NOVARTIS

Global Clinical Development - General Medicine

QVM149B (Indacaterol acetate/Glycopyrronium bromide/Mometasone furoate)

Clinical Trial Protocol CQVM149B2306 / NCT03158311

A multicenter, partially-blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled study to compare the efficacy and safety of QVM149 with a free triple combination of salmeterol/fluticasone + tiotropium in patients with uncontrolled asthma

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List of abbreviations

ACQ-7	Asthma Control Questionnaire-7
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AQLQ(S)	Asthma Quality of Life Questionnaire
AST	Aspartate Aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
BMI	Body Mass Index
BPH	Benign prostatic hyperplasia
b.i.d.	twice a day
CCV	Cardiovascular and Cerebrovascular
CFR	US Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
DALYs	Disability- Adjusted Life Years
DAR	Dose Administration Record
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
ER	Emergency Room
EU	European Union
FAS	Full analysis set
FDC	Fixed dose combination
FEF_{25-75}	Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
GGT/γGT	Gamma Glutamyl Transferase
gMCP	Graph Based Multiple Comparison Procedures
HCP	Health Care Practitioner
[redacted]	[redacted]
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IB	Investigator Brochure
ICS/LABA	Combination of inhaled corticosteroid and long acting beta agonist
IEC	Independent Ethics Committee

IgE	Immunoglobulin E
IM	Intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
LABA	Long-acting β adrenoceptor agonists
LAMA	Long Acting Muscarinic Antagonist
LFT	Liver function test
LTRA	Leukotriene receptor antagonists
MCID	Minimal important difference
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Model for repeated measure
NI	Non-inferiority
OCS	Oral corticosteroid
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	once a day
PEF	Peak Expiratory Flow
[redacted]	[redacted]
p.o.	oral(ly)
PPS	Per protocol set
PRO	Patient Reported Outcome
QoL	Quality of Life
SABA	Short Acting β2 Agonist
SAE	Serious Adverse Event
SAMA	Short acting anticholinergics
SAP	Statistical analysis plan
SCS	Systemic corticosteroid
SDDPI	Single dose dry powder inhaler
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TD	Treatment Discontinuation
ULN	Upper limit of normal
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg o.d., 75 mg b.i.d.)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Period	A portion of the study which serves a specific purpose. Typical periods are: screening/recruitment, wash-out, treatment, and follow-up Synonymous with the term “Epoch”
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
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/subjects with established disease and in those with newly-diagnosed disease
Patient/subject ID	A unique subject identification (ID) number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, 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

Amendment 2

Amendment rationale

In a population with uncontrolled asthma it is the investigator's responsibility to ensure that patients are treated adequately. At the time of randomization, the investigator needs to make an informed decision about the most appropriate treatment for each individual patient. If the most appropriate treatment is not a LABA+LAMA+ICS, the patient should be screen-failed and be treated according to his/her individual needs.

The purpose of this amendment is to support this informed decision making by adding relevant assessments at the run-in visit, i.e. measurement of blood total IgE and antigen-specific IgE (ImmunoCAP) for common perennial aeroallergens.

Furthermore, this amendment includes a change in the hypotheses testing strategy. The key secondary objective (To evaluate efficacy of QVM149 high ICS dose and QVM149 medium ICS dose compared to salmeterol/ fluticasone + tiotropium in terms of Trough FEV1 after 24 weeks of treatment) will be treated as a regular secondary objective. The testing strategy will include only the primary objective (The non-inferiority of QVM149 high ICS dose and QVM149 medium ICS dose compared to salmeterol/ fluticasone + tiotropium free combination in terms of change from baseline in AQLQ total score after 24 weeks of treatment).

In addition, the amendment will address comments received from the Ethics Committee and Health Authority in Germany to clarify some procedures and data protection measures.

Recruitment for the study has not initiated as of time of protocol amendment finalization. These changes will not influence the study population, the results of the study nor is there any impact to patient safety.

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Changes to the protocol

- Update to the Protocol summary, Section 4 and Section 9.8 with a reduction in the number of patients in the study population
- Removed key secondary objective and considering it as one of the secondary objectives, Table 2-1, Objectives
- Updated patient inclusion criteria No. 1 & 6, Section 4.1 to ensure:
  - only legally competent patients can be included in the trial (No.1) and
  - the historical severe exacerbation is based on documented data and not on patients recall only (No. 6)
- Updated patient inclusion criterion No. 8 in Section 4.1 to clarify:

  - a positive reversibility test or a historic positive reversibility test performed according to ATS/ERS guidelines will be acceptable at V101
- Provided detailed instructions for the investigator regarding the need to pause or terminate concomitant medication for patient randomization into the trial, Section 5.5.8 Prohibited Medications and Table 5-3 Prohibited Medications
- Clarified definition of the end of the trial, Section 5.6.1
- Added serum total IgE and antigen-specific IgE (ImmunoCAP) assessments at run-in phase Table 6-1 Assessment Schedule [redacted]
- Added spirometry at Trial Discontinuation (TD) visit as Spirometry is part of the ACQ-7 assessment, Table 6-1 Assessment Schedule
- Removed central review of ECGs by central laboratory and requirement to print tracings in duplicate, Section 6.5.5
- Described measures for data protection to avoid unauthorized access, to ensure confidentiality of records and to prevent security breach Section 8.2
- Removed the key secondary variable (change in trough FEV1 from baseline to week 24) using only the primary variable for hypotheses testing and adjusting for multiplicity. Testing strategy has been changed from global Simes test to trimmed Simes test, Sections 9.4.1, 9.4.2, 9.4.3, 9.4.4,and 9.4.5
- Included the change in trough FEV1 from baseline to week 24 as one of the secondary variables and the corresponding analysis, Section 9.5.1.2
- Changed the sample size calculations and power adjustments based on updated testing strategy of using only the primary endpoint, Section 9.8
- Corrected for consistency throughout document; updated formatting, typographical errors

Amendment 1

Amendment rationale

The primary reasons for this amendment are to ensure consistency across sections of the protocol and to update drug supply sourcing strategies and operational details/ processes.

Protocol sections have been harmonized with respect to the escalation and de-escalation of controller or maintenance therapy allowed during the treatment period. The drug supply sourcing strategy is updated as local sourcing for the comparative treatment arm (salmeterol/fluticasone and tiotropium) and the run-in medication (salmeterol/fluticasone) may occur, in addition to global sourcing.

Recruitment for the study has not initiated as of time of protocol amendment finalization. These changes will not influence the study population, the results of the study nor is there any impact to subject safety.

Changes to the protocol

- Changed formatting of inclusion criteria 1-7 with numeric numbering of criteria from bullets for internal consistency (Section 4.1).

- Corrected error for exclusion criteria 19, ECG to be performed at Visit 101 and not V1 (Section 4.2).
- Corrected typo for exclusion 26, patients on maintenance immunotherapy for allergies **for** less than 3 months; changed "or" to "for" (Section 4.2).
- Added open-label comparative treatments (salmeterol/fluticasone and tiotropium) and run-in medication (salmeterol/fluticasone) which may be sourced locally from commercial supplies. (Section 5.1.1 and Section 5.1.2)
- Clarified that packaging with 2 part labeling is applicable for globally sourced treatments; all labeling will comply with local regulations (Section 5.5.2)
- Removed SmPC (Summary of Product Characteristics) as a reference for appropriate use of step-up and step-down therapy; refer to local approved label (Section 5.5.5)
- Added footnote to Table 5-4, "Medications allowed under certain circumstances" to align with Section 5.5.5 which describes the step-up and/or step down of patient's background medication (controller or maintenance) treatment options allowed during the treatment phase of the trial. (Section 5.5.8)
- Provided clarification that patients will be instructed by Investigators to contact the trial site when patient receives eDiary notifications when asthma worsening criteria is met. (Section 6.4.4).
- Added description of the baseline reference for SABA use in run-in and treatment periods (Section 6.4.4).
- Aligned protocol sections with updated regional stratification and statistical analysis plan (Section 9).

Protocol summary

Protocol number	CQVM149B2306
Full Title	A multicenter, partially-blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled study to compare the efficacy and safety of QVM149 with a free triple combination of salmeterol/fluticasone + tiotropium in patients with uncontrolled asthma
Brief title	Efficacy study of QVM149 in uncontrolled asthma patients
Sponsor and Clinical Phase	Novartis 3b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this trial is to demonstrate that the efficacy of two strengths of the fixed-dose combination product QVM149 (IND/GLY/MF150/50/80 µg and IND/GLY/MF 150/50/160 µg) is non-inferior to the efficacy of the free combination of salmeterol xinafoate/fluticasone propionate 50/500 µg + tiotropium 5 µg in uncontrolled asthmatics.
Primary Objective(s)	To demonstrate non-inferiority of either QVM149 high-dose or QVM149 medium-dose to comparator salmeterol / fluticasone + tiotropium after 24 weeks of treatment in terms of Asthma Quality of Life Questionnaire.
Secondary Objectives	• To evaluate efficacy of QVM149 high-dose and QVM149 medium-dose compared to salmeterol/ fluticasone + tiotropium in terms of Trough FEV_1 after 24 weeks of treatment. • To evaluate efficacy of QVM149 high-dose and QVM149 medium-dose compared to salmeterol/ fluticasone + tiotropium in terms of Asthma Quality of Life Questionnaire over 24 weeks of treatment. • To evaluate efficacy of QVM149 high-dose and QVM149 medium-dose compared to salmeterol/ fluticasone + tiotropium in terms of Asthma Control Questionnaire over 24 weeks of treatment. • To evaluate efficacy of QVM149 high-dose and QVM149 medium-dose compared to salmeterol/ fluticasone + tiotropium in terms of lung function over 24 weeks of treatment.
Study design	This study uses a multicenter, partially-blinded, randomized, 24-

	week, parallel-group, non-inferiority, open-label active controlled design. The study will consist of a screening period of up to 1-week, run-in period of 2-weeks, randomized treatment period of 24-weeks, and a follow-up of period of 1-week.
Population	The study population will consist of approximately 1251 male and female patients with uncontrolled asthma aged 18 and above.
Key Inclusion criteria	• Written informed consent must be obtained before any study-related assessment is performed; only fully legally competent patients can be included. • Male and female adult patient ≥ 18 years old. • Patients with a diagnosis of asthma for a period of at least 6 months prior to Visit 1 with current asthma severity ≥ step 4 (GINA 2017). • Patients who have used ICS/LABA combinations for asthma for at least 3 months and at stable medium or high dose of ICS/LABA for at least 1 month prior to Visit 1. • Patients must be symptomatic at screening despite treatment with medium or high stable doses of ICS/LABA as defined by ACQ-7 score ≥ 1.5 at visits 101 and 201 (randomization visit). • Patients with history of at least one severe asthma exacerbation (see Section 6.4.5) which required medical care from a physician, Emergency Room (ER) visit (or local equivalent structure) or hospitalization in the 12 months prior to Visit 1 and required systemic corticosteroids (SCS) treatment for at least 3 days including physician guided self-management treatment with oral corticosteroids (OCS) as part of written asthma action plan. • Pre-bronchodilator FEV_1 of < 85 % of the predicted normal value for the patient after withholding bronchodilators prior to spirometry at both Visit 101 and Visit 201. • Patients who demonstrate an increase in FEV_1 of ≥ 12% and 200 mL.
Key Exclusion criteria	• Patients who have a smoking history of greater than 20 pack years. • Patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD). • Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of Visit 1 (Screening). • Patients treated with a LAMA for asthma within 3 months prior to Visit 1. • Patients who have had a respiratory tract infection or clinical

	significant asthma worsening as defined by Investigator within 4 weeks prior to Visit 1 or between Visit 1 and Visit 201.
Study treatment	• QVM149 (indacaterol acetate/glycopyrronium bromide/MF) • Open label salmeterol xinafoate /fluticasone propionate + tiotropium
Efficacy assessments	• Health Status (PROs: AQLQ, ACQ-7, [redacted]) • Spirometry [redacted]
Key safety assessments	• Medical history and physical examination • Vital signs • Labs: Hematology, Blood chemistry, Urinalysis • ECG • Adverse events (AE) including serious adverse events (SAE) • Pregnancy (female patients) • Serious asthma outcomes (asthma-related hospitalizations, intubations or deaths) • CCV (Cardiovascular and cerebrovascular) events and new onset of atrial fibrillation
Other assessments	• [redacted]
Data analysis	**Analysis of primary variable** The non-inferiority of QVM149 150/50/160 µg o.d. versus free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg and QVM149 150/50/80 µg o.d. versus free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg, in terms of change from baseline in AQLQ total score. The primary variable will be analyzed using a mixed model for repeated measure (MMRM) on the full analysis set (FAS).
Key words	QVM149, Asthma

1 Introduction

1.1 Background

Asthma is a chronic inflammatory disorder of the airways associated with airways hyper responsiveness 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 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. Exacerbations of asthma are episodic whereas inflammation is chronic (GINA 2017).

