypersensitivity or intolerance to any of the study drugs (including excipients) • Patients with narcolepsy and/or insomnia. • Patients on Maintenance Immunotherapy (desensitization) for allergies for less than 3 months prior to Visit 2 or patients on Maintenance Immunotherapy for more than 3 months prior to Visit 2 but expected to change throughout the course of the study. • Pregnant or nursing (lactating) women • Women of child-bearing potential must use Highly effective contraception methods • Patients who have discontinued LAMA therapy in the past for any safety, tolerability or perceived lack of efficacy reason. • History of paradoxical bronchospasm in response to inhaled medicines. • Patients with a history of clinically relevant bronchoconstriction upon repeated forced expiratory maneuvers. • Patient with a serum potassium level below the laboratory limit of normal at screening.

Study treatment	<ul style="list-style-type: none"> • QVM149 150/50/160 µg o.d. (indacaterol acetate 150 µg/ glycopyrronium bromide 50 µg/ MF 160 µg once daily) • QVM149 150/50/80 µg o.d. (150 µg/ 50 µg/ 80 µg once daily) • salmeterol/fluticasone FDC 50/500 µg b.i.d.
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Key safety assessments	<ul style="list-style-type: none"> • Physical examination • Vital signs • Laboratory evaluations; hematology, blood chemistry and urinalysis • Electrocardiogram (ECG)
Other assessments	<ul style="list-style-type: none"> • Patient diary to record; Rescue medication use, Study treatment administration: am and pm and PEF measurements: am and pm • Device training for the e-diary/peak flow meter device used to collect information on rescue medication use and to store PEF meter measurements. Subject will also be trained with inhalation devices using respective training kits.
Data analysis	<p>The primary objective is to demonstrate superiority in peak bronchodilator effect of QVM149 at a dose of 150/50/160 µg o.d. and 150/50/80 µg o.d. compared to a FDC of salmeterol/fluticasone at a dose of 50/500 µg b.i.d. after 3 weeks of treatment in patients with asthma.</p> <p>The primary endpoint is the peak FEV₁ (mL) defined as the highest bronchodilatory effect on FEV₁ during a period of 5 min to 4 h after the last dose of the preceding 3-week treatment period.</p> <p>The following hypothesis will be tested for each of QVM149 doses versus salmeterol/fluticasone separately:</p> <p>H₀: There is no difference in terms of the peak FEV₁ after 21 days of treatment between:</p> <ul style="list-style-type: none"> • the QVM149 high dose and salmeterol/fluticasone <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • the QVM149 mid dose and salmeterol/fluticasone <p>H₁: There is a difference in terms of the peak FEV₁ after 21 days of treatment between:</p> <ul style="list-style-type: none"> • the QVM149 high dose and salmeterol/fluticasone <p style="text-align: center;">AND</p> <ul style="list-style-type: none"> • the QVM149 mid dose and salmeterol/fluticasone <p>Each test will be conducted at a one-sided 2.5% level.</p> <p>The primary variable will be analyzed using a linear mixed model. The model will include period, treatment, and sequence as fixed effect factors and patient as a random effect. Restricted maximum likelihood method will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.</p> <p>No adjustment for multiplicity is planned because both tests are required to be positive.</p>

	The pairwise treatment differences of each QVM149 dose versus salmeterol/fluticasone along with the corresponding 2-sided 95% confidence intervals will be presented.
Key words	Asthma

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 ([GINA2016](#)).

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 acetate, 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.

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 the 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 ^{Corporate Confidential Information} 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 in the QVM149 FDC.

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.

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. Glycopyrronium bromide has been studied in adults and demonstrated optimal bronchodilation from the first dose; efficacy was maintained with once-daily dosing for treatment periods of up to a year with good safety and tolerability.

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 ≥ 4 years of age and is approved in over 55 countries world-wide for the treatment of asthma in adults and adolescents ≥ 12 years of age. The recommended daily doses of Asmanex[®] Twisthaler[®] range from 200 µg to 800 µg.

LABA/ICS dual combination QMF149

QMF149 combines two of the components of QVM149 in a fixed-dose combination of indacaterol acetate and MF. This dual combination is also currently being developed for the once daily maintenance treatment of asthma. As in QVM149 (please see below) 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. Corporate Confidential Information

In a 4-week study in patients with persistent asthma (Study CQMF149E2201), MF doses of 80 µg and 320 µg delivered once daily via Concept1 showed comparable efficacy and systemic exposure to MF doses of 200 µg and 800 µg (2 x 400 µg) delivered once daily via Twisthaler® confirming appropriate dose adjustment of the MF component for QMF.

QVM149

Due to QVM149 formulation requirements when adding the LAMA to LABA/ICS (QMF149) the dose of MF (ICS component) in QVM149 needed to be adjusted ([Table 3-1](#)): the nominal doses of MF in QVM149 are 80 µg and 160 µg to ensure that the fine particle mass Corporate Confidential Information in the lactose blend formulation for QVM149 is similar to the nominal MF doses of 160 µg and 320 µg 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

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. The COPD population investigated in this context, however, had a high prevalence of CV 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 acetate 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 in 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 broncho-dilator 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 alternative treatment option to theophylline, systemic corticosteroids or biologics for GINA Step ≥ 4 asthma patients inadequately controlled on medium- or high-dose LABA/ICS.

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 peak FEV1 of two doses of QVM149 compared to a fixed-dose combination of salmeterol/fluticasone (50/500µg b.i.d.) and to characterize the respective 24 hour bronchodilator effect profiles in patients with asthma. Data from this study will complement lung function data obtained in the pivotal QVM149 phase 3 program by assessing the bronchodilatory effect of QVM149 at multiple time-points over an entire dosing interval of 24 hours.

2 Study objectives and endpoints

2.1 Primary objective(s)

Objective	Endpoint
<ul style="list-style-type: none"> To demonstrate superiority in peak bronchodilator effect of QVM149 at a dose of 150/50/160 µg o.d. and 150/50/80 µg o.d. compared to a FDC of salmeterol/fluticasone at a dose of 50/500 µg b.i.d. after 3 weeks of treatment in patients with asthma 	<ul style="list-style-type: none"> Peak FEV1 (mL) defined as the highest bronchodilatory effect on FEV1 during a period of 5 min to 4 h after the last evening dose of each treatment period.

2.2 Secondary objective(s)

Objective	Endpoint
<ul style="list-style-type: none"> To evaluate the bronchodilator effect of each dose of QVM149 compared to salmeterol/fluticasone FDC after 3 weeks of treatment. 	<ul style="list-style-type: none"> FEV1, Forced Vital Capacity (FVC), and FEV1/FVC ratio at the following timepoints in relation to evening dose : - 45 min, -15 min, 5 min, 15 min, 30 min, 1 h, 2 h, 3h, 4 h, 8 h, 10 h, 11 h 55 min, 14 h, 18 h, 21 h, 23 h 15 min, 23 h 45 min.
<ul style="list-style-type: none"> To evaluate the bronchodilator effect of each dose of QVM149 compared to salmeterol/ fluticasone FDC by measuring standardized FEV1 AUCs after 3 weeks of treatment respective period. 	<ul style="list-style-type: none"> FEV1AUC 5 min - 1 h (Day 21) FEV1AUC 5 min - 4 h (Day 21) FEV1AUC 5 min (Day 21) - 23 h 45 min (Day 22)
<ul style="list-style-type: none"> To evaluate post-dose trough bronchodilator effect of each dose of QVM149 compared to salmeterol/fluticasone FDC after 3 weeks of treatment in the respective treatment period. 	<ul style="list-style-type: none"> Trough FEV1 (mL; mean of FEV1 at 23 h 15 min and 23 h 45 min post-dose)

Objective	Endpoint
<ul style="list-style-type: none">To evaluate safety and tolerability of each dose of QVM149 and salmeterol/fluticasone FDC when administered for 3 weeks.	<ul style="list-style-type: none">HematologyBlood chemistryUrine analysisVital signsECGAdverse events

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3 Investigational plan

3.1 Study design

This is a confirmatory, randomized, double-blind, double-dummy, active-controlled, 3-period complete cross-over study. During the 2-week screening period, patients will be required to abstain from using any asthma medication before screening lung function assessments in line with cessation periods detailed in [Section 5.2](#). Patients are allowed to use their previous asthma medication between screening spirometry and randomization but need to stop at randomization when study drug administration commences.

Short-acting beta-2-agonist bronchodilators will be provided to each patient to be used as rescue medication throughout the trial as detailed in [Section 5.2](#). Rescue medication use will be recorded in the patient diary.

The 2-week screening period may be divided into more than one visit for operational reasons with the informed consent being obtained prior to any study related activities.

Eligible subjects may be re-screened once if they are not included in the study within the allowed 2 week screening period. Subjects may also be re-screened at the discretion of the Investigator, and following discussion with the Medical Monitor and/or Sponsor, if the reason for screen failure was considered temporary in nature. All screening data must be obtained within 2 weeks prior to administration of study medication, as stipulated above. Subjects who are re-screened will re-consented and will be allocated a new screening number.