Despite existing therapies there are still significant unmet medical needs 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 (Masoli, 2004).

Many patients with asthma fail to achieve adequate control of symptoms and exacerbations when treated with inhaled corticosteroids (ICS) or combinations of ICS and long-acting beta-agonists (LABA). Failure to respond to inhaled therapy may be due to multiple factors, including poor adherence, inadequate inhaler technique or corticosteroid resistance.

Tiotropium (Spiriva® Respimat®) has been approved in European Union (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 (≥ 800µg budesonide/day or equivalent) and long-acting β2-agonists and who experienced one or more severe exacerbations in the previous year.

Following tiotropium regulatory approval in asthma, GINA guideline (2017) recommends tiotropium as a new add-on option on top of ICS/LABA for steps 4 and 5 in patients with a history of exacerbations (in step 4 in the list of other controller options and in step 5 in the list of preferred controller choices).

QVM149 is a fixed-dose combination of indacaterol acetate (inhaled LABA with 24 hour duration of action), glycopyrronium bromide (inhaled LAMA with 24 hours duration of action), and mometasone furoate (MF, ICS with 24 hour duration of action) in development for once-daily maintenance treatment of asthma GINA step ≥ 4. All three mono-components have previously been developed as individual drugs for either COPD (indacaterol maleate and glycopyrronium bromide) or Asthma (mometasone furoate). Novartis is developing QVM149 (LABA/LAMA/ICS) fixed dose combination (FDC) as a lactose-blended inhalation powder to be delivered via Concept1 (Breezhaler®), a single dose dry powder inhaler (SDDPI) for maintenance treatment for severe asthma (GINA 2017 Step ≥ 4).

Data from mono-components:

QVM149 is being developed in parallel with QMF149 (indacaterol acetate/mometasone furoate). Existing efficacy and safety data for the three mono-components (indacaterol/mometasone/glycopyrronium) of the QVM149 FDC as well as for the two

combinations indacaterol/mometasone (QMF149) and glycopyrronium/indacaterol (Ultibro®) support investigation in Phase III.

Indacaterol maleate, delivered via Concept1, a single dose dry powder inhaler (SDDPI) (Onbrez® Breezhaler®), is approved in over 110 countries worldwide for the once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD.

Treatment guidelines state that LABAs are most effective when combined with an ICS (GINA 2017). The Phase III clinical development of indacaterol maleate that included studies in patients with asthma (who were receiving background ICS therapy), demonstrated that indacaterol maleate was effective and well-tolerated. A study in adolescent and adult patients with moderate to severe persistent asthma showed that doses of up to 600 µg o.d. over a 24-week treatment period (when administered with concomitant ICS therapy) was well-tolerated and resulted in effective bronchodilation which was superior to that provided by salmeterol (CQAB149B2338). Studies comparing the indacaterol maleate salt with the acetate salt found that the alternative salts were associated with a lower incidence of post-inhalation cough (CQAB149B2102) with no impact on efficacy, safety or systemic exposure (CQAB149D2301).

Glycopyrronium bromide (50 µg once daily in a lactose-based formulation) is registered in the EU since 2012 as Seebri® Breezhaler® (Concept1) 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 is also registered in the EU as Ultibro® Breezhaler®. Glycopyrronium bromide has been studied in adults and demonstrated optimal bronchodilation from the first dose and efficacy was maintained on once-daily dosing for treatment periods of up to a year, with good safety and tolerability.

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 worldwide for the treatment of asthma in adults and adolescents ≥ 12 years of age.

1.2 Purpose

The purpose of this trial is to demonstrate that the efficacy of two strengths of the fixed-dose combination product QVM149 (IND/GLY/MF150/50/80 µg and IND/GLY/MF 150/50/160 µg) is non-inferior to the efficacy of the free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg in uncontrolled asthmatics.

2 Study objectives and endpoints

All objectives will consider the following 2 comparison groups:

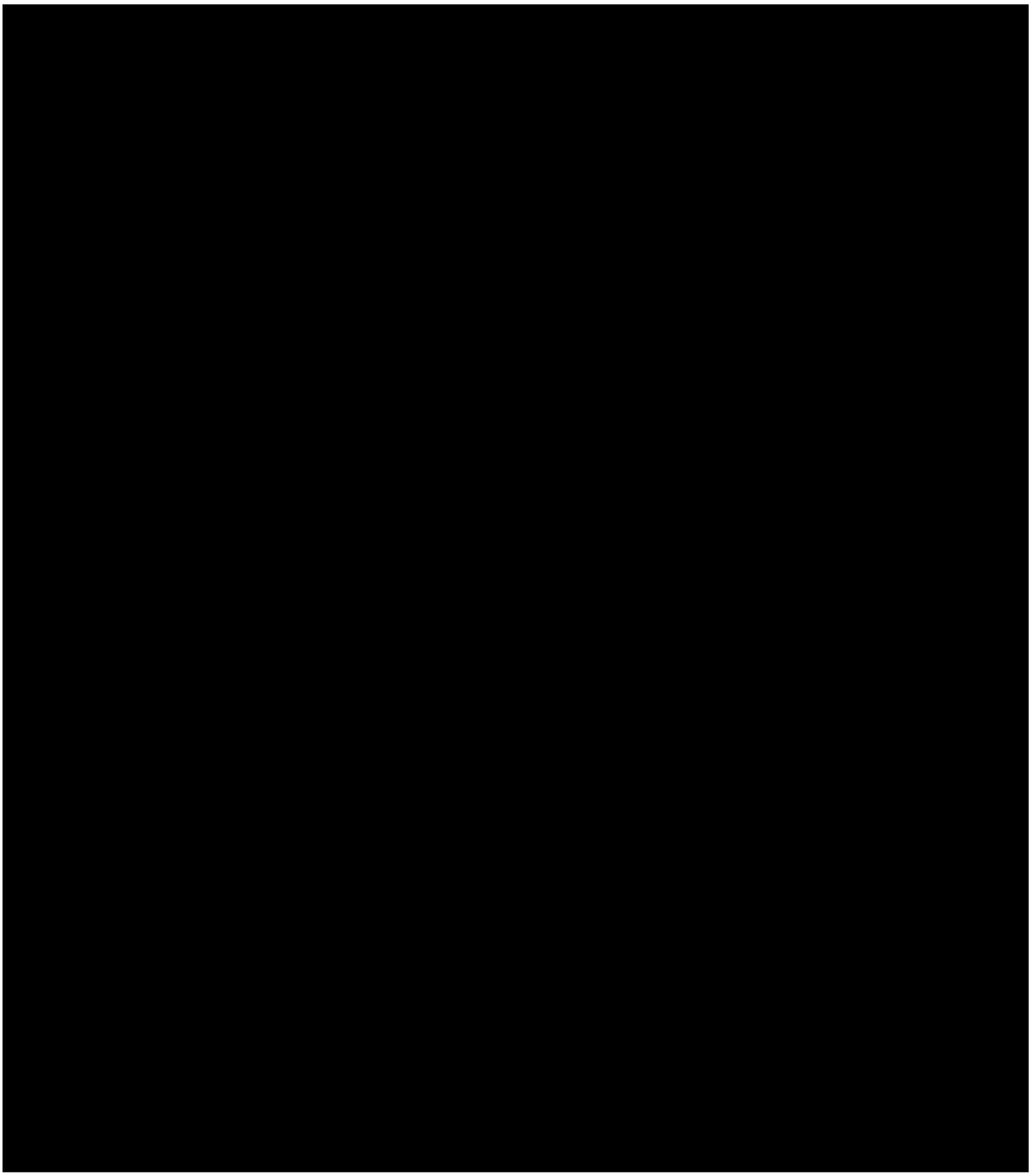
QVM149 150/50/80 µg o.d. delivered via Concept1 compared with open label salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d. delivered via Accuhaler® + tiotropium 5 µg o.d. delivered via Respimat®

QVM149 150/50/160 µg o.d. delivered via Concept1 compared with open label salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d. delivered via Accuhaler® + tiotropium 5 µg o.d. delivered via Respimat®

2.1 Study Objectives and Endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective • To demonstrate non-inferiority of either QVM149 high-dose or QVM149 medium-dose to comparator salmeterol/ fluticasone + tiotropium in terms of Asthma Quality of Life Questionnaire (AQLQ)	**Endpoint for primary objective** • Change from baseline in Asthma Quality of Life Questionnaire (AQLQ) total score after 24 weeks of treatment
Secondary Objectives • To evaluate efficacy of QVM149 high-dose and QVM149 medium-dose compared to salmeterol/ fluticasone + tiotropium in terms of Trough FEV_1 • To evaluate efficacy of QVM149 high-dose and QVM149 medium-dose compared to salmeterol/ fluticasone + tiotropium in terms of Asthma Quality of Life Questionnaire • To evaluate efficacy of QVM149 high-dose and QVM149 medium-dose compared to salmeterol/ fluticasone + tiotropium in terms of Asthma Control Questionnaire • To evaluate efficacy of QVM149 high-dose and QVM149 medium-dose compared to salmeterol/ fluticasone + tiotropium in terms of lung function	**Endpoints for secondary objectives** • Change from baseline in Trough FEV_1 after 24 weeks of treatment • Change from baseline in Asthma Control Questionnaire (ACQ-7) total score over 24 weeks of treatment • Change from baseline in Asthma Quality of Life Questionnaire (AQLQ) total score over 24 weeks of treatment • Percentage of patients achieving the minimal important difference (MCID) decrease from baseline ACQ-7 $\geq$ 0.5 over 24 weeks of treatment (responder rate) • Percentage of patients achieving the minimal important difference (MCID) change from baseline AQLQ $\geq$ 0.5 over 24 weeks of treatment (responder rate) • Change from baseline in FVC over 24 weeks of treatment • Change from baseline in Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity (FEF_{25-75})



3 Investigational plan

3.1 Study design

This study uses a multicenter, partially-blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled design.

The study will consist of a screening period of up to 1-week, run-in period of 2-weeks, randomized treatment period of 24-weeks, and a follow-up of period of 1-week.

At Visit 1, informed consent will be obtained before any study related assessments or procedures are performed. All patients signing informed consent must be registered in the Interactive Response Technology (IRT). Asthma medications and eligibility criteria will be reviewed. All patients must have used inhaled LABA+ ICS for at least 3 months and been on stable medium or high dose LABA+ ICS for at least 1 month prior to Visit 1. If necessary, arrangements will be made to adjust concurrent and prohibited medications (Table 5-2, Table 5-3, and Table 5-4) before moving forward to Visit 101. Once concurrent medications comply with the requirements of the study patients will conduct Visit 101. Visit 1 and Visit 101 may be performed on the same day if concurrent medications comply with the requirements of the study (LABA + ICS must not be used within 12 hours for twice daily and 24 hours for once daily before Visit 101). Visit 1 and Visit 101 should be conducted as close together as possible based on adjustments of prohibited medications.

All patients that meet eligibility criteria at Visit 1 will be provided a short-acting β-2 agonist (salbutamol) for use as a rescue inhaler on an "as needed" basis throughout the study; for more details on rescue medication please refer to Section 5.5.6.

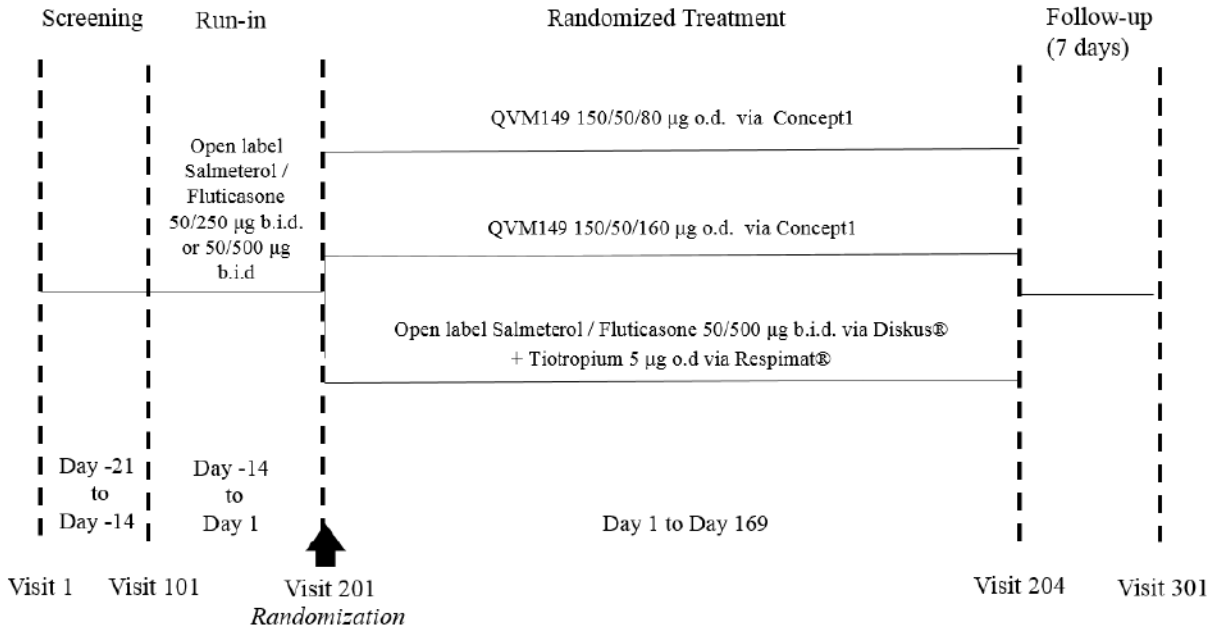
At Visit 101 all additional screening assessments, including a reversibility test to assess eligibility (see Appendix 2 Spirometry), and an ECG to evaluate patients' cardiovascular safety, must be conducted. Patients who qualify will enter a 2-week run-in period. Patients will be supplied with open-label LABA/ICS salmeterol /fluticasone 50/250 µg b.i.d. or 50/500 µg b.i.d, to match their background medication, which will be used throughout the Run-in and stopped at Visit 201. Patients will also be supplied with an electronic diary (eDiary) combined with Peak Flow meter to record asthma symptoms, rescue medication use, and PEF.

Upon completion of the run-in period at Visit 201 patients will return to the clinic. All patients who meet the eligibility criteria will be randomized in a 1:1:1 ratio to one of the three treatment arms (Section 5.2). Patients will be stratified at Visit 201 randomization according to the ICS dose component of background ICS/LABA (medium or high dose) and region.

The first dose of study medication will be administered at the clinic in the evening (between 5:00 and 8:00 pm) at Visit 201 (Day 1). Randomized patients will enter the 24 week treatment period during which visits must be scheduled to allow randomized study treatment to be taken in the evening at the clinic. Patients must be instructed not to take their evening dose of study medication prior to all future clinic visits, as these doses will be administered in clinic after all pre-dose assessments have been performed. All treatment period visits should be conducted at approximately the same time throughout the study to ensure pre-dose spirometry is performed and study treatment is taken at approximately the same time.

All randomized patients will be contacted (by telephone) 7 days following the last dose of study medication or last visit, whichever is later, for Visit 301 (Safety Follow-up).

Figure 3-1 Study design



3.2 Rationale for study design

A multicenter, partially-blinded, randomized, 24-week, parallel-group, non-inferiority, open-label active controlled study in patients with uncontrolled asthma on medium to high dose ICS/LABA was chosen to evaluate the efficacy and safety of 2 strengths of the fixed triple combination treatment QVM149 vs the free triple combination treatment salmeterol/ fluticasone + tiotropium. The general design is well-established in respiratory clinical trials and enables the study treatments to be given for an appropriate and practical length of time to assess the efficacy and safety of the treatments. The study has an open-label component (free triple combination of salmeterol/fluticasone + tiotropium for which investigators and patients will have full knowledge of treatment allocation. However, in order to minimize the potential impact, measures will be taken to blind the sponsor team from knowledge of treatment allocation. In addition, within the two QVM149 treatment arms all parties including patients and investigators will remain blinded to the actual dose. The identity of the QVM149 strengths will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

The open-label design of the study will reduce the burden of a triple dummy treatment regimen for participating patients.

An improvement of 0.5 points in AQLQ score is considered to be the minimally clinically important difference (MCID) in asthma. A non-inferiority margin of 0.25 points reduction in AQLQ score has been designated for the study based upon 50% of the MCID. If the MCID of 0.5 points reduction in the AQLQ is considered clinically important, it is reasonable to use a non-inferiority margin of one-half of this difference, which is 0.25 points.

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

Selection of the QVM149 combination product strengths (150/50/80 µg o.d. and 150/50/160 µg o.d.) for evaluation in this Phase IIIb study are the same as those used in the Phase III program and based on the doses of the constituent monotherapies which have been approved for either COPD or asthma.

Indacaterol acetate:

Indacaterol maleate at a dose of 150 µg o.d. is marketed for the maintenance treatment of COPD. A dose-ranging study of indacaterol maleate in asthmatic patients demonstrated that a dose of 150 µg o.d. was safe and effective (Study CQAB149B2357). The acetate salt of indacaterol was found to result in a lower incidence of the post-inhalation cough, observed for indacaterol maleate, without impact on efficacy or safety CQAB149D2301. 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 to placebo were investigated. Indacaterol acetate 150 µg showed positive trends in terms of trough FEV_1, PEF and rescue medication use compared with indacaterol acetate 75 µg. In study QMF149A2210, QMF149 150/160 µg o.d. showed beneficial effects on asthma exacerbations in terms of the time to first exacerbation and the cumulative incidence of serious asthma exacerbations.

Therefore, a dose of indacaterol acetate 150 µg o.d. has been selected for use in the QVM149 program.

Mometasone furoate:

Since available data for the MF component exists in the Twisthaler® device, a 3 step bridging approach was conducted to determine MF dose for Concept1 which is comparable to each of the registered daily doses of Asmanex Twisthaler® (mometasone furoate, inhalation powder).

This is due to difference in device performance characteristics between the Twisthaler® and Concept1 devices. Step 1: pharmacokinetic bridging utilizing pharmacokinetic characterization in study CQMF149E2101 (Vaidya S et al, 2012) followed by in-vitro fine particle mass adjustment (step 2) and finally pharmacodynamic evaluation of efficacy in asthma patients in study CQMF149E2201 (step 3).

For Step 1 and 2, the data of study CQMF149E2101 (Vaidya S et al, 2012), along with in vitro fine particle mass adjustments have led to the selection of 80, 160 and 320 µg as doses of MF in Concept1 device that are comparable to the approved doses 200 µg, 400 µg and 800 µg (2 x 400 µg) MF in Twisthaler®.

For Step 3, two of the MF doses in Twisthaler® and Concept1 were further evaluated for pharmacodynamic and clinical comparability in a 4-week study (CQMF149E2201) in patients with persistent asthma. MF doses of 80 µg and 320 µg delivered once daily via Concept1 showed comparable efficacy in trough FEV_1 and slightly lower systemic exposure compared to MF doses of 200 µg and 800 µg (2 x 400 µg) delivered once daily via Twisthaler® confirming the selected doses for MF Concept1 are appropriate for further QMF149 Concept1 development.

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

For QVM149 program, as a result of a component interaction, 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 80 µg o.d., 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 Concept1 and with 80 µg QVM149 via Concept1; all provide similar fine particle mass and thereby expected to provide similar lung and systemic exposure, since oral bioavailability of MF is low.

Glycopyrronium bromide:

The dose chosen for glycopyrronium bromide of 44 µg (expressed as dose active moiety delivery by the mouthpiece of the inhaler) is the one first approved in the EU on 28- Sep-2012 for the indication of maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Outside the EU, the dose of Seebri® Breezhaler® is generally expressed as the dose of active moiety in the capsule, i.e. 50 µg.

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®.

Tiotropium 5 µg once daily has been approved in Europe for treatment of asthma as add on to high dose LABA/ICS in patients with a history of exacerbations. This is equivalent to the dose approved in COPD. It is recommended by GINA guideline (2017) as an add-on option (on top of the preferred controller choice) for Steps 4 and 5 in patients with a history of exacerbations.

Based on head to head comparative data conducted in patients with COPD, it is expected that glycopyrronium bromide 50 µg once-daily will provide similar efficacy in an asthma population.

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).

Based on the available data glycopyrronium bromide 50 µg is considered an appropriate dose to bring forward into Phase III/IIIb asthma program as part of triple FDC QVM149 (LABA/LAMA/ICS).

3.4 Rationale for choice of comparator

Salmeterol/fluticasone is widely used standard of care in asthma treatment. Salmeterol /fluticasone high dose 50/500 µg b.i.d. delivered by DPI (dry-powder inhaler) is marketed as Seretide® Accuhaler® or Seretide® Diskus® depending on the countries for the treatment of asthma in adults and adolescents 12 years and older.

Tiotropium 5 µg o.d. has been approved in Europe for treatment of asthma as add-on to high dose LABA/ICS in patients with a history of exacerbations and is marketed as Spiriva® Respimat® Soft Mist™. Tiotropium is the only approved LAMA for this indication worldwide. It is recommended by GINA guideline (2017) as an add-on option (on top of the preferred controller choice) for Steps 4 and 5.

The intention of this trial is to compare a fixed dose combination of LABA/LAMA/ICS in two different dose strengths with the active comparator loose combination of these 3 components (LABA, LAMA, and ICS). The active comparator is based on the GINA guideline recommendations in this population and represents the standard of care. The active comparator free combination of salmeterol/fluticasone plus tiotropium also represents the most commonly used drugs which can form the free triple combination. Therefore, it is of scientific interest to conduct a direct comparison study to demonstrate that the fixed triple combination QVM149 is non-inferior to the free triple combination of salmeterol/fluticasone plus tiotropium.

3.5 Purpose and timing of interim analyses/design adaptations

No interim analysis for efficacy is planned.

3.6 Risks and benefits

Dual bronchodilation with ICS controller would be expected to achieve good symptom control, minimize airflow obstruction, minimize risk of exacerbations, and hospitalizations in this population. Use of multiple, often different devices represents a significant burden for asthma patients. Availability of three effective once-daily controller medications in a single device may offer advantages in terms of improved adherence and convenience.

The available asthma clinical trial data suggest that a LAMA may confer bronchodilator effects in terms of improved lung function when used in addition to ICS alone or in conjunction with LABA/ICS (i.e., “free combination” or “loose” triple therapy) (Fardon 2007, Peters 2010, Bateman 2011, Kerstjens 2011, Kerstjens 2012, Guyer 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 (FEV_1 and peak expiratory flow) (Befekadu 2014).

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

tiotropium increased the time to the first severe exacerbation (282 days vs. 226 days), with an overall reduction of 21% in the risk of a severe exacerbation.