At the end of the screening period, patients will be randomized to one of 6 possible treatment sequences ([Figure 3-1](#)), each consisting of 3 double-blind, double-dummy treatment periods of 21 days (cross-over design). Details of study drug administration procedures are provided in [Section 6](#).

There is no washout period between treatment periods since drug effects from the previous period are not expected to be present after 3 weeks with current treatment in each period.

The treatments are:

1. QVM149 150/50/160 µg o.d. (indacaterol acetate 150 µg/ glycopyrronium bromide 50 µg/ MF 160 µg once daily)
2. QVM149 150/50/80 µg o.d. (150 µg/ 50 µg/ 80 µg once daily)
3. salmeterol/fluticasone FDC 50/500 µg b.i.d.

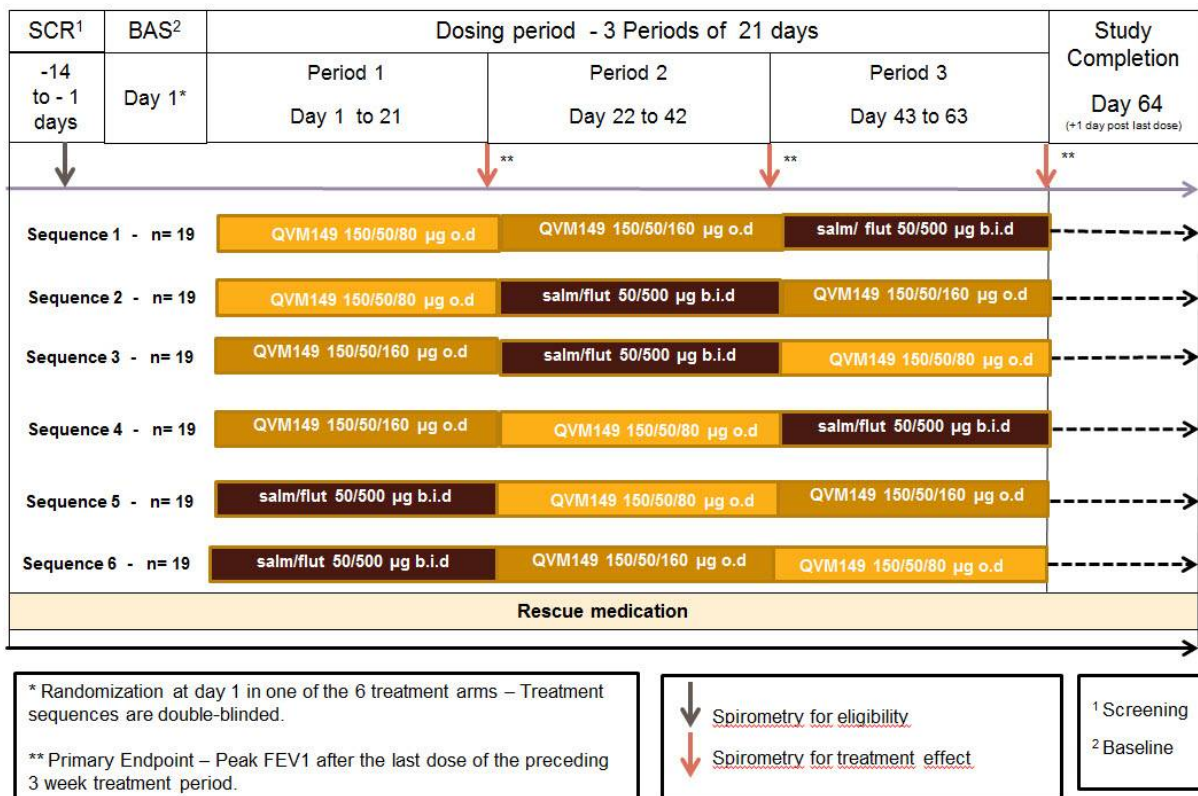
Each treatment sequence will have approximately 19 subjects.

Procedures in treatment periods two and three are identical to the procedures of treatment period one. At the end of the last treatment period, subjects will then undergo Study Completion evaluations and will be discharged from the study site.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry and urinalysis), adverse event and serious adverse event monitoring.

The study design is shown in [Figure 3-1](#).

Figure 3-1 Study design



3.2 Rationale for study design

This short-term treatment cross-over design is chosen to characterize the bronchodilator effects of two doses of once daily QVM149 (indacaterol/glycopyrronium/MF 150/50/160 µg and 150/50/80 µg) compared to the FDC salmeterol /fluticasone 50/500 µg b.i.d. 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.

The entire treatment epoch consists of 3 successive treatment periods of 21 days each (up to 25 days if required for operational reasons). Patients will receive successively the 3 study treatments, one treatment per period plus placebo that matches the comparator in a double-dummy fashion to enable adequate blinding (e.g. QVM149 medium dose plus placebo to the salmeterol/fluticasone FDC). The crossover design (rather than a parallel group design) was chosen because within patient variability is expected to be less than between subject 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. The three treatment periods will not be separated by a washout -period and lung function assessments will be conducted at the end of each 21-day treatment period only. During each 21-day treatment period the bronchodilatory effects of the study drug administered during this

period will replace the effect of the preceding period's study drug. The effect of indacaterol on FEV₁, which has a longer duration of action than salmeterol, is expected to last for approximately 48 hours after the last dose based on data from study CQAB149B2223. Based on 24-hour spirometry data, the half-life of the bronchodilatory effect of glycopyrronium is estimated to be ≤ 80 hours. Therefore the bronchodilatory effect is expected to be washed -out at the very latest 17 days after the last dose.

The direct succession of treatment periods also allows for minimizing the risk of patients' health deteriorating over the course of the trial since patients will continuously be either on LABA/ICS (standard of care) or LABA/ICS plus LAMA.

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

Dose/regimen

The components of QVM149 at the daily doses investigated in this trial are approved for COPD or asthma. QVM149 will be 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[®] and Seebri Breezhaler[®] 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. The two QVM149 doses (differing in MF content) also reflect the doses investigated in Phase 3 pivotal trials.

For indacaterol, the acetate salt will be used due to a lower incidence of post -inhalation cough compared to the marketed maleate salt. Data suggest comparable efficacy between the acetate and maleate salts (study CQAB149D2301).

Details for 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 (Study 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. Thus the acetate salt of indacaterol is selected to be the LABA component of the QVM149 FDC (see also [Section 1.1](#)). 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 PEF and rescue

medication use compared with indacaterol acetate 75 µg and significantly improved lung function compared to placebo.

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 (Studies CNVA237A2205 and CNVA237A2303). It is therefore expected that glycopyrronium bromide 50 µg once daily will provide similar efficacy in an asthma population as tiotropium Respimat® 5 µg once daily (recently approved in Europe for treatment of asthma and considered comparable to tiotropium 18 µg administered via HandiHaler®).

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, a 3 step bridging approach was conducted 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.

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Step 1 and 2,

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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 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 (2x400 µg) delivered once daily via Twisthaler[®] confirming the selected doses for MF Concept 1 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 Concept 1.

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 has 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 Concept 1 (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.

Table 3-1 Comparison of the comparable nominal MF component doses between Asmanex Twisthaler, QMF149 and QVM149

MF dose level	Asmanex Twisthaler	MF in QMF149	MF in QVM149
Low	200 µg	80 µg	N/A
Mid	400 µg	160 µg	80 µg
High	800 µg	320 µg	160 µg

Duration of treatment

The treatment duration of 21 days per treatment period was chosen for this study to allow for plateauing of the ICS effects on lung function as assessed by spirometry. The time-course of bronchodilatory action of ICS in asthma was investigated in study CQMF149E2201 which compared mometasone at two different doses in two different inhalers (Concept 1 and Twisthaler[®]) over 28 days. Most of the benefit on FEV1 was achieved after one week of treatment with incremental additional benefits observed after two and three weeks of treatment. No consistent additional benefit was observed thereafter suggesting that ICS effect on FEV1 plateaued after two to three weeks of treatment.

Bronchodilatory effects of the long-acting bronchodilators (LABAs and LAMA) used in this study within the fixed-dose combinations elicit a maximal or near maximal effect shortly after initiation of treatment. Indacaterol maleate achieves pharmacodynamic steady state within 14 days (Studies CQAB149B2357 and ^{Corporate Confidential Information}). In a 12 week lung function study (study CQMF149E2203) with indacaterol acetate in asthma patients this has been confirmed: a near maximal FEV1 effect was seen on Day 2 of treatment already. In addition, based on the comparability of the two salts from the 7-day PD and systemic exposure data from Study CQAB149D2301, the acetate salt of indacaterol is not expected to differ from that of an identical nominal dose of indacaterol maleate in terms of time to full bronchodilatory effect.