Addition of LAMA (tiotropium 5 µg Respimat®) to ICS/LABA is now a recommended treatment option in GINA guideline (2017) 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 (Chapman 2014).

Overall, as concluded from the clinical studies glycopyrronium bromide o.d. was safe and well tolerated by the COPD patients and comparable to open label tiotropium. Reporting rates for known class effect AEs for anti-cholinergic drugs were low and generally consistent with those expected for this class (i.e. constipation, urinary retention, glaucoma, dry mouth). No enhanced risk of cardio- or cerebrovascular events relative to placebo was apparent, and the death rate in glycopyrronium bromide at all doses was lower than that observed in the placebo group.

In summary, as the benefit risk profile of glycopyrronium bromide has shown to be positive in COPD patients in which there are more comorbidities than asthmatic patients. The safety profile in an asthma population (which is generally younger with less co-morbidities) is expected to also be positive.

In this current Phase IIIb study, two QVM149 strengths will be compared to salmeterol/ fluticasone + tiotropium during 24 weeks of treatment. Participating patients in this study will be randomized to receive either one of the two strengths/doses of QVM149 or salmeterol/ fluticasone + tiotropium.

The use of other controller medications, i.e. sustained release theophylline, leukotriene modifiers and anti IgE (Xolair®) in stable doses will be permitted due to the severity of the disease and per treatment guideline (GINA 2017).

The expected potential benefit for the patient include an improvement in the pulmonary function, better asthma control such as reductions in symptoms, rescue medication use and lower frequency/ severity of asthma exacerbations, and improved quality of life. A thorough medical evaluation of the patients' disease and close clinical monitoring for the duration of the study will provide additional benefit to the patient care.

Frequent and regular contacts will occur in terms of clinic visits and telephone contacts when needed, to each patient throughout the 24-week treatment. In addition, safety monitoring (e.g. symptom collection and rescue medication use via electronic diary), and PEF (daily) measurements at regular intervals throughout the study will help assess status of the patient's asthma symptom control. Therefore, investigators may have an early indication of worsening symptoms and will be able to monitor the patient closely throughout the study.

In line with current medical treatment guidelines, all patients participating in the study will receive active "controller" treatment for their asthma throughout the 24-week treatment period. In addition, providing the patients with rescue medication for use as needed to treat any sudden constriction helps mitigate these risks. At no time, will any patient be without treatment for asthma.

The risk to the patients in the study is that QVM149 is under development in asthma and therefore it is possible that unexpected safety issues may be identified and the risk will be minimized by compliance with the eligibility criteria and close clinical monitoring of patients. The risks of side effects from the study medication are those known for the individual components indacaterol acetate, glycopyrronium bromide and mometasone furoate. No additional risks have been identified which might occur when the three components are administered concurrently or from the same inhaler. Detailed risk-benefit information can be obtained from the QVM149 Investigator's Brochure.

Guidance to manage potential worsening of asthma symptoms will be provided to investigators consistent with guideline recommendations (GINA 2017). Patients will receive 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 if, on balance, he/she believes that continuation would be detrimental to the patient's well-being. Patients are also instructed that they can discontinue study treatment at any time, and for any reason.

In summary, based on available data of components, it is anticipated that QVM149 150/50/80 µg and QVM149 150/50/160 µg will have a favorable benefit to risk profile in patients with uncontrolled asthma.

4 Population

The study population will consist of approximately 1251 male and female patients with uncontrolled asthma aged 18 and above.

It is anticipated that approximately 2500 patients will need to be screened in order to randomize approximately 1251 patients into the three treatment groups of the study with a randomization ratio of 1:1:1, (i.e. approximately 417 patients in each of the treatment groups).

Drop-outs after randomization will not be replaced. This study will enroll multi-nationally and patients will be stratified by previous ICS dose component of ICS/LABA therapy (medium or high) and region.

4.1 Inclusion criteria

1. Written informed consent must be obtained before any study-related assessment is performed. Only fully legally competent patients can be included (patients that are not able to consent cannot be recruited in this trial).
2. Male and female adult patient ≥ 18 years old.
3. Patients with a diagnosis of asthma for a period of at least 6 months prior to Visit 1 with current asthma severity ≥ step 4 (GINA 2017).
4. Patients who have used ICS/LABA combinations for asthma for at least 3 months and at stable medium or high dose of ICS/LABA for at least 1 month prior to Visit 1 (Appendix 10).
5. Patients must be symptomatic at screening despite treatment with medium or high stable doses of ICS/LABA as defined by ACQ-7 score ≥ 1.5 at visits 101 and 201 (randomization visit).

6. Patients with history of at least one severe asthma exacerbation (Section 6.4.5) which required medical care from a physician, ER visit (or local equivalent structure) or hospitalization in the 12 months prior to Visit 1 and required systemic corticosteroid (SCS) treatment for at least 3 days including physician guided self-management treatment with oral corticosteroids as part of written asthma action plan.
   - Previous severe asthma exacerbation in this context must be supported by documentation (i.e. such as in source notes, pharmacy records, hospital records, or chart records) of unplanned need for medical care at any primary care physician, pulmonologist, emergency room and hospital due to an aggravation of asthma symptoms and treatment with systemic corticosteroids due to severe asthma exacerbation including physician guided self-management treatment with oral corticosteroids as part of written asthma action plan.
7. Pre-bronchodilator FEV_1 of < 85 % of the predicted normal value for the patient after withholding bronchodilators prior to spirometry (Table 5-2) at both Visit 101 and Visit 201.
   - Repeat testing is allowed once at each visit (by rescheduling the visit). Repeat of Visit 101 should be scheduled on a date that would provide sufficient time to receive confirmation from the spirometry central reviewer before randomization.
   - Re-screening is allowed once if patient fails to meet the criteria at the repeat visit.
8. Patients who demonstrate an increase in FEV_1 of ≥ 12% and 200 mL 15 to 30 minutes after administration of 400 µg salbutamol or 360 µg albuterol (equivalent dose) through a spacer device at Visit 101. Patients need to demonstrate reversibility at V101 by either a positive reversibility test or with historical evidence of reversibility or positive bronchial provocation test that was performed within 5 years prior to Visit 1 and according to ATS/ERS guidelines. If reversibility is not demonstrated at Visit 101 the reversibility test may be repeated once.

   If reversibility is not demonstrated at Visit 101 (or after repeat) and historical evidence of reversibility is not available (or was not performed according to the ATS/ERS guidelines) the patients must be screen failed.

4.2 Exclusion criteria

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

1. Patients who have a smoking history of greater than 20 pack years (Note: 1 pack is equivalent to 20 cigarettes. 10 pack years = 1 pack /day x 10 yrs., or ½ pack/day x 20 yrs.).
2. Patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD).
3. Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of Visit 1 (Screening). If patients experience an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit between Visit 1 and Visit 201 they may be re-screened 6 weeks after recovery from the exacerbation.

4. Patients who have ever required intubation for a severe asthma attack/exacerbation.
5. Patients who have a clinical condition which is likely to be worsened by ICS administration (e.g. glaucoma, cataract and fragility fractures) who are according to investigator's medical judgment at risk participating in the study.
6. Patients treated with a LAMA for asthma within 3 months prior to Visit 1.
7. 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.
8. Patients who have had a respiratory tract infection or clinical significant asthma worsening as defined by Investigator within 4 weeks prior to Visit 1 or between Visit 1 and Visit 201. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening.
9. 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.
10. Patients with a history of chronic lung diseases other than asthma, including (but not limited to) sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis and active tuberculosis.
11. Patients with uncontrolled Type I or Type II diabetes.
12. Patients who have a clinically significant laboratory abnormality at Visit 101.
13. Use of other investigational drugs within 30 days or 5 half-lives of enrollment, until the expected pharmacodynamics effect has returned to baseline, whichever is longer.
14. Patients who, in the judgment of the investigator, have 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, hyper adrenergic state, or ophthalmologic disorder or patients with a medical condition that might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study.
15. 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 Visit 101 with a resting ventricular rate < 100/min.
16. Patients with a history of myocardial infarction within 12 months prior to Visit 1.
17. Concomitant use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of study.
18. Patients with a history of long QT syndrome or whose QTc measured at Visit 101 (Fridericia method) is prolonged (> 450 msec for males and > 460 msec for females). These patients should not be rescreened.

19. Patients who have a clinically significant ECG abnormality at Visit 101(ECG evidence of myocardial infarction at Visit 101 should be clinically assessed by the investigator with supportive documentation).
20. 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.
21. Patients with a history of hypersensitivity to lactose, any of the study drugs or its excipients, or to similar drugs within the class including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof.
22. Patients who have not achieved an acceptable spirometry result at Visit 101 (confirmed by over read) and Visit 201 (spirometer) in accordance with ATS /ERS criteria for acceptability and repeatability. (Repeat is allowed once for each visit, scheduled as close as possible but not on the same day). If the patient fails the repeat assessment, the patient may be rescreened once).
23. Patients receiving any medications in the classes listed in Table 5-3.
24. Patients receiving any asthma-related medications in the classes specified in Table 5-2.
25. 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.
26. Patients on maintenance immunotherapy (desensitization) for allergies for less than 3 months prior to Visit 101 or patients on Maintenance Immunotherapy for more than 3 months prior to Visit 101 but expected to change throughout the course of the study.
27. Patients who are serving a custodial sentence, do not have a permanent residence or who are detained under local mental health legislation/regulations.
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, Accuhaler®/Diskus®, Respimat® or a metered dose inhaler. Spacer devices are not permitted for use with study treatment.
30. History of alcohol or other substance abuse that based on judgement of the investigator would interfere with study conduct.
31. Patients with a known history of non-compliance to medication or who were unable to complete a patient eDiary, use electronic Peak Flow Meter, or complete questionnaires (PROs).
32. Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., inconsistent night shift workers). Consistent night shift workers may be considered for inclusion.
33. 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.
34. 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 follow-up period.

    Highly Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, 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 sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before Visit 201 (Randomization / Start of treatment period). Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The Investigational treatments are as follows:

- QVM149 (indacaterol acetate/glycopyrronium bromide/MF) 150/50/80 µg o.d. delivered as powder in hard capsules via Concept1
- QVM149 (indacaterol acetate/glycopyrronium bromide/MF) 150/50/160 µg o.d. delivered as powder in hard capsules via Concept1

The Comparative treatment is:

- Open label salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. delivered as powder via Accuhaler® + tiotropium 5 µg o.d delivered via Respimat®

Under no circumstances is an alternative inhalation device to be used for the administration of the investigational or reference therapies during the treatment period.QVM149 will be provided as global clinical blinded supplies and will be packed and labeled under the responsibility of Novartis, Drug Supply Management

- The Comparative treatments, salmeterol xinafoate /fluticasone propionate 50/500 µg delivered as powder via Accuhaler® + tiotropium 5 µg delivered via Respimat®, will

either be sourced as local commercial supply by Novartis or provided globally by Novartis as clinical open label supplies.

5.1.2 Additional treatment

Starting with Visit 1 patients will receive short acting beta agonist (salbutamol or albuterol) inhaler to use as rescue medication on an "as needed" basis. At Visit 101 patients will also be supplied with open label run-in medication, salmeterol / fluticasone 50/250 µg b.i.d. or 50/500 µg b.i.d. to match their background medication via IRT. It is required for all patients to take the open-label run-in medication, salmeterol / fluticasone twice daily from Visit 101 to Visit 201. The rescue medication will be provided as needed to the patients for the duration of the study. More details regarding rescue medication are in Section 5.5.6

Open-label run in medication, salmeterol xinafoate/fluticasone propionate 50/250 µg or 50/500 µg delivered as powder via Accuhaler® will either be sourced as local commercial supply or provided as global clinical open label supplies by Novartis. Salbutamol rescue medication will either be supplied to the investigator sites locally by Novartis or provided by the study center and reimbursed by Novartis.

5.2 Treatment arms

Patients will be randomized to one of the following three treatment arms in a ratio of 1:1:1:

- QVM149 150/50/80 µg o.d. delivered via Concept1
- QVM149 150/50/160 µg o.d. delivered via Concept1
- Salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler® plus tiotropium 5 µg o.d delivered via Respimat®

5.3 Treatment assignment and randomization

At Visit 201 all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

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

Randomization will be stratified by previous ICS dose of ICS/LABA therapy (medium or high dose) and region.

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

5.4 Treatment blinding

The study is partially blinded. The free triple combination of salmeterol/fluticasone + tiotropium is open-label for which investigators and patients will have full knowledge of treatment allocation. However, in order to minimize the potential impact, measures will be taken to blind the sponsor team, including data analysts, from knowledge of treatment allocation by using the following methods: (1) Randomization data and treatment codes are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study (2) Case Report Forms that reveal the treatment arm will be blinded from the sponsor team.

Specifically within the two QVM149 treatment arms patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the QVM149 treatment dose from the time of randomization until database lock, using the following additional method: (3) The identity of the QVM149 treatment dose will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9) and at the conclusion of the study.

5.5 Treating the patient

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

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT system. The site should select the e-Case Report Form (e-CRF) book with a matching Subject Number from the EDC system to enter data.

If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was a screening/run-in failure. The reason for screening/run-in failure will be entered on the applicable Study Period Disposition eCRF. Re-screened patients will be assigned a new sequential patient number and the investigator or staff will register them into the IRT system.

5.5.2 Dispensing the study drug

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance. All Novartis globally supplied treatments will have study drug packaging with a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the three treatment arms. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

All study treatment labels will comply with the legal requirements of each country, including locally sourced treatments.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

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

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

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

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

5.5.3.2 Handling of additional treatment

The following non-investigational treatment has to be monitored as follows:

The non-investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Clinical supplies are to be dispensed only in accordance with the protocol.

The investigator must maintain an accurate record of the shipment and dispensing of the non-investigational treatment in a drug accountability log. Monitoring of drug accountability will

be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused non- investigational treatment and packaging at the end of the run-in for the run-in medication and at the end of the study or at the time of discontinuation of investigational treatment for the rescue medication.

These medications are:

- Salbutamol (100 µg) or albuterol (90 µg) used as rescue medication
- Salmeterol xinafoate/fluticasone propionate 50/250 µg b.i.d. or 50/500 µg b.i.d. via Accuhaler® used as run-in medication

Details are described in the CRF completion guidelines.

5.5.4 Instructions for prescribing and taking study treatment

At Visit 1 all patients will be instructed on how to use a Metered Device Inhaler (MDI) to administer rescue medication, salbutamol. Patients will be instructed to take rescue medication on an "as needed" basis throughout the study. In order to standardize measurements, patients will be instructed to abstain from taking rescue medication within 6 hours of the start of each visit unless absolutely necessary.

At Visit 101 patients will be trained on how to properly use open-label run-in medication salmeterol/fluticasone via Accuhaler® and will be instructed to take b.i.d. per instructions in Appendix 4.

At Visit 201 patients will be trained on how to properly use the Concept1 inhaler device or the Accuhaler® plus Respimat® inhaler devices based on the randomized treatment arm provided by IRT. Patients who are unable to use the assigned device(s) correctly at Visit 201 will not continue in the study. At clinic visits the investigator should check the patient's use of the inhalational devices to ensure that they are using each device correctly. Additional device training should be provided as required.

QVM149 Treatment arms once daily evening dose:

Patients will be instructed to inhale 1 QVM149 capsule using the provided Concept1 device (pack bearing only a moon ☾ pictogram) in the evening between 5:00 and 8:00 pm. QVM149 study treatment must only be taken once a day in the evening. The first dose will be administered in the clinic at Visit 201.

Open label salmeterol /fluticasone twice daily + tiotropium once daily evening dose:

Patients will be instructed to take:

- MORNING between 5:00 and 8:00 am: 1 inhalation from the Accuhaler® device containing salmeterol/fluticasone (package bearing both a sun ☀ and moon ☾ pictogram)
- EVENING between 5:00 and 8:00 pm: 1 inhalation from the Accuhaler® device containing salmeterol/fluticasone (package bearing both a sun ☀ and moon ☾ pictogram) followed directly by 2 inhalations from the Respimat® device containing tiotropium (package bearing only a moon ☾ pictogram). Tiotropium via Respimat® must only be taken once a day in the evening. The first dose will be administered in the clinic at Visit 201.

Table 5-1 Study Treatments

Treatment arm	Morning ☀	Evening ☾
QVM149 150/50/80 µg or QVM149 150/50/160 µg	No dose	1 capsule via Concept1
Salmeterol xinafoate/fluticasone propionate 50/500 µg + Tiotropium 5 µg o.d	1 inhalation via Accuhaler®	1 inhalation via Accuhaler® + 2 inhalations via Respimat®

Patients will be instructed to rinse their mouth after inhalation of study drug (2 times with approximately 30 mL water). Water used for mouth rinsing should be spat out and should NOT be swallowed. When sequential inhalations of study drugs from two devices are required, mouth rinsing should be done after the last inhalation. Patients will also be instructed to take medication at approximately the same designated time while at home in between visits.

Instructions for use of the Concept1, Accuhaler®, and Respimat® devices are given in Appendix 3, Appendix 4, and Appendix 5.

The study treatment can be taken without regard to sleep, meals, and other activities. On days of scheduled clinic visits, patients should take their evening dose of study treatment at the clinic.

The duration of active treatment is 24 weeks, with the last dose of study treatment occurring at Visit 204.

All kits of investigational treatment assigned by the IRT will be recorded in the IRT. All used and unused study medication/packaging (except used capsules) must be returned by the patient at each study visit and/or at the time of discontinuation.

The investigator should promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

If any faults are identified with either the device and/or the blisters, these should be returned to Novartis Drug Supply Management with the completed Device Return Form. The forms will be supplied to each investigator site by the Field Monitor.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational treatment dose adjustments and/or interruptions are not permitted unless the investigator considers an interruption is necessary for the treatment of an adverse event. Any interruption of study medication should be for the shortest time period possible. Every interruption due to an adverse event must be recorded in the Dosage Administration Record CRF (e-CRF). Interruptions of more than 5 days for other reasons must also be recorded in the Dosage Administration Record CRF (e-CRF).

To reflect as near as possible the clinical practice setting in this trial, there is freedom to escalate ("step-up") and de-escalate ("step-down") the background medication.

Stepping-up asthma treatment

The treating physician may "step-up" patient's background medication and/or add-on maintenance treatment options if they remain uncontrolled or experience severe asthma exacerbations. Examples of background medication and add-on other maintenance treatment options: oral corticosteroids, biologic therapy, theophylline, leukotriene receptor antagonists (LTRAs), among others. These medications should be used according to approved local labels. [redacted]

Stepping-down treatment when asthma is well controlled

As per GINA guidelines and as part of periodic reassessment of disease control the investigator could consider stepping down treatment once good asthma control has been achieved and maintained for 3 or more months to find the minimum effective treatment that controls symptoms and exacerbations while minimizing side-effects (GINA 2017). The treating physician may perform a de-escalation or "step-down" of therapy beginning with OCS if the patient's asthma symptoms are well controlled with stable lung function for 3 or more months and the patient is not at risk for an exacerbation. Tiotropium may also be discontinued ONLY in the open label "free combination" comparator arm (salmeterol xinafoate/fluticasone propionate+ tiotropium) if the patient's asthma symptoms are well controlled with stable lung function for 3 or more months and the patient is not at risk for an exacerbation. The ICS and LABA component in any treatment arm cannot be adjusted or discontinued.

GINA guidelines recommend choosing an appropriate time for step-down (no respiratory infection, patient not travelling) and document baseline status (symptom control and lung function), provide a written asthma action plan, monitor symptoms, and book a follow-up visit.

5.5.6 Rescue medication

At Visit 1, all patients will be provided with a short acting β2-agonist (100 µg salbutamol MDI or equivalent albuterol MDI) which they will be instructed to use throughout the study as rescue medication. Nebulized salbutamol is not allowed as rescue medication throughout the entire trial. No other rescue treatment is permitted.

In order to standardize measurements, patients will be instructed to abstain from taking rescue medication (salbutamol or albuterol) within 6 hours of the start of each visit where spirometry is being performed unless absolutely necessary. If rescue medication is taken within 6 hours prior to spirometry assessments, then the visit should be rescheduled to the next day if possible.

The rescue salbutamol or albuterol provided at Visit 1 for use during the study should NOT be recorded on the asthma-related prior/concurrent medication page of the eCRF. From Visit 1, daily use of rescue medication (number of puffs taken in the previous 12 hours) will be

[redacted]

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

5.5.7 Concomitant medication

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded.

Bronchodilator medications that the patients used prior to Visit 1 must be recorded in the asthma-related prior/concurrent medication page of the eCRF. The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies eCRF. Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

5.5.8 Prohibited medications

The classes of medication listed in Table 5-2 (unless for the treatment of asthma exacerbations) and Table 5-3 are not permitted to be taken during the study. Before making the decision to pause or terminate prohibited concomitant medication according to Table 5.3, the investigator must make a careful medical assessment of the risks and benefits. It is not acceptable to pause or terminate any medication only to fulfill the inclusion/exclusion criteria of this trial. The medications in Table 5-4 are only permitted under the circumstances given. Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it is allowed. If in doubt, the investigator should contact the medical monitor before randomizing a patient or allowing a new medication to be started.

Table 5-2 Prohibited asthma-related medications

Class of medication	Minimum washout period prior to Screening (Visit 1), Run-in (Visit 101) and Randomization (Visit 201) [1,2,3]
Long-acting anticholinergics (LAMA)	Must not be used within 3 months prior to Visit 1
Short acting anticholinergics (SAMA)	Must not be used within 8 hours prior to Visit 101
Fixed combinations of β2-agonists and inhaled corticosteroids	Must not be used within 12 hours (24 hours for once daily combination) prior to Visit 101
Fixed combinations of short-acting β2-agonist and short-acting anticholinergic	Must not be used within 12 hours prior to Visit 101
Short acting β2-agonists (SABAs) (other than site provided trial rescue medication) [4]	Must not be used within 6 hours prior to Visit 1 and are not permitted during the study
Parenteral (IV/IM) corticosteroids	Must not be used within 4 weeks prior to Visit 101

Class of medication	Minimum washout period prior to Screening (Visit 1), Run-in (Visit 101) and Randomization (Visit 201) [1,2,3]
Intra-muscular depot corticosteroids	Must not be used within 3 months prior to Visit 101

[1] Treatment for recorded asthma exacerbation as defined in Section 6.4.5 is allowed ONLY until the asthma exacerbation is resolved

[2] This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.

[3] These medications are also prohibited if administered for other indications.

[4] Study supplied rescue medication (salbutamol/albuterol rescue medication) provided at Visit 1 is allowed during treatment but should be withheld for at least 6 hours prior to spirometry measurements at clinic visits. Clinic visits may be rescheduled if rescue medication were taken less than 6 hours prior to the spirometry assessments.

Table 5-3 Prohibited Medications

Class of medication [1]	Minimum cessation period prior to Run-in (Visit 101)
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug)	7 days
Non-selective systemic β –blocking agents	7 days
Cardiac anti-arrhythmics Class Ia	7 days
Cardiac anti-arrhythmics Class III	7 days, amiodarone 3 months
Other drugs with potential to significantly prolong the QT interval (e.g. mizolastin and terfenadine)	14 days or 5 half-lives, whichever is longer
All antipsychotic agents (first, second and third generation, inclusive of atypical antipsychotics). Combinations of antipsychotic agents with antidepressants are prohibited	14 days
Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)	14 days
Monoamine-oxidase inhibitors	14 days
Systemic anticholinergics	7 days
Strong inhibitors of cytochrome P4503A e.g. ketoconazole	7 days
Tricyclic antidepressants (Please note that tetracyclics which are similar in class with regards to drug interaction are also to be excluded)	14 days
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Noradrenaline reuptake inhibitors	7 days
Live attenuated vaccine	30 days

[1] This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria. Before starting wash-out of any of the listed prohibited medications in this table, the investigator has to assess the benefit and risk carefully for each individual patient.Terminating any medication solely for the purpose of meeting inclusion/exclusion criteria is not acceptable.