Based on data from COPD patients and the comparability of bronchodilatory mechanism of LAMAs in COPD and asthma it is expected that glycopyrronium reaches its maximum bronchodilator effect within the first few days of dosing.

Clinically meaningful improvements in spirometric measurements were observed after one week of treatment with glycopyrronium in study CNVA237A2205. Similarly, in study CNVA237A2208, which investigated lung function over 28 days, FEV1 was improved on all assessment days compared to placebo (Day 1, Day 14, Day 28; no assessments on Day 7). The totality of data in COPD patients suggests that no substantial further increase in lung function is observed after 7 days of treatment.

3.4 Rationale for choice of comparator

Salmeterol xinafoate/fluticasone propionate was selected as the active comparator in this study as it is widely used standard of care in asthma treatment. Salmeterol xinafoate/fluticasone propionate high dose 50/500 µg b.i.d. delivered by DPI (dry-powder inhaler) is marketed as Seretide[®] Accuhaler[®] or Seretide[®] Diskus[®] depending on region/country for the treatment of asthma in adults and adolescents 12 years and older. Lung function improvements of QVM149 compared to this current standard of care will provide valuable insight into the additional patient benefit provided by QVM149.

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3.6 Risks and benefits

The risks to which subjects 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) and the active comparator (FDC of salmeterol/fluticasone).

Subjects 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 3 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.

In light of their underlying asthma disease and the inclusion requirement in this study, subjects have been exposed to LABA/ICS combinations before entering the trial. The safety and tolerability profile of indacaterol, the LABA component in QVM149 and of MF, the ICS component of QVM149 is comparable to that of other medications of the same classes. This also holds true for the FDC of salmeterol/fluticasone which is the active comparator used in this study.

The third component of QVM149, glycopyrronium bromide 50 µg 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 subjects and COPD patients across 34 completed studies. Addition of LAMA (tiotropium 5 µg 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 benefit risk 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. Subjects 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 subjects 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[®]) as well as Seretide[®] SmPC (the FDC active comparator used in this study). Subjects 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.

The expected potential benefit for the patient in the current study may 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 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.

Frequent and regular contacts between patients and study staff will occur in terms of clinic visits throughout the treatment periods. In addition, safety monitoring (e.g. collection of symptoms and rescue medication use via an 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.

QVM149 and QMF149 are both 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 are concerns that LABA treatment used alone in asthma might cause severe asthma exacerbations. To address this safety concern all patients are treated with a FDC of LABA/LAMA/ICS or LABA/ICS in this study so LABA alone will not be allowed. This treatment regimen is in-line with the treatment that the patients received before entering the study since only patients who were on LABA/ICS before screening will be enrolled. In addition, providing the patients with rescue medication for use as needed to treat any bronchoconstriction throughout study mitigates patient risks. At no time, will any patient be without treatment for asthma.

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.

Women of child bearing potential should 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 (see [Section 4.2](#)). If there is any question that the subject will not reliably comply, they should not be entered in the study.

Since glucocorticosteroids are teratogenic in rodents and rabbits only women of child bearing potential (WOCBP) who agree to use highly effective methods of contraception (see [Section 4.2](#)) will be permitted to participate in the study.

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

In conclusion, the risk-benefit assessment for this study suggests that the subjects 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 approximately 110 mL of blood is planned to be collected over a period of 78 days, from each subject as part of the study. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

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, together with instructions for all sample collection, processing, storage and shipment information.

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

4 Population

The study population will consist of male and female patients aged between 18 and 75 years with asthma and who have been treated with ICS and LABA for at least 12 months prior to screening.

A total of approximately 114 patients will be enrolled and randomized with the intention that at least 95 patients complete the study.

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

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

Replacement subjects may be enrolled to replace subjects who discontinue the study for reasons other than safety. Patients dropped out may be replaced if the drop-out rate reaches 10 %.

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

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria as assessed at Screening and Baseline:

1. Written informed consent must be obtained before any study assessment is performed.
2. Male and female adult patients ≥ 18 years old and ≤ 75 years at Baseline.
3. Patients with a documented physician diagnosis of asthma for a period of at least 12 months prior to Screening.
4. Patients who have used ICS and LABA combinations for asthma for at least 3 months and at a stable medium or high dose of ICS for at least 1 month prior to Screening.

5. Pre-bronchodilator FEV1 of < 80 % of the predicted normal value for the patient (after withholding bronchodilators) at Screening (spirometry will not be repeated at baseline prior to randomization).
 - Withholding periods of bronchodilators prior to spirometry are given in [Table 5-1](#) (also applicable for inclusion criterion 6)
 - Re-testing is allowed once during screening period. 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.
6. Patients who demonstrate an increase in FEV1 of $\geq 12\%$ and ≥ 200 mL after administration of 400 μ g salbutamol/360 μ g albuterol (or equivalent dose) at Screening. All patients must perform a reversibility test at Screening. If reversibility is not demonstrated at Screening, then, reversibility testing may be repeated once during the screening period.

If reversibility is not demonstrated at Screening (retesting allowed once), patients must be screen failed. Spacer devices are not permitted during reversibility testing.
7. At screening, and first baseline, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position and again (when required) in the standing position as outlined in the SOM. Corporate Confidential Information

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

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If vital signs are outside these ranges, the Investigator should obtain two additional readings, so that a total of up to three consecutive assessments are made, following the procedure in the SOM.

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4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study.

1. Current smokers and patients who have smoked or inhaled tobacco products within the 6 month period prior to Visit 1, 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 $\frac{1}{2}$ pack/day x 20 yrs.).
2. Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of Screening or during screening period. If patients experience an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit during screening period, they may be re-screened 6 weeks after recovery (on investigator's judgment) from the exacerbation.
3. Patients who have ever required intubation for a severe asthma attack/exacerbation.

4. Patients who have had a respiratory tract infection or asthma worsening within 4 weeks prior to Screening or during screening period. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening.
5. Patients with evidence upon visual inspection (laboratory culture is not required) of clinically significant (in the opinion of investigator) oropharyngeal candidiasis Screening or at Baseline (prior to randomization), with or without treatment. Patients may be re-screened once their candidiasis has been treated and has resolved.
6. 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.
7. 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.
8. Patients with Type I diabetes or uncontrolled Type II diabetes (HbA1c > 9% at screening).
9. Patient with a serum potassium level below the laboratory limit of normal at screening.
10. Patients who have a clinically significant laboratory abnormality at Visit 1 in the opinion of the investigator (Screening visit, one re-test is allowed before the randomization).
11. Use of other investigational drugs within 30 days or 5 half-lives of screening in this study, until the expected pharmacodynamics effect has returned to baseline, whichever is longer.
12. 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
13. Patients with paroxysmal (e.g., intermittent) atrial fibrillation are excluded. 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., selective 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 the screening (Visit 1) and prior to randomization visits with a resting ventricular rate <100/min.
14. Concomitant use of an agent known to prolong the QT interval unless it can be discontinued for the duration of study.
15. Patients with a history of myocardial infarction within the previous 12 months.
16. Patients with a history of long QT syndrome or whose QTc measured at Visit 1 (Fridericia method) is prolonged (> 450 msec for males and > 460 msec for females), these patients should not be rescreened.
17. Patients who have a clinically significant ECG abnormality at Baseline e.g. second or third degree AV block, or ventricular arrhythmias.

18. Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia (BPH) or bladder-neck obstruction or severe renal impairment or urinary retention. BPH patients who are stable on treatment can be considered.
19. Patients with a history of hypersensitivity or intolerance to any of the study drugs (including excipients) or to similar drugs within the class including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof.
20. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
21. 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.
22. Patients receiving any asthma-related medications in the classes specified in [Table 5-1](#) unless they undergo the required washout period prior to Screening and follow the adjustment to treatment program.
23. Patients receiving any prohibited medications in the classes listed in [Table 5-2](#) and [Table 5-3](#).
24. Patients receiving medications in the classes listed in [Table 5-4](#) should be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met.
25. Patients on Maintenance Immunotherapy (desensitization) for allergies for less than 3 months prior to Baseline or patients on Maintenance Immunotherapy for more than 3 months prior to Baseline but expected to change throughout the course of the study.
26. Patients who are serving a custodial sentence do not have a permanent residence or who are detained under local mental health legislation/regulations.
27. Subjects incapable of understanding the nature, significance and implications of the clinical trial and therefore incapable of giving consent personally
28. Patients who are directly associated with any members of the study team or their family members
29. Patients unable to use the Concept1 dry powder inhaler or a metered dose inhaler.
30. History of alcohol or other substance abuse during 5 years prior to enrolment.
31. 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.
32. Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers).
33. Patients with narcolepsy and/or insomnia.
34. 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.

35. 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 of study treatment and up to 30 days after completion of study medication.

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 study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male partner sterilization (at least 6 months prior to screening). For female study patients, the vasectomised male partner should be 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 contraceptive medication 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 (i.e., 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.

A pregnancy test will be done on 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.

36. Patients who have discontinued LAMA therapy in the past for any safety, tolerability or perceived lack of efficacy reason.

37. History of paradoxical bronchospasm in response to inhaled medicines.

38. Patients with a history of clinically relevant bronchoconstriction upon repeated forced expiratory maneuvers.

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 Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must 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 requirement for **highly effective contraception** requirement for the duration of the study. If there is any question that the effective subject will not reliably comply, they should not be entered or continue in the study.

There is no requirement for males to use contraception.

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 any spirometry assessment during the trial

Class of Medication	Minimum cessation prior spirometry
SABA	≥ 6 hrs
SAMA	≥ 8 hrs.
LABA or fixed dose combination of ICS/LABA b.i.d	≥ 24 hrs.
LABA or fixed dose combination of ICS/LABA o.d	≥ 48 hrs.
LAMA	≥ 48 hrs.
xanthines	≥ 7 days

Table 5-2 Prohibited asthma medication during treatment period

Medication	Action to be taken
Long-acting anti-cholinergic agents (e.g. tiotropium bromide)	<i>subject to be withdrawn</i>
Short-acting anti-cholinergics	<i>subject to be withdrawn</i>
Fixed-combinations of long-acting β_2 -agonists and inhaled corticosteroids	<i>subject to be withdrawn</i>
Long-acting β_2 -agonists (other than study drug)	<i>subject to be withdrawn</i>
Short acting β_2 -agonists (other than those prescribed in the study)	<i>subject to be withdrawn</i>
Theophylline and other xanthines	<i>subject to be withdrawn</i>
Parenteral or oral corticosteroids	<i>subject to be withdrawn</i>
Leukotriene antagonists, ketotifen, inhaled cromolyn, nedocromil	<i>subject to be withdrawn</i>

Table 5-3 Prohibited treatment, cessation periods

Medication	Minimum cessation period prior to Baseline or as indicated
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug)	7 days prior to Baseline
Non-selective systemic β -blocking agents	7 days prior to Baseline
Cardiac anti-arrhythmics Class Ia	7 days prior to Baseline
Cardiac anti-arrhythmics Class III	7 days, amiodarone 3 months prior to Baseline
All antipsychotic agents (first, second and third generation, inclusive of atypical antipsychotics). Combinations of antipsychotic agents with antidepressants are prohibited	14 days prior to Baseline
Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)	14 days prior to Baseline
Monoamine-oxidase inhibitors	14 days prior to Baseline
Systemic anticholinergics	7 days prior to Baseline
Mizolastin or terfenadine (H ₁ antagonists)	5 days prior to Baseline
Strong inhibitors of cytochrome P4503A e.g., ketoconazole	7 days prior to Baseline
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 Baseline
Other investigational drugs	30 days or 5 half-lives, whichever is longer prior to Baseline
Parenteral or oral corticosteroids	Within 30 days prior to baseline
Noradrenaline reuptake inhibitors	7 days prior to Baseline
Live attenuated vaccine	not within 30 days prior to 1st dose and anytime thereafter during the trial

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 mizolastin 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, subjects should refrain from the following:

- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods and ice-cold beverages for 4 hours prior to spirometry
- Alcohol for 4 hours prior to spirometry
- Strenuous activity for 12 hours prior to spirometry
- Smoking within at least 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 subjects) strenuous physical exercise 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 subject numbering, prescribing/dispensing and taking study treatment are outlined in the Site Operations Manual.

6.1.1 Investigational and control drugs

The investigational drug, QVM149 (indacaterol acetate/glycopyrronium bromide/MF) 150/50/80 µg, 150/50/160 µg and salmeterol xinafoate/fluticasone propionate 50/500 µg as well as their respective matching placebos will be prepared by Novartis and supplied to the Investigator as single blind patient kits with a tear off label.

Table 6-1 Overview of study medication

Study drug name	Formulation	Unit dose	Packaging	Provided by
QVM149 and Concept1 Inhaler	Capsules with powder for Inhalation	150/50/80µg	Provided as single blind supplies including Concept1 Management devices	Novartis Drug Supply Management
QVM149 and Concept1 Inhaler	Capsules with powder for Inhalation	150/50/160µg	Provided as single blind supplies including Concept1 Management devices	Novartis Drug Supply Management
Placebo to QVM149 and Concept1 Inhaler	Capsules with powder for Inhalation	0µg	Provided as single blind supplies including Concept1 Management devices	Novartis Drug Supply Management
salmeterol xinafoate/fluticasone propionate	Inhalation powder, pre-dispensed in inhalation device	50/500µg	Provided as single blind supplies devices	Novartis Drug Supply Management
Placebo to salmeterol xinafoate/ fluticasone propionate	Inhalation powder, pre-dispensed in inhalation device	0µg	Provided as single blind supplies devices	Novartis Drug Supply Management

Study drug name	Formulation	Unit dose	Packaging	Provided by
Placebo to QVM149 and Concept 1 Inhaler as training kit	Capsules with powder for Inhalation	0µg	Blister +Inhaler	Novartis Drug Supply Management
Placebo to salmeterol xinafoate/ fluticasone propionate as training kit	Inhalation powder, pre-dispensed in inhalation device	0µg	Supplied as training inhalation devices	Novartis Drug Supply Management

6.1.2 Additional study treatment

No additional treatment beyond investigational drug and control drug are included in this trial.

6.2 Treatment Arms

Study treatments are defined as:

- A: QVM149 150/50/80 µg o.d.
- B: QVM149 150/50/160 µg o.d.
- C: salmeterol/fluticasone FDC 50/500 µg b.i.d.

Subjects 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	A	C	B
3	B	C	A
4	B	A	C
5	C	A	B
6	C	B	A

6.3 Treatment assignment and randomization

At the randomization visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or delegate will contact the IRT after confirming that the subject fulfills all the eligibility criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers (not needed). A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

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

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

The investigator will enter the screening number and medication number in the eCRF. IRT will assign subject ID at screening – will be kept throughout the study – no medication number.

6.4 Treatment blinding

This is a subject, investigator and sponsor-blinded study. Subjects, 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.

A double-dummy design is used because the identity of the study treatments cannot be disguised due to their different forms.

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

Sponsor staff

The following unblinded sponsor roles are required for this study:

Sponsor clinical staffs are required to assist in the management and re-supply of investigational drug product.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions. Sample data may be provided to the independent committee/analysis team, if used, under unblinded conditions.

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 6-3](#) for an overview of the blinding/unblinding plan.

Table 6-3 Blinding and unblinding plan

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis
Subjects/Patients	B	B	UI	B
Site staff	B	B	UI	B
Unblinded site staff (see text for details)	NA	NA	NA	NA
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff (see text for details)e.g. for drug re-supply, sample analyst(s)	B	B	UI	B
Statistician/statistical programmer/ data analysts (e.g. biomarker, PK)	B	B	UI	B
All other sponsor staff not identified above	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 subject

For each treatment period, the subject will be dispensed with one medication set of both study medications listed below:

- QVM149 or matching placebo in blisters, will be administered via the Concept1 inhalation device
- Salmeterol xinafoate/fluticasone propionate or matching placebo pre-dispensed inhalation device, will be administered via the pre-dispensed inhalation device

In total, three medication kits of QVM149 blisters/Concept1 and three Salmeterol xinafoate/fluticasone propionate pre-dispensed inhalation devices will be provided for the whole duration of the study.

IP administration will occur at the site by the subject on Day 1 morning and will be administered by the subject at the subject's home from Day 1 evening to Day 21 morning for each treatment period.

The evening dose on Day 21 should be taken at the site. A new medication set will be dispensed to the subject on Day 22 (same day as Day 1 of next Treatment period, applicable for Treatment period 2 & 3).

Subjects 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). Subjects 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. In the evening when sequential inhalations of study drugs from two devices are required, mouth rinsing should be done after the last inhalation.

The morning dose (to be taken between 05:00 and 08:00 am) will consist of a single inhalation of either salmeterol/fluticasone or placebo.

The evening dose (to be taken between 05:00 and 08:00 pm) will consist of sequential single inhalations:

- One inhalation of either QVM149 or placebo
- One inhalation of either salmeterol/fluticasone or placebo

Inhalations from the two devices should be taken as close together as possible. Instructions for use of the Concept1 and the device by which the FDC of salmeterol/fluticasone are administered are given in [Appendix 2](#) and [Appendix 3](#). Further details are provided in the SOM.

Administration of study medication at the same time of Day on Day 21 and 22 of each treatment period +/- 1 h will ensure that corresponding assessments are done at approximately the same time of the day in each treatment period.

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 subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the 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/code break cards at any time in case of emergency. The investigator will need to provide:

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

In addition, the investigator must provide oral and written information to inform the subject 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 subject.

6.8 Treatment exposure and compliance

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

For QVM149 doses administered at the site, after inhalation in each treatment period, the capsule shell will be checked for residual powder. If residual powder is found the inhalation procedure will be repeated up to a maximum of 3 times provided that total inhalation time does not exceed 2 minutes. The finding will be recorded in the drug administration section of the (e)CRF.