Table 5-4 Medications allowed under certain conditions

Class of medication	Condition

Class of medication	Condition
Monoclonal antibody: IgE inhibitors (e.g. omalizumab), IL-5 inhibitors (e.g. mepolizumab) **	Allowed if at stable dose for at least 3 months prior to Visit 1
Oral corticosteroids * **	Allowed if at stable dose for at least 1 month prior to Visit 1
Leukotriene Antagonist and leukotriene synthesis inhibitors **	Allowed if at stable dose for at least 1 month prior to Visit 1
Long-acting theophylline (methylxanthine) preparations **	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial. Not administered within 24 h prior to study visit.
Short- acting theophylline (methylxanthine)**	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial. Not administered within 12 h prior to study visit.
Mucolytic agents not containing bronchodilators	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial
Systemic mast cell stabilizers e.g. cromoglycate, nedcromil, ketotifen	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial
Selective Serotonin Reuptake Inhibitors (must have no documented effect on any other neurotransmitters or other biological pathways. E.g. muscarinic pathway)	Treatment regimen is stable for at least one month at Visit 1
Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine	Not administered within 48 hours prior to a study visit
Intra-nasal corticosteroids	Stable dose for at least 4 weeks prior to Visit 101. In the case of as needed, provided an established pattern of use has been documented.
Topical corticosteroids for the treatment of eczema	In recommended doses and dosage regimens
Maintenance immunotherapy for allergies	Stable dose for at least 3 months prior to Visit 101 and throughout the trial.

* Oral corticosteroids may be continued at a low stable dose after a course of steroid taper for exacerbations at the discretion of the investigator.

**During the treatment period, “step up” or add-on as well as “step-down” or de-escalation of maintenance treatments are allowed, as described below and in Section.5.5.5. These treatments must be used according to approved local labels.

If indicated for the treatment of an asthma exacerbation, any treatment deemed necessary by the treating physician for the safety of the patient is allowed from the start of the asthma exacerbation event (defined as per protocol Section 6.4.5) until the asthma exacerbation event is resolved. If deemed necessary, the treating physician may “step-up” patient’s background medication and/or add-on maintenance treatment options if they remain uncontrolled or experience severe asthma exacerbations, refer to Section 5.5.5. Patients may NOT self-medicate (other than administration of rescue medication) or adjust therapy without permission/guidance from treating physician.

5.5.9 Emergency breaking of assigned treatment code

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

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

- protocol number
- study drug name
- patient number

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

Study treatment must be discontinued if the treatment code of QVM149 treatment arm has been broken (actual dose of QVM149 unblinded) after emergency unblinding or inadvertently broken. This does not apply to the free triple treatment arm (salmeterol xinafoate/ fluticasone propionate + tiotropium) which is open label for investigators and patients.

5.6 Study Completion and Discontinuation

5.6.1 Study completion, post-study treatment and end of trial

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol (Visit 301).

Continuing care should be provided by investigator and/or referring physician based on patient availability.

For all randomized patients, a safety follow-up Visit 301 should be conducted by telephone 7 days after last visit. The information to be collected at this follow up visit includes adverse events and survival status.

The entire trial will be completed when the last randomized patient completes the last visit (Visit 301) of this protocol. In case the last patient randomized discontinues treatment prematurely (see Section 5.6.2) or voluntarily withdraws consent (see Section 5.6.3) the finalization of the trial is considered at patient's last visit. The trial will also end if Novartis is terminating the trial due to reasons related to benefit/risk assessment (see Section 5.6.5).

5.6.2 Discontinuation of Study Treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator. In such cases the patient should be asked to continue in the trial through the scheduled final visit in order to ensure the scientific integrity of the trial.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation of study treatment would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy
- Any situation in which study treatment might result in a safety risk to the patient

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. For this study it is very important to continue collecting data on all patients that discontinue treatment, especially for primary endpoint and safety. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit. Treatment discontinuation visit assessments detailed in Table 6-1 should be completed and recorded in the eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information in the End of Study Treatment eCRF. The investigator and study staff must also discuss continued participation with the patient.

Patients who discontinue study treatment prematurely should continue with limited study assessments. They should return to the clinic for each scheduled visit during the treatment period according to Assessment Schedule Table 6-1 but only conduct the assessments indicated in Table 5-5 Assessments for Patients who Discontinue Study Treatment. Patients should also conduct the safety follow-up Visit 301 (via telephone) after completing the intended treatment period.

Table 5-5 Assessments for Patients who Discontinue Study Treatment

Assessment
AQLQ[1]
Spirometry[1]
Record AEs
Record SAEs
Record Asthma Exacerbations
Review Concomitant Medication
Review Surgery and Procedures
[redacted]

[1] PROs should be completed before any other assessment. AQLQ and Spirometry must be performed pre-dose for standard of care treatment.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment. If study drug discontinuation occurs because treatment code of QVM149 treatment arm has been broken (actual dose of QVM149 unblinded), please refer to Section 5.5.9.

5.6.3 Withdrawal of informed consent

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

Withdrawal of consent (WoC) occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material. A patient is NOT considered to have withdrawn consent if they agree to follow-up visits.

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

5.6.4 Lost to follow-up

For randomized patients who are lost to follow-up (i.e. those patients whose status is unclear because he/she fails to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by making appropriate efforts to re-establish contact with patient and attempts to contact the patient should be documented in the source documents, e.g. dates of telephone calls/emails, registered letters, etc. If contact has not been re-established, all efforts should still be made to locate the patient and obtain information at the end of the 24 weeks intended treatment and at the safety follow-up visit (Visit 301). A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all the assessments to be performed for the study and indicates with an "X" the visits at which they will be performed. Patients should be seen for all visits on the designated day or as close as possible to that date. Visits during the treatment period should be performed within +/- 7 days of the designated day or as close as possible. All data obtained for these assessments must be supported in the patients' source documentation.

The following assessments are scheduled to be performed in order as follows: Patient reported outcome (PRO) questionnaires (i.e. AQLQ, ACQ, [redacted]), ECG, Vital signs (pulse rate and blood pressure), blood sample/urine samples, followed by spirometry in a manner that the

spirometry measurements occur at the scheduled time point (See Table 6-2 for Timed Assessments).

Whenever other assessments are scheduled at the same time-point, spirometry must take precedence such that it occurs at the scheduled time point or as near as possible. As required, other assessments can be done after spirometry.

Table 6-1 Assessment schedule

Period	**Screening**	**Run-in**	**Treatment**					**Follow-up** **Study Completion**
Visit number	**1**	**101**	**201**	**202**	**203**	**204**	**TD**	**301[4]**
Day	**-21 to -14**	**-14**	**1**	**57**	**113**	**169**		**176**
Week	**-3 to -2***	**-2**	**0**	**8**	**16**	**24**		**25**
Obtain Informed consent	X							
Contact IRT (IVRS/IWRS)	S	S	S	S	S	S	S	S
Prior and Current medication review/adjustment	X							
Review Concomitant medication		X	X	X	X	X	X	
Review Surgery and Procedures		X	X	X	X	X	X	
Inclusion/Exclusion criteria review	X	X	X					
Relevant Medical History, Demography	X							
History of Asthma Exacerbation	X							
Physical examination		S				S	S	
Smoking history and status	X							
Issue/collect rescue medication as required and review use	S	S	S	S	S	S		
Pregnancy test (serum)[1]		X				X	X	
Pregnancy test (urine)[1]			X	X	X			
Antigen-Specific IgE (Immunocap)		X						
Serum Total IgE		X						
Vital signs		X				X	X	
ECG		X				X	X	
Height		X						
Weight		X				X	X	

Period	**Screening**	**Run-in**	**Treatment**					**Follow-up** **Study Completion**
Visit number	**1**	**101**	**201**	**202**	**203**	**204**	**TD**	**301[4]**
Day	**-21 to -14**	**-14**	**1**	**57**	**113**	**169**		**176**
Week	**-3 to -2***	**-2**	**0**	**8**	**16**	**24**		**25**
Reversibility Spirometry test(SABA)[3]		X						
Spirometry			X	X	X	X	X	
Safety Lab assessments (haematology, clinical chemistry, urinalysis, blood eosinophil count)		X				X	X	
Issue and train on eDiary / [redacted]		S	S	S	S	S	S	
Review eDiary / [redacted]			S	S	S	S	S	
Accuhaler® device training		S						
Dispense Run-in medication via IRT		S						
Issue Run-in medication		X						
Randomization via IRT			S					
Dispense study treatment via IRT			S	S	S			
Concept1 or Accuhaler® + Respimat® device training			S	S	S			
Study Treatment Compliance			X	X	X	X		
Study treatment administration at visit			X	X	X	X		
AEs recording	X[2]	X	X	X	X	X	X	X
SAEs recording	X	X	X	X	X	X	X	X
ACQ-7		X	X		X	X	X	
AQLQ			X		X	X	X	
[redacted]								
Survival Status								X
[redacted]								

* Time between Visit 1 and 101 can be shortened/adapted according to the required wash-out from previous asthma medication.
TD: Trial discontinuation
S: These assessments are source documentation only and will not be entered into the e-CRF
X: Assessment to be reported in the clinical database

[1] For females of child-bearing potential only unless surgically sterile.

[2] If patient is screen failure, any non-serious AEs must only be recorded in the source documentation (S)

[3] If reversibility fails on the first attempt at V101, historical reversibility or bronchoprovocation would be acceptable as specified in Section 4.1

[4] Information about patients' status will be obtained by a telephone call, 7 days after the patient's last dose of study drug for completed patients or at any time during the study treatment period when indicated. For patients who withdraw early, please refer to discontinuation of study treatment and premature patient withdrawal section.

Table 6-2 Timed Assessments

Visit (Day)	Timepoint[1]	PROs (AQLQ, ACQ-7, [redacted])	Spirometry[4] (FEV_1, FVC)	Labs (Hematology, Chemistry, Urinalysis)	Urine Pregnancy Test[3]	ECG Vitals[2]
Visit 201 (Day 1)	>-45 min	X			X	
	-45 min		X			
	-15 min		X			
	0 min	EVENING DOSE				
Visit 202 (Day 57)	>-45 min				X	
	-45 min		X			
	-15 min		X			
	0 min	EVENING DOSE				
Visit 203 (Day 113)	>-45 min	X[redacted]			X	
	-45 min		X			
	-15 min		X			
	0 min	EVENING DOSE				
Visit 204 (Day 169)	>-45 min	X				X
	- 45 min		X			
	- 45 to -20 min			X[5,6]		
	-15 min		X			
	0 min	EVENING DOSE				

[1] Study drug timed doses. All study medication doses to be administered in the clinic. Time relates to the dose given from first device at visit. >-45 refers to any time before the -45 spirometry time point. Assessments scheduled -45 to -20 min can be done at any time pre-dose if more convenient or efficient.

[2] Systolic and diastolic blood pressure and heart rate (radial pulse)

[3] Urine pregnancy test can be done at any time pre-dose if more convenient or efficient.

[4] A minimum of 3 minutes rest must be observed prior to the start of spirometry at each time-point. A minimum of 1 minute rest is to be observed between each spirometry maneuver.

[5] Urine analysis is to be done only if the urine dipstick is abnormal, and only done pre-dose

[6] Serum pregnancy test done with safety labs at Visit 204

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the run-in period will have the screening disposition page for the screening period, demographics, eligibility criteria, and serious adverse events (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data only.

All patients who are entered into the run-in period of the study will additionally have all adverse events occurring after informed consent is signed recorded on the AE page and have the run-in disposition page for run-in period collected.

6.2 Patient demographics/other baseline characteristics

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

- Date of birth (where allowed by local legislation)
- Age (calculated)
- Sex
- Race and ethnicity
- Patients initials (where allowed by local legislation)
- Height and Weight
- BMI (calculated)
- Baseline physical examination (not databases other than in the context of relevant medical history)
- Vital signs
- ECG
- Date of diagnosis of asthma
- Relevant medical history/ current medical condition present before signing the informed consent
- Smoking history and status
- Asthma Quality of Life (AQLQ)
- Asthma Control (ACQ-7)
- [redacted]
- Prior concomitant medication (Both asthma related and non-asthma related)
- Pre and post-bronchodilator spirometry (run-in spirometry and reversibility testing)

6.3 Treatment exposure and compliance

Study treatment compliance should be assessed by the investigator and/or site personnel at all visits. Where necessary, the Investigator will discuss compliance issues with the patient.

6.4 Efficacy

The following assessments of efficacy will be performed:

- Health Status (PROs: AQLQ, ACQ-7, [redacted])
- Spirometry
- [redacted]

6.4.1 Health Status (Patient Reported Outcomes)

A patient- reported outcome (PRO) is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.

Patient-reported outcomes may provide quantitative information for patients regarding the 'impact on daily life', which is of key importance, for patients and their physicians and also for health technology assessments.

In this study, the main efficacy variable is a PRO to assess the impact of uncontrolled asthma and the disease's management beyond lung function. All PROs should always be completed before any other assessments are performed to avoid influencing the responses. When occurring at the same visit they are to be completed in the following order: AQLQ-S, ACQ-7, [redacted]

6.4.1.1 Asthma Quality of Life Questionnaire (AQLQ-S)

The AQLQ is a 32-item asthma specific questionnaire designed to measure functional impairments that are most important to patients with asthma (Appendix 7). It consists of 4 domains: symptoms, emotions, exposure to environmental stimuli and activity limitation. Patients are asked to recall their experiences during the previous 2 weeks and to score each item on a 7-point scale (Juniper 1992, Juniper 1993). The overall AQLQ score is the mean response to all 32 questions. Clinically important differences in scores between any two assessments have been determined by the authors of the AQLQ. Changes in scores of 0.5 are considered clinically meaningful; changes of 1.0 are considered as moderate and > 1.5 as large changes for any individual domain or for the overall summary score (Juniper 1994).

AQLQ should be completed by the patient (self-administered) at the clinic as per Assessment Schedule Table 6-1.

6.4.1.2 Asthma Control Questionnaire (ACQ-7)

In this study, the ACQ-7 (Appendix8) will be used to assess improvements in asthma symptom control. The ACQ-7 (Juniper 1999; Juniper 2005; Juniper 2006) is a seven-item disease-specific instrument developed and validated to assess asthma control in patients in clinical trials as well as in individuals in clinical practice. The ACQ-7 questionnaire will be provided to the site. The ACQ-7 questionnaire consists of five items to assess symptoms and activity limitations, one question to assess rescue medication use, and one question to assess airway caliber (FEV_1% predicted). All seven items are scored on a 7-point Likert scale, with 0 indicating total control and 6 indicating poor control. The questions are equally weighted and the total score is the mean of the seven items. The proportion of patients who achieve a~~n~~ improvement of at least 0.5 in ACQ-7 (i.e. decrease of ACQ-7 score of at least 0.5 from baseline) at post-baseline visits will also be analyzed.

The first 6 questions of the ACQ-7 should be completed by the patient based on one recall over the prior week. The last question should be completed by the investigator at the site using data from the spirometer. The ACQ-7 should be completed at the clinic as per Assessment Schedule Table 6-1.

6.4.2 Spirometry

The following spirometric assessments will be made:

- Forced expiratory volume in one second (FEV_1)
- Forced Vital Capacity (FVC)
- Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity (FEF_{25-75})

Spirometric assessments will be performed per Assessment Schedule Table 6-1 and Timed Assessments Table 6-2.

Trough FEV_1 for QVM149 150/50/80 µg and QVM149 150/50/160 µg o.d. delivered via Concept1 is the mean of the two FEV_1 values measures at -45 min and -15 min prior to evening dose. Trough FEV_1 for the 'free' triple combination of salmeterol/fluticasone 50/500 µg b.i.d. delivered as powder via Accuhaler® + tiotropium 5 µg o.d delivered via Respimat® is the mean of the two FEV_1 values measures at -45 min and -15 min prior to evening dose.

Please refer to the Spirometry Guidance in Appendix 2.

6.4.4 Worsening of asthma

Investigators and patients will be instructed how to deal with worsening of asthma symptoms. The data captured in the patient diary and site spirometer will be used to alert the patient and/or investigator to possible signs of worsening asthma. The patient eDiary will instruct the patient to contact the study site if any asthma worsening criteria is met. The investigator will instruct the patient to contact the investigator if at any time during the trial from the run-in onwards one or more of the following criteria of worsening asthma develops:

Asthma Worsening Criteria:

1. > 20% decrease in FEV_1 from baseline value (this criterion applies to Investigator review at the time of a study visit or via spirometry report)
2. > 50% increase in SABA use and >8 puffs per day on 2 out of any 3 consecutive days compared to baseline
3. ≥ 20% decrease in morning (AM) or evening (PM) PEF from baseline on 2 out of any 3 consecutive days compared to baseline
4. < 60% of predicted or personal best PEF compared to baseline
5. Night time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights

6. Urgent unscheduled clinic visit due to asthma related deterioration

Note: The reference for the worsening of asthma during the run-in period would be the FEV_1 and PEF taken at Visit 101. The baseline FEV_1, and PEF for the treatment period is taken at treatment Day 1 (Visit 201). The baseline for SABA use during the run-in period will be >8 puffs and the baseline for the treatment period is taken from the average of the 7 days prior to V201.

If any of the above criteria (including the alert from e-diary) are met while a patient is in the run-in or treatment period, the investigator should assess the patient's condition. If this occurs during run-in period and it is considered a clinically significant asthma worsening in the investigator's opinion, the patient should be treated as appropriate and discontinued prior to randomization. Once the condition is resolved, if eligibility criteria are met, the patient may be reconsidered for rescreening.

If patients develop any of the above criteria during treatment, the patient should notify the investigator and be evaluated by the investigator and treated as clinically appropriate.

Worsening of asthma symptoms may require unscheduled evaluation between visits. Study site personnel must be available to monitor and document patient's progress until asthma control is regained.

6.4.5 Asthma Exacerbation

A **severe asthma** exacerbation (Draft note for guidance on clinical investigation of medicinal products for treatment of asthma CHMP/EWP/2922/01 Rev.1) is defined as an aggravation of asthma symptoms (like shortness of breath, cough, wheezing, or chest tightness) that requires Systemic Corticosteroid (SCS) for at least three consecutive days and/or a need for an ER visit (or local equivalent structure), hospitalization due to asthma or death due to asthma.

Start date and end date:

- In case of the use of SCSs for at least three days, the first day of treatment will determine the onset date of the event while the last day of treatment will define the stop date.
- In the event that an ER visit and/or hospitalization due to asthma exacerbation were not associated with a course of SCSs as described above, start and end dates would be defined by the corresponding dates entered by the Investigator in the CRF.

A **moderate asthma** exacerbation in this protocol is defined as the occurrence of two or more of the following:

1. Progressive increase of at least one of the asthma symptoms like shortness of breath, cough, wheezing, or chest tightness. The symptoms should be outside the patient's usual range of day-to-day asthma and should last at least two consecutive days.
2. Increased use of "rescue" inhaled bronchodilators defined by:
    - $\geq$ 50% increase in SABA use and >8 puffs on 2 out of any 3 consecutive days compared to baseline captured

    Or

    - Night time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights

3. Deterioration in lung function, which last for two days or more but usually not severe enough to warrant SCSs for more than 2 days or hospitalization. This deterioration would be defined by:
   - ≥ 20% decrease in FEV_1 from baseline value

   Or
   - ≥ 20% decrease in morning (AM) or evening (PM) PEF from baseline on 2 out of any 3 consecutive days compared to baseline.

   Or
   - < 60% of predicted PEF compared to baseline

A **mild asthma** exacerbation is defined as the occurrence of one of the following criteria:

1. Deterioration of at least one asthma symptoms like shortness of breath, cough, wheezing or chest tightness.
2. Increased use of "rescue" inhaled bronchodilators
3. Deterioration in lung function, which last for two days or more but usually not severe enough to warrant SCSs or hospitalization. This deterioration would be defined by:
   - ≥ 20% decrease in FEV_1 from baseline value

   Or
   - ≥ 20% decrease in morning (AM) or evening (PM) PEF from baseline on 2 out of any 3 consecutive days compared to baseline.

     Or
   - < 60% of predicted PEF compared to baseline

"Start and end dates" of each reported event in the CRF will be used to determine whether two consecutively reported events should be considered as separate events or as a prolonged one. If a second exacerbation is reported less than 7 days after the end date of a previous episode, then this will be assumed to be one continuous exacerbation with the start date taken from the first episode and the end date from the second or last episode. If two events are merged based on this "7 day rule", the highest reported severity will be used to describe the overall severity of the prolonged event.

The treatment of asthma exacerbations including the initiation of SCS or increase in the maintenance dose of OCS should be done according to investigator's or treating physician's medical judgement and should be in line with national and international recommendations. If SCS are required, a patient may return to the study after successfully completing a taper.

[redacted]

6.4.7 Appropriateness of efficacy assessments

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

The primary endpoint, Asthma Quality of Life (AQLQ), refers to the perceived impact that asthma has on the patient's quality of life (QoL). This endpoint is widely used in asthma trials and in more than six published validation studies conducted worldwide and has shown very strong measurement properties. It is increasingly recognized that the evaluation of therapeutic interventions should include assessment of outcomes that matter to patients. The QOL measures can provide unique information and can thus provide a more complete characterization of the study population's asthma and of the benefits or drawbacks of particular interventions.

6.5 Safety

The following safety assessments will be performed:

- Medical history and physical examination
- Vital signs
- Hematology, Blood chemistry, Urinalysis
- ECG
- Adverse events including serious adverse events
- Pregnancy (female patients); additional pregnancy testing might be performed if requested by local requirements
- Serious asthma outcomes (asthma-related hospitalizations, intubations or deaths)
- CCV events and new onset of atrial fibrillation

An independent adjudication committee will be established to assess serious asthma outcomes (asthma-related hospitalizations, intubations and deaths), serious cardiovascular and cerebrovascular (CCV) events, new onset of atrial fibrillation and flutter as well as all deaths. Refer to Section 8.5 for more information.

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed as detailed in Schedule of Assessments Table 6-1.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to informed consent being signed must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after informed consent (Visit 1) is given which meet the definition of an Adverse Event must be recorded on the Adverse Event eCRF.

6.5.2 Vital signs

Systolic and diastolic blood pressure and radial pulse rate (over a 30 sec interval), performed in the sitting position, will be recorded at scheduled visits as detailed in Schedule of Assessments Table 6-1. Vitals can be performed just before or just after ECG.

6.5.3 Height and weight

Height in centimeters (cm) will be measured. Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured according to Schedule of Assessments Table 6-1. BMI will be calculated based on height and weight.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

All patients with laboratory tests containing clinically significant abnormalities should be followed regularly until the values return to within the normal ranges or until a valid reason other than drug-related adverse experiences is identified, even after the medication has discontinued.

Safety Laboratory assessments (hematology, clinical chemistry, urinalysis) will be performed according to Schedule of Assessments Table 6-1.

6.5.4.1 Hematology

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

6.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, AST (SGOT), ALT (SGPT), bilirubin, creatinine, γ-GT, glucose, potassium, magnesium, BUN and uric acid will be measured.

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

6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, pH, protein, glucose and blood will be performed according to the Schedule of Assessments Table 6-1.

If the urine dipstick is abnormal, the sample will be sent to central laboratory for additional testing, including assessment of WBC and RBC sediments.

6.5.5 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline.