For Salmeterol xinafoate/fluticasone propionate, a dose indicator on its device indicates the number of doses left.

Compliance will be assessed by the Investigator and/or study personnel at each visit using capsule counts, device indicator and information provided by the subject. 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 a subject diary in which all subjects will record administration each day.

6.9 Recommended treatment of adverse events

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

6.10 Rescue medication

At Visit 1, all subjects will be provided with a short acting β_2 -agonist (100 μ g salbutamol/90 μ g albuterol). Subjects will be instructed to use it throughout the study as rescue medication on an 'as needed basis'. Subjects will be advised that between visits they can take their rescue medication for symptoms of intercurrent bronchospasm. No other rescue treatment is permitted.

In order to standardize measurements, subjects will be instructed to abstain from taking rescue medication (salbutamol/albuterol) within 6 hours of the start of each visit during which spirometry is being performed unless absolutely necessary. If rescue medication is taken within 6 h prior to the first spirometry assessments, then the visit should be rescheduled to the next day if possible and within permitted windows (Day 21 plus up to 4 days).

Bronchodilator medications that the subjects used prior to Visit 1 must be recorded in the asthma-related prior/concurrent medication page of the e-CRF. For screening spirometry assessments cessation periods in accordance with [Table 5-1](#) must be adhered to. After screening spirometry until randomization subjects may take the asthma medication they had before Visit 1. The rescue salbutamol/albuterol provided at Visit 1 for use during the study should NOT be recorded on the asthma-related prior/concurrent medication page of the e-CRF. From Visit 1, daily use of rescue medication will be recorded by the subject in their electronic diary.

The rescue salbutamol/albuterol will be provided to the subjects by the study center and reimbursed locally by Novartis or supplied to the investigator sites locally by Novartis.

6.11 Concomitant treatment

The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject 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 subject or allowing a new medication to be started, or if the subject is already enrolled, to determine if the subject should continue participation in the study.

7 Study Completion and Discontinuation

7.1 Study completion and post-study treatment

Each subject 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 subject 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 subjects should have a safety follow-up call conducted 30 days after last visit. 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 subject should be recorded in the source documentation.

7.2 Discontinuation of study treatment

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

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

- Subject decision - subjects may choose to discontinue study treatment for any reason at any time
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of trial participation
- Any protocol deviation that results in a significant risk to the subject'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 per recommendations in [Section 5.2](#) (Prohibited Treatment)

For liver events, refer to [Section 15-Appendix 1: Liver Event Definitions and Follow-up Requirements](#))

- Emergence of the following adverse events:
 - on two ECGs at least a minute apart:
 - absolute QTcF > 500 msec or an increase from screening of > 60 msec is noted
 - treatment-emergent second or third degree AV block, clinically relevant atrial or ventricular arrhythmias.
 - Reflex bronchoconstriction or other severe intolerance reaction to study drug inhalation
 - 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
 - Patients who have a decline in PEF from the reference PEF (during screening period) of ≥ 30% for 6 consecutive scheduled PEF readings (including readings taken in the morning and evening) at any point during the study.
 - ≥ 3 days in any one treatment period in which ≥12 inhalations/day of albuterol/salbutamol were used
 - Clinical asthma worsening which required additional asthma treatment other than study medication or study-defined rescue medication (albuterol/salbutamol)
- The following deviations from the prescribed dose regimen for the study drug:
 - Subject missed more than 6 consecutive doses of study medication in any one treatment 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

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

- Positive drug screen (suspected related to drug abuse): Drugs of abuse (DOA) testing maybe performed anytime at the discretion of the investigator.
- Any of the following laboratory abnormalities:
 - clinically significant abnormal laboratory value(s) or test procedure e.g. subjects with hemoglobin levels below 11.0 g/dL may be withdrawn from the study at the discretion of the investigator
- Use of concomitant treatment that would confound the interpretation of the pharmacodynamic data (after consultation with Novartis medical expert)

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

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

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see [Section 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 subject/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 subject's discontinuation from study treatment.

Subjects who are prematurely withdrawn from the study for reasons other than safety may be replaced on a case by case basis.

7.3 Withdrawal of informed consent

Subjects 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 subject:

- 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 subject's decision to withdraw his/her consent and record this information.

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

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

7.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject 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 three 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, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

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

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

Table 8-1 Assessment Schedule

Epoch	Screening		Treatment 1/2/3					
	Screening	Baseline	Treatment Period 1 / Treatment Period 2 / Treatment Period 3			Study completion		
Visit Numbers ¹	V1 ²	V2	V101	V102	V103	V104	V199 ²⁰	
Visit Numbers			V201	V202	V203	V204	V299 ²⁰	
Visit Numbers			V301	V302	V303	V304	V399 ²⁰	
Study Day(s)	-14 to -1	1	1 22 43	14 ³ 35 ³ 56 ³	21 42 63	22 43 64	22 43 64	
Time (post-dose)	-	-	-	-	predose	0h	24h	-
Informed consent ⁴	X							
Corporate Confidential Information	X							
Inclusion / Exclusion criteria	X	X ⁶						
Review/adjust asthma medication	X	X						X
Medical history/current medical conditions	X	X						
Concomitant therapies			X					
Demography	X							
Smoking history	X							

Epoch	Screening		Treatment 1/2/3					
Study Phase	Screening	Baseline	Treatment Period 1 / Treatment Period 2 / Treatment Period 3			Study completion		
Visit Numbers ¹	V1 ²	V2	V101	V102	V103	V104	V199 ²⁰	
Visit Numbers			V201	V202	V203	V204	V299 ²⁰	
Visit Numbers			V301	V302	V303	V304	V399 ²⁰	
Study Day(s)	-14 to -1	1	1 22 43	14 ³ 35 ³ 56 ³	21 42 63	22 43 64	22 43 64	
Time (post-dose)	-	-	-	-	predose	0h	24h	-
Physical examination	X	X			X			X
Body height	X							
Body weight	X	X			X			X
Body temperature	X	X			X			X
Blood pressure	X ²²	X ²²			X			X
Pulse rate	X ²²	X ²²			X			X
ECG evaluation	X		X		X			X
Hematology	X	X ⁷	X ⁹					X
Blood chemistry	X ²³	X ⁸	X ⁹					X
Alcohol, Drug Screen, and Cotinine Test ²¹	X							
Urinalysis ¹⁹	X	X						X
Corporate Confidential Information		X						
Randomization		X						
Subject domiciled					X			
Subject discharged							X ¹⁰	X
Study drug administration at site			X ¹¹			X	X ¹²	
Study drug administration by subject at home			X ¹³					
Unused study drug collection								X
Device training ¹⁴	X	X			X			
e-Diary record ¹⁵			X					

Epoch	Screening		Treatment 1/2/3					
Study Phase	Screening	Baseline	Treatment Period 1 / Treatment Period 2 / Treatment Period 3				Study completion	
Visit Numbers ¹	V1 ²	V2	V101	V102	V103	V104	V199 ²⁰	
Visit Numbers			V201	V202	V203	V204	V299 ²⁰	
Visit Numbers			V301	V302	V303	V304	V399 ²⁰	
Study Day(s)	-14 to -1	1	1 22 43	14 ³ 35 ³ 56 ³	21 42 63	22 43 64	22 43 64	
Time (post-dose)	-	-	-	-	predose	0h	24h	-
Peak Flow Meter record	X							
Spirometry	X ¹⁶					X ¹⁷		
Rescue medication ¹⁸	X							
Rescue medication accountability		X					X	
Adverse events	X							
Liver event reporting	X							
Comments	As required							
Study completion information							X	

Footnotes

¹ Visit structure given for internal programming purpose only –Visits windows are defined in the Study Operations Manual.

² Screening visit assessments can be performed at different days within 14 day screening period.

³ Day 14 of each treatment period will be a visit on the phone to assess subject safety.

⁴

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⁶ Review of inclusion/exclusion criteria and current medical conditions is required at baseline before the randomization.

⁷ If hematology at screening is done within 7 days prior to baseline, baseline hematology doesn't need to be repeated.

⁸ If blood chemistry at screening is done within 7 days prior to baseline, baseline blood chemistry doesn't need to be repeated.

⁹ Only required during treatment period 2 and 3.

¹⁰ Subject discharged from the site after completion of last assessments.

¹¹ First study drug intake at Day 1 will be on site and after all other visit assessments have been completed.

¹² For each treatment period, study drug administration at subject's home from Day 1 evening to Day 21 morning.

¹³ Day 22 should also be considered as first treatment day of the subsequent treatment period.

¹⁴ Include Peak flow meter, e-Diary and inhalation devices training. These data remains at source.

¹⁵ Completed daily.

¹⁶ Spirometry for eligibility: reversibility testing can be repeated once during the screening period if necessary

¹⁷ Refer to [Table 8-2](#) Spirometry Assessments for detailed time-points.

¹⁸ Refer to concomitant treatment section for rescue medication details.

¹⁹ Serum pregnancy test at screening and urinary pregnancy test at baseline and at end of trial. Additional pregnancy testing can be performed if required by local regulations.

²⁰ Assessments to be performed if subject terminates early or at V399 Study completion (for a continuing subject the required assessments are completed under the first visit of treatment period 2 or 3.

²¹ These data remains at source.

²² Both standing and supine/sitting blood pressure measurements are required at this time point. Only sitting or supine blood pressure measurements are required at the other visits. Subjects' positions during measurement collections should be consistent between visits (sitting or supine throughout the study).

²³ HbA1c will be collected at *screening only*

Table 8-2 Spirometry – Assessments

For each treatment period	Spirometry (timing in relation to study drug administration)
Day 21 (Visit 103) (Visit 203) (Visit 303)	Timing prior to study drug administration -45 min -15 min
	Study drug - evening dose Day 21 Timing post evening dose + 5 min + 15 min + 30 min + 1 h + 2 h + 3 h + 4 h
Day 22 (Visit 104) (Visit 204) (Visit 304)	Day 22 Timing post evening dose day 21 + 8 h + 10 h + 11 h 55 min
	Study drug morning dose + 14 h + 18 h + 21 h + 23 h 15 min + 23 h 45 min
Day 22 <i>Day 22 = Day 1 of the subsequent treatment period</i>	First evening dose of the next study period

8.2 Informed consent procedures

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

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

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

Novartis will provide to investigators a proposed informed consent form that complies with the ICH E6 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 subject agrees to 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 subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

Ensure subjects 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.

8.3 Subject screening

Re-screening is allowed under certain circumstances. Please refer to [Section 3.1](#) Study design and [Section 4.2](#) Exclusion criteria (2, 5, and 6) for details.

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

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. 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 subjects will be screened substances of abuse and cotinine. See the Site Operations Manual for details.

8.4.2 Reversibility

To be measured during screening. If reversibility is not achieved then the reversibility assessment may be repeated **once** prior the randomization.

All reversibility evaluations should follow the recommendations of the [Miller et al 2005a](#) unless otherwise indicated by inclusion/exclusion criteria of the study.

A spirometry assessment should be performed at screening after respective washout period of bronchodilators is fulfilled. Please refer to [Table 5-1](#) for details.

400 µg (4 x 100 µg) of salbutamol is then administered following completion of the baseline assessment. A second spirometry assessment is then performed starting within 30 minutes of the administration of the salbutamol.

Reversibility (%) is calculated as:

$(FEV_1 \text{ (post-bronchodilator)} - FEV_1 \text{ (pre-bronchodilator)} \times 100) / FEV_1 \text{ (pre-bronchodilator)}$

The findings of the reversibility evaluations will be recorded in the CRF.

8.5 Efficacy / Pharmacodynamics

Pharmacodynamic assessments will be conducted at the timepoints defined in the [Assessment schedule](#). Follow instructions outlined in the Site Operations Manual.

Pharmacodynamic (PD) assessments will be obtained and evaluated in all subjects for all treatment periods.

8.5.1 Spirometry

Forced Expiratory Volume in 1 second (FEV₁), Corporate Confidential Information
Forced Vital Capacity (FVC), Corporate Confidential Information will be
measured at screening, pre-dose, and specific time points for approximately 24 hours post
dose (on Days 21 and 22) in each treatment period. Corporate Confidential Information

For each subject, *the spirometric measurements* should be taken at approximately the same *corresponding time of day in each treatment period* as closely as practically possible.

Pre-dose FEV₁, ^{Corporate Confidential Information} FVC, ^{Corporate Confidential} assessments will be conducted before the first on-site administration of study medication in treatment period 1. Timing is minus 45 min and minus 15 min in relation to first inhalation of study medication.

Spirometry timepoints following the last dose of study medication in each treatment period are as follows:

- Day 21 pre-dose: - 45 min and -15 min
- Day 21/22 post-dose: 5 min, 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 8 h, 10 h, 11 h 55 min, 14 h, 18 h, 21 h, 23 h 15 min, 23 h 45 min

All spirometry evaluations should follow the recommendations of the (ATS/ERS 2005 Task force: Standardization of Lung Function Testing [Miller et al 2005a](#)).

The spirometry equipment used during the trial must meet or exceed the minimal ATS/ERS recommendations for diagnostic spirometry equipment as defined in the guideline ([Miller et al 2005b](#)). Calibration of the spirometry equipment is mandatory on all visit days and must be performed before the first study measurement. All calibration reports and subject spirometry reports should be stored as source data.

The same spirometry equipment should be used for all assessments performed by a subject. A limited number of staff, as designated by the investigator, will evaluate all subjects at all visits throughout the entire trial. Where possible the same technician should perform all maneuvers for an individual subject. All staff conducting the spirometry tests must have received appropriate training which must be documented.

Results for *spirometry assessments* are highly dependent on effort and cooperation from the subject. Thus, throughout the maneuver, enthusiastic coaching of the subject is required.

All spirometry maneuvers should be performed in sitting position whilst wearing nose-clips. At least three acceptable maneuvers should be performed for each time point, and the results must meet within-test and between-test criteria for acceptability. A maximum of eight maneuvers should be performed at any time point.

The highest value obtained of FEV₁, ^{Corporate Confidential Information} and FVC from any of the three maneuvers that meet acceptability criteria (can be from different curves) will be recorded on the CRF. All displaceable volumes will be reported in liters (L) at body conditions: normal body temperature (37°C), ambient pressure, saturated with water vapor (BTPS).

The following data will be collected:

- The time at which the first determination of FEV₁, Corporate Confidential Information took place
- FEV₁, Corporate Confidential Information measurements
- FVC measurement
- FEV₁% predicted
- FVC% predicted
- FEV₁/FVC ratio
Corporate Confidential Information

8.5.2 Peak expiratory flow

PEF will be measured on **all** days from screening through the end of study visit. The PEF will be measured twice daily, once in the morning prior to asthma medication usage during the screening period and prior to study drug during treatment periods and once in the evening, approximately 12 hours later again prior to asthma medication usage during the screening period and prior to study drug during treatment periods.

Each subject will be provided with a PEF meter and diary into which they will record their results (this may be done electronically) and the use of rescue medication. PEF meter training should occur at screening and repeated at the beginning of each treatment period. PEF measurements should be taken prior to pre-dose assessments.

Subjects should measure PEF in triplicate and record the best value. The diary data will be available to the Investigator for review to monitor subject safety and compliance (to verify subjects are performing the assessments twice daily as instructed). The Investigator must make all efforts to achieve compliance from their subjects.

The PEF value recorded at the first screening visit will become the reference value for PEF safety monitoring. This value should be recorded on the subject diary and the subjects should monitor their PEF readings using this value to detect a decline. The investigator should instruct the subject to call the site if the PEF drops below the limit required for discontinuation (see [Section 7.2](#) Discontinuation of study treatment) and this should be tracked by the site to track when the subject meets stopping criteria.

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 rate

8.6.3 Height and weight

- Height in cm.
- Body weight in kg.

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.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differentials, platelet count, aPTT and PT/INR will be measured.

Clinical chemistry

Sodium, potassium, creatinine, BUN/urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, CK, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated. HbA1c will be included in the *screening panel only*.

Urinalysis

Urine test by dipstick e.g. Combur9: leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/ hemoglobin

If the dipstick result is positive for protein, nitrite, leucocytes or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

8.6.5 Electrocardiogram (ECG)

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

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

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

Clinically significant abnormalities must be reported in the AE CRF.

8.6.6 Pregnancy and assessments of fertility

Women of child-bearing potential are not eligible to participate in this study unless they are using highly effective methods of contraception during dosing of study treatment and up to 30 days after completion of study medication as defined in [Section 4.2](#) Exclusion criteria.

In all enrolled women, including postmenopausal and surgically sterile women, a serum pregnancy is performed at screening. At baseline and at the end of trial a urinary pregnancy test is performed.

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^a.

*If additional pregnancy testing is needed per local requirements, those additional results will be kept as source documentation only.

8.7 Pharmacokinetics

Not applicable.

8.8 Other assessments

8.8.1 Patient diary

Each subject will be provided with an electronic diary to record study assessments while at home (from screening through treatment periods).

Subjects will record:

- Rescue medication use
- Study treatment administration: am and pm
- PEF measurements: am and pm

The diary will contain instructions for the subjects to perform PEF measurements prior to the intake of study treatment. Whilst it is preferred that PEF measurements are made prior to (6-hours) the administration of salbutamol (as rescue medication), subjects should not withhold their rescue medication in the event that their clinical condition deemed the immediate use of medication.

Subjects will be informed of their alert values for PEF at screening and after randomization so that if they meet stopping criteria related to PEF measurements whilst at home, they can contact the clinic immediately and appropriate action taken for review and withdrawal/ongoing management of their asthma.

8.8.2 Device training

Subjects will be provided with device training for the e-diary/peak flow meter device. The electronic device will be used to collect information on rescue medication use and to store PEF meter measurements. Subject will also be trained with inhalation devices using respective training kits.

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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 of disease) in a subject or clinical investigation subject *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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination 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 subjects with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver related events are included in [Appendix 1](#).

Adverse events must 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
 - No Relationship to study treatment or other investigational treatment or
 - Relationship to study treatment or
 - Relationship to other investigational treatment or
 - Relationship to both study treatment and other investigational treatment or indistinguishable

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). 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 subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject'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.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug

- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject 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 subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. 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 (see Annex IV, ICH-E2D Guideline).

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 Drug Safety & Epidemiology (DS&E) as per [Section 9.2.2](#).

9.2.2 SAE reporting

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

Note: SAEs reported by subjects deemed to be screen failures must be reported to Novartis as outlined here with appropriate information also captured in the CRFs as specified in the Site Operations Manual.

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

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

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

Please refer to [Table 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 γ 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 subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.

If the initial elevation is confirmed, close observation of the subject will be initiated, including:

- Consideration of treatment interruption if deemed appropriate
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to [Section 7.2](#) (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
 - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and γ GT. 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 subject 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.

9.4 Medication 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/subject or consumer (EMA definition).

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

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

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 Novartis Drug Safety and Epidemiology 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 Drug Safety and Epidemiology. 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 Summary of reporting requirements for medication errors

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

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

9.5 Pregnancy reporting

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

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology 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 a SAE form.

The study drug must be discontinued.

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 CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, 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 subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to 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 subject 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](#) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

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

10.3 Database management and quality control

Novartis staff or CRO working on behalf of Novartis review the data entered into the CRFs 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.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

Diary data will be entered into an electronic diary by the subject. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis or designated CRO.

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

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

The occurrence of any 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 by joint written agreement between the COAR Analytics NIBR Franchise Head and the relevant NIBR TA Head.

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

11.1 Analysis sets

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

All subjects that received study drug and with no protocol deviations with relevant impact on safety will be included in the safety analysis set.

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

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence and subject. Summary statistics will be provided for all subjects, 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 subject.

11.3 Treatments

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

11.4 Analysis of the primary variable(s)

The primary objective is to demonstrate superiority in peak bronchodilator effect of QVM149 at a dose of 150/50/160 µg o.d. and 150/50/80 µg o.d. compared to a FDC of salmeterol/fluticasone at a dose of 50/500 µg b.i.d. after 3 weeks of treatment in patients with asthma.

11.4.1 Variable(s)

The primary endpoint is the peak FEV₁ (mL) defined as the highest bronchodilatory effect on FEV₁ during a period of 5 min to 4 h after the last evening dose of the preceding 3-week treatment period.

11.4.2 Statistical model, hypothesis, and method of analysis

The following hypothesis will be tested for each of QVM149 doses versus salmeterol/fluticasone separately:

H₀: There is no difference in terms of the peak FEV₁ after 21 days of treatment between:

QVM149 (150/50/160 µg) and salmeterol/fluticasone

OR

QVM149 (150/50/80 µg) and salmeterol/fluticasone

H₁: There is a difference in terms of the peak FEV₁ after 21 days of treatment between:

QVM149 (150/50/160 µg) and salmeterol/fluticasone

AND

QVM149 (150/50/80 µg) and salmeterol/fluticasone

Each test will be conducted at a one-sided 2.5% level.

The primary variable will be analyzed using a linear mixed model. The model will include period, treatment, and sequence as fixed effect factors and patient as a random effect. Restricted maximum likelihood method will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

No adjustment for multiplicity is planned because both tests are required to be positive.

The pairwise treatment differences of each QVM149 dose versus salmeterol/fluticasone along with the corresponding 2-sided 95% confidence intervals 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

A sensitivity analysis will be conducted to evaluate the presence of any potential carry-over effects by applying the same model as described above and adding a factor modeling the carry-over effects.

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

The secondary endpoints obtained from spirometry data are:

- FEV₁, FVC and FEV₁/FVC ratio at the following timepoints in relation to evening dose at Day 21: -45 min, -15 min, 5 min, 15 min, 30 min, 1 h, 2 h, 3h, 4 h, 8 h, 10 h, 11 h 55 min, 14 h, 18 h, 21 h, 23 h 15 min, 23 h 45 min
- Standardized AUC in FEV₁ across different time intervals (5 min – 1 h, 5 min – 4 h, 5 min – 23h 45 min) at Day 21

- Trough FEV1 (mL; mean of FEV1 at 23 h 15 min and 23 h 45 min post-dose) at Day 21

Standardized AUC in FEV1 (5 min-23 h 45 min), AUC in FEV1 (5 min - 1 h), AUC in FEV1 (5 min - 4 h) and trough FEV1 will be analyzed by fitting the same model as described for the primary endpoint above in addition to summary statistics. The standardized AUCs are derived using the linear trapezoidal rule and adjusting for the length of the assessment interval.

Other secondary endpoints including FEV1, FVC and FEV1/FVC will be reported using descriptive statistics by treatment.

11.5.2 Safety

All safety parameters will be summarized on the safety set.

Clinical laboratory evaluations

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

Vital signs

All vital signs data will be listed by treatment sequence, subject, 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, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

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

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 subjects 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 period and continuing into the next period is counted only in the onset period. A subject with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

11.5.3 Other assessments

Not Applicable.

11.7 Sample size calculation

The sample size was chosen to provide at least 80% power for comparing peak FEV1 in both QVM149 doses vs. salmeterol/fluticasone.

For the treatment differences in peak FEV1 the following effects are expected:

- at least 100 mL after treatment with QVM149 150/50/160 µg vs. treatment with salmeterol/fluticasone
- and at least 80 mL after treatment with QVM149 150/50/80 µg vs. treatment with salmeterol/fluticasone.

The assumptions of the variability were based on the historical cross-over studies QVA149A2210 and tiotropium (Beeh et al 2014). The within subject standard deviations observed in these above studies varied between ~98 mL and ~210 mL. Based on this a standard deviation of 190 mL is used for powering the current study. With 95 patients

completing the study the power for both doses of QVM149 vs salmeterol/fluticasone in peak FEV1 to become significant on a 1-sided 2.5% alpha would be at least 80%.

To ensure at least 95 patients complete the study approximately 114 patients will be enrolled assuming a drop-out rate of up to 15% and ensuring equal assignment to the 6 sequences.

11.8 Power for analysis of key secondary variables

Not applicable.

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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, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

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

12.3 Publication of study protocol and results

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

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects 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 subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

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

14 References

References are available upon request

- Bateman ED, Kornmann O, Schmitt P, et al (2011) Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *J Allergy Clin Immunol* 2011; 128:315-22.
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- Befekadu E, Onofrei C, Colice GL (2014) Tiotropium in asthma, a systemic review. *JAA*; 7: 11-21.
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- Testi R (2014) White Paper, Long Acting Muscarinic Agent (LAMA). A new Frontier for COPD and Asthma Treatment. Available on www.cromsource.com

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 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	<ul style="list-style-type: none"> ALT or AST > 3 × 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 × 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 × ULN
Isolated ALP elevation	<ul style="list-style-type: none"> 5 × ULN < ALT/AST ≤ 8 × ULN 3 × ULN < ALT/AST ≤ 5 × ULN
Others	<ul style="list-style-type: none"> ALP > 2 × ULN (in the absence of known bone pathology) 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	<ul style="list-style-type: none"> Discontinue the study treatment immediately
ALT or AST elevation with coagulopathy	<ul style="list-style-type: none"> Hospitalize, if clinically appropriate
ALT or AST elevation accompanied by symptoms	<ul style="list-style-type: none"> Establish causality
Isolated ALT or AST elevation > 8 × ULN	<ul style="list-style-type: none"> Complete CRFs per liver event guidance
Jaundice	
Isolated ALT or AST elevation > 5 to ≤ 8 × 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 to ≤ 5 × 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

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, γGT, 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

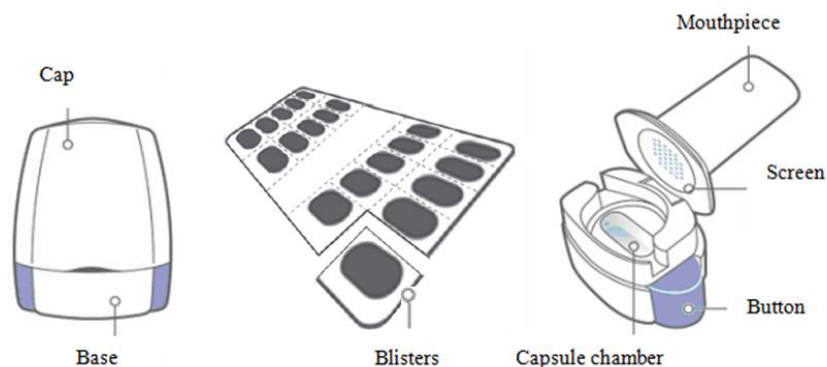
Do not swallow capsules.

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.

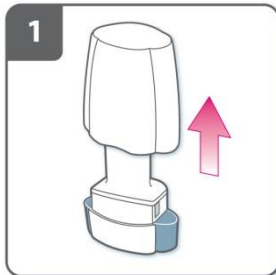
- Capsules are supplied in blisters.
- Inhaler consists of a cap, mouthpiece and a base.



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

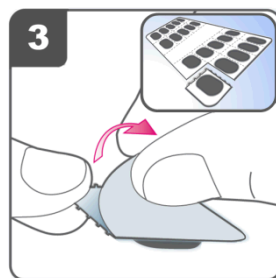


Pull off cap.



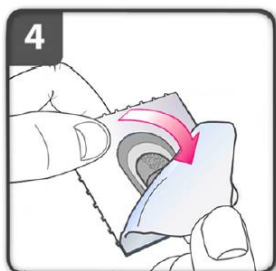
Open inhaler:

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:

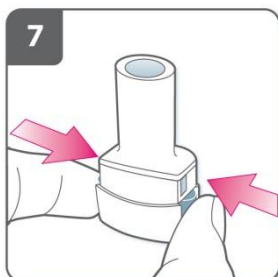
Place the capsule into the capsule chamber.

Never place a capsule directly into the mouthpiece.



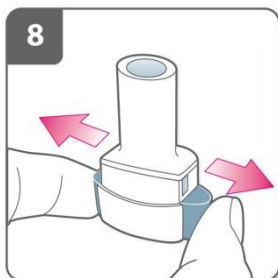
Close the inhaler:

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

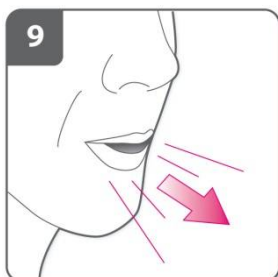


Pierce the capsule:

- 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.



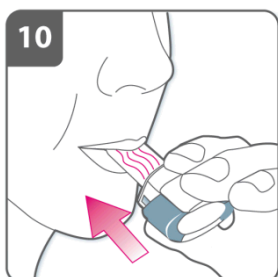
Release the side buttons fully.



Breathe out:

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

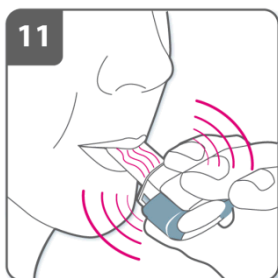
Do not blow into the mouthpiece.



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.

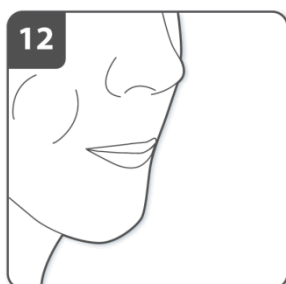
If there is powder left in the capsule:

- 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 21 days. Dispose of each inhaler after the end of a treatment period of 21 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

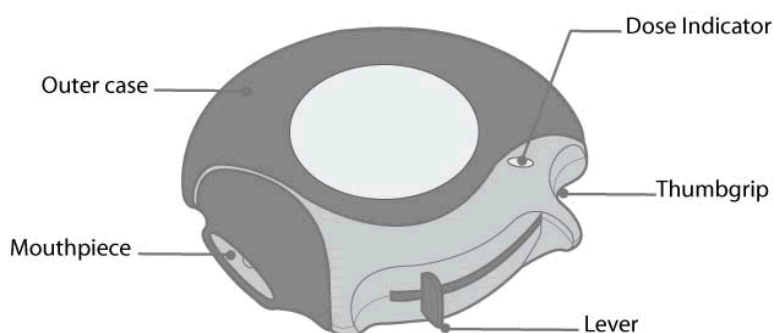
- Clean your inhaler once a week.
- Wipe the mouthpiece inside and outside to remove any powder with a clean, dry lint-free cloth.
- Do not wash your inhaler with water. Keep it dry.
- Do not take the inhaler apart.

17 Appendix 3: How to Use salmeterol xinafoate/ fluticasone propionate and its inhaler

Instructions for use

Follow the instructions below for using your inhalation device. **You will breathe in (inhale) the medicine from the inhaler.** Do not use the inhaler unless your healthcare provider has taught you, and you understand everything. If you have any questions, ask the doctor, nurse or pharmacist personnel at the study site.

Figure 1 Parts of the inhaler



Take the inhaler out of the medication pack given to you. The inhaler will be in the closed position. The **dose indicator** on the top of the inhaler tells you how many doses are left. The dose indicator number will decrease each time you use the inhaler. After you have used 55 doses from the inhaler, the numbers 5 to 0 will appear in **red** to warn you that there are only a few doses left (see [Figure 2](#)).

Figure 2 Dose Indicator for the inhaler

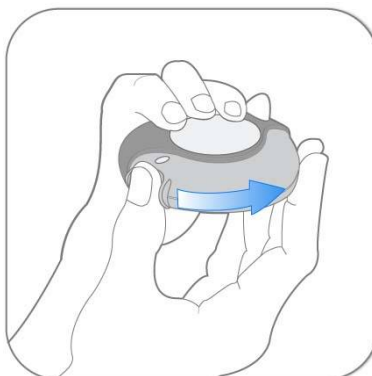


Taking a dose from the inhaler requires the following 3 steps: Open, Click, Inhale.

1. OPEN

Hold the inhaler in one hand and put the thumb of your other hand on the **thumbgrip**. Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position (see [Figure 3](#)).

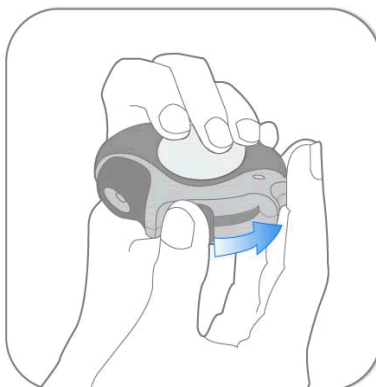
Figure 3 Opening the Mouthpiece Cover



2. CLICK

Hold the inhaler in a level, flat position with the mouthpiece towards you. Slide the **lever** away from you as far as it will go until it **clicks** (see [Figure 4](#)). The inhaler is now ready to use.

Figure 4 Sliding the Lever Until It Clicks



Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the inhaler is ready:**

- Do not close the inhaler.
- Do not tilt the inhaler.
- Do not play with the lever.
- Do not move the lever more than once.

3. INHALE

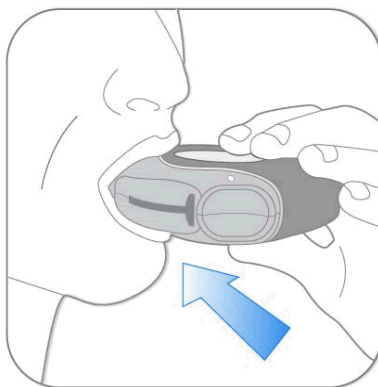
Before inhaling your dose from the inhaler, breathe out (exhale) fully while holding the inhaler level and away from your mouth (see [Figure 5](#)). **Remember, never breathe out into the inhaler mouthpiece.**

Figure 5 Exhaling



Put the mouthpiece to your lips (see [Figure 6](#)). Breathe in quickly and deeply through the inhaler. Do not breathe in through your nose.

Figure 6 Inhaling

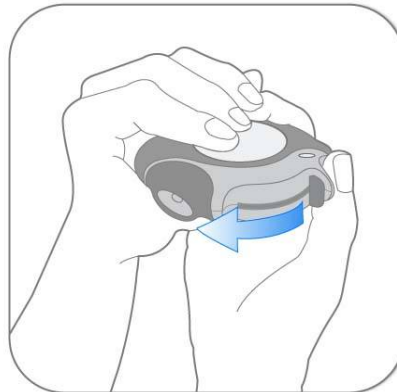


Remove the inhaler from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly. The inhaler delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the inhaler if you do not feel or taste the medicine.

4. CLOSE

Close the inhaler when you are finished taking a dose so that the inhaler will be ready for you to take your next dose. Put your thumb on the thumbgrip and slide the thumbgrip back towards you as far as it will go (see [Figure 7](#)). The inhaler will click shut. The lever will automatically return to its original position. The inhaler is now ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4 at that time).

Figure 7 Closing the Mouthpiece Cover



Remember:

- Never breathe into the inhaler.
- Never take the inhaler apart.
- Always ready and use the inhaler in a level, flat position.
- Do not use the inhaler with a spacer device.
- Never wash the mouthpiece or any part of the inhaler. **Keep it dry.**
- Always keep the inhaler in a dry place.
- Never take an extra dose, even if you did not taste or feel the medicine.