Centralized ECG equipment:

ECGs will be measured pre-dose. All electrocardiograms should include 12 standard leads. An ECG tracing will be taken for those patients who prematurely discontinue from the study.

Each ECG will be sent electronically from the ECG machine to the central laboratory. A print out of the ECG record will be generated and kept at the investigator site as source documentation and as back-up for submission to the central laboratory in case of problems with the electronic transmission. Each print out will be kept at the investigator site and will be dated and signed. The subject's number, the date, actual time of the tracing, and Study Code must appear on each page of the tracing.

Full details of all procedures relating to the ECG collection and reporting will be contained in an investigator manual to be provided by the central laboratory to each investigator site. A clinically significant abnormality should be reported as an AE. If necessary a cardiologist may be consulted.

Clinically significant ECG findings at baseline must be discussed with the sponsor before administration with investigational treatment.

If a patient experiences a clinically significant change in cardiac rhythm or other clinically significant cardiovascular abnormality, the investigator should consider withdrawing the patient from the study.

Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions/AE CRF/e-CRF page as appropriate.

New cases (not present during screening/run-in periods) of atrial fibrillation reported from the ECG measurements (or reported as an AE during the course of the study) will be adjudicated. Additional information regarding the Atrial Fibrillation/Atrial Flutter may be requested to be sent to the Adjudication Committee. All cases of atrial fibrillation, regardless of seriousness, will be reviewed by the Adjudication Committee.

6.5.6 Pregnancy and assessments of fertility

A urine or serum pregnancy test will be performed in pre-menopausal women who are not surgically sterile (tests provided by the Central Laboratory) per Schedule of Assessments Table 6-1. If the urine pregnancy test is positive, a plasma testing is to be done to confirm the pregnancy. A positive pregnancy test during the study requires the patient to be discontinued from the study treatment. Refer to Section 5.6.2 and Section 7.5 for more details. Additional pregnancy testing might be performed if requested by local requirements.

6.5.7 Appropriateness of safety measurements

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

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study 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 product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, 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 must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

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

- 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

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 adjusted/temporarily interrupted
- [investigational] treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2) for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product 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 has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the

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

7.2 Serious adverse events

7.2.1 Definition of SAE

A 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 (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (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 patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

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

7.2.2 SAE reporting

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

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A 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.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to *each specific component of study treatment,* complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. 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. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

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.

7.3 Liver safety monitoring

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

The following two categories of abnormalities/adverse events have to be considered during the course of the study (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 Appendix 1 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Appendix 1 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 13-1 Liver Event and Laboratory Trigger Definitions.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

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

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

For the liver events:

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

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

7.4 Reporting of study treatment errors including misuse/abuse

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

Medication errors are usually unintentional, although a patient can intentionally 'commit' a medication error due to a lack of medical knowledge or sound judgment (e.g. intentionally removing drug from capsule and dissolving in juice) or there is an accidental drug omission by an HCP). Medication errors are not considered to be misuse or abuse.

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.

Medication errors with randomized study treatment (study treatment errors) will be collected on the DAR (dose administration record) eCRF. Refer to Section 5.5.5 for information regarding interruptions of study treatment.

Misuse or abuse of randomized study treatment will be collected on the AE eCRF and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes, even if not associated with AE	Yes, even if not associated with SAE

7.5 Pregnancy reporting

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

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis 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.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

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

8.2 Data collection

Designated investigator site staff will not be given access to the system until they have been trained. All data will be handled in alignment with current legislation on data protection. Study documents including patients' files will be stored secure at clinical site. Only a principal investigator and named study personal will have access to patients' files. Data transferred to Novartis systems are coded and protected from unauthorized break-in. Identified site users will receive an individual login and password or biometric fingerprint identification. Passwords used to access Novartis (and its vendors) systems need to be of appropriate strength and need to be changed regularly. Novartis personal computers require two factor authorizations. Additionally access to all data server rooms used to store hardware and software for this trial is restricted only to those staff with appropriate access rights. Access to systems which are no longer in use will be removed; also access of users no longer involved in the conduct of the study will be removed. On the contrary, new staff will be carefully trained before being allowed to access confidential or personal files (on-site training, investigator meeting and vendor specific trainings). Staff must ensure that unauthorized persons are unable to view or process personal or sensitive information in a paper form or displayed electronically. Personal data are stored centrally only in pseudonymous form. Electronic transfer of data is always encrypted and takes place via secure on-line channels providing the highest level of security. Spirometers and any other devices capturing clinical or personal data must not contain unauthorized, unlicensed or personally licensed software. All software must be authorized and procured through Novartis or its vendors. Electronic devices are secured by up-to-date anti-virus, anti-spyware and personal firewall. Only known machines are allowed to remotely access centrally held personal or sensitive data. In addition Novartis as well as clinical site regulate use of information and communication technologies by their staff in order to avoid unauthorized break-in to the network.

8.3 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. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

Diary data will be entered into an electronic diary by the patient and patients will fill in their PRO data in a site based tablet. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

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

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

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

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

An independent adjudication committee will be established to assess serious asthma outcomes (asthma-related hospitalizations, intubations and deaths), serious cardiovascular and cerebrovascular (CCV) events, new onset of atrial fibrillation and flutter as well as all deaths. All serious CCV events occurring from the time of randomization until the 30 days after the permanent discontinuation of study drug, where applicable, will be adjudicated.

The committee will consist of experts outside Novartis who are not involved in the study conduct, who will periodically review blinded, pertinent patient data and the supporting documentation to settle the specified adjudication objectives.

Further details will be provided in the Adjudication Committee Charter.

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. A detailed Statistical Analysis Plan (SAP) will be finalized before the study database lock. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

The following analysis sets are defined for data analysis.

The randomized (RAN) set will consist of all patients who were assigned a randomization number, regardless of whether or not they actually received study medication. Patients in RAN will be analyzed according to the treatment they were randomized to.

The Full Analysis Set (FAS) will consist of all patients in the RAN set who received at least one dose of study medication. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

The Per-Protocol set (PPS) will include all patients in the FAS who did not have any major protocol deviations. Major protocol deviations will be defined in the statistical analysis plan prior to database lock and the un-blinding of the study. Patients will be analyzed according to the treatment they received.

The Safety Set will consist of all patients who received at least one dose of study medication. Patients will be analyzed according to the treatment they received.

The FAS will be used in the analysis of all efficacy variables. The RAN set will be used for a summary of patient disposition, demographics and baseline characteristics. The PPS will be used for supportive analysis of the primary analysis only. The Safety Set will be used in the analysis of all safety variables.

Note that the FAS and Safety Sets are the same except that the Safety Set allows the inclusion of non-randomized patients who received study drug in error. Also, the FAS assign randomized treatment and the Safety Set assigned received treatment.

9.2 Patient demographics and other baseline characteristics

Demographic and baseline characteristics measured before randomization including age, gender, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, screening spirometry parameters: (FEV_1, FVC, FEV_1/FVC and FEF_{25-75}), FEV_1 reversibility, % of predicted FEV_1, duration of asthma, history of asthma exacerbations, smoking history, prior concurrent medications (asthma-related and non-asthma-related), vital signs (systolic and diastolic blood pressure, pulse rate), QTc using Fridericia's correction and baseline AQLQ-S, ACQ-7, [redacted] will be summarized by treatment group.

Continuous variables will be summarized using descriptive statistics (mean, median, standard deviation, minimum, and maximum) and categorical variables will be summarized in terms of the number and percentage of patients in each category for the treatment groups.

Baseline is defined as the last measurement before first dose of study drug. No statistical analyses will be provided for baseline comparability among the treatment groups.

9.3 Treatments

Study drug administration and concomitant medication data will be summarized using Safety set.

The duration of exposure and the number of patients randomized who completed the study and who discontinued from study medication will be summarized. Medications started and stopped prior to study drug, and taken concomitantly will be summarized by treatment group in separate tables in the Safety Set.

Concomitant therapies will be recorded, listed and summarized separately for asthma related medications/non-drug therapies and other medications. Concomitant asthma related medications will be summarized by route of administration, the recorded pre-specified drug subcategories (including types of combination) and preferred term. Concomitant medications not related to asthma will be summarized by route of administration and preferred term. SABA usage (number of puffs) during the run-in period will be summarized. Patients taking prohibited concomitant medications will be noted in the summary of protocol deviations. Treatment compliance with study medication over the study period will be summarized.

[redacted]

9.4 Analysis of the primary variable

9.4.1 Variables

Primary variable

The change from the baseline at week 24 for the AQLQ total score will be used as the primary variable to assess the non–inferiority of both strengths of QVM149 (QVM149 150/50/80 µg and QVM149 150/50/160 µg via Concept1) to the free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg.

The primary analysis will include on treatment data from all patients in FAS, i.e. data for primary, collected after treatment discontinuation will be used for supportive analysis only.

9.4.2 Statistical model, hypothesis and method of analysis

Analysis of primary variable

The non-inferiority of QVM149 150/50/160 µg o.d. Versus free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg and QVM149 150/50/80 µg o.d. versus free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg, in terms of change from baseline in AQLQ total score, will be assessed by testing the following null hypothesis (H_1 & H_2) versus the alternative hypothesis (H_{a1} & H_{a2}):

H_1: QVM149 150/50/160 µg o.d. is inferior to free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg in change from baseline for AQLQ total score at Week 24

H_{a1}: QVM149 150/50/160 is non-inferior to free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg in change from baseline for AQLQ total score at Week 24

H_2: QVM149 150/50/80 µg is inferior to free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg in change from baseline for AQLQ total score at Week 24

H_{a2}: QVM149 150/50/80 is non-inferior to free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg in change from baseline for AQLQ at total score Week 24

The primary variable will be analyzed using a mixed model for repeated measure (MMRM) on the FAS. The model will contain treatment, region, visit, background ICS/LABA (medium or high dose), baseline-by-visit interaction and treatment-by-visit interaction as fixed effects with baseline AQLQ total score as the covariate, and center nested within region as a random effect. The within-patient correlation will be modeled using the unstructured covariance matrix in the mixed model. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger,1997). If the model does not converge, then the compound symmetry covariance matrix will be used in the mixed model. Restricted maximum likelihood method will be used.

The least squares means of the treatment differences, standard errors, 97.5% (one-sided) CI, and one-sided p-values for non-inferiority test (adjusted and unadjusted) and nominal two-sided p-values at week 24 of each dose QVM149 vs. the combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg, will be presented.

Non-inferiority of QVM149 will be claimed if the multiplicity adjusted one-sided p-value is < 0.025.

9.4.3 Handling of missing values/ early discontinuations

The MMRM model, which is used for the analysis of primary variable is based on missing at random assumption for the missing values and assesses the treatment effects without explicit imputation.

The estimand for this study is difference between the effect of initially randomized treatments had all patients remained on their randomized treatment throughout the study.

AQLQ

The total AQLQ score is the mean response to all 32 questions; no imputation will be used for missing questions or missing total score.

9.4.4 Multiplicity Adjustment

To control the family-wise type-I error rate at the one-sided 2.5% significance level, a multiple testing procedure based on the trimmed Simes test in Brannath et. al. (2009) is used. The family for the overall type-I error rate control contains total 2hypotheses for the primary endpoint, AQLQ.. Denote the two hypotheses for the primary endpoint as H_1 and H_2 for comparing QVM149 150/50/160 µg o.d. Versus free combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg and QVM149 150/50/80 µg o.d. versus free combination of salmeterol/fluticasone 50/500 µg + tiotropium 5 µg, in terms of change from baseline in AQLQ total score.

Below is a brief description of the testing procedure based on the generalized Simes test in Brannath et al (2009).

Let p_1 and p_2 be the corresponding p-values (1-sided, p-value related to NI hypotheses) of the two hypotheses of H_1 andH_2.

Step 1: Retain both H_1 and H_2 if ANY $p_i \geq 0.975$(i.e. Loose triple is performing better than QVM) for i=1, 2stop here; otherwise go to step 2;

Step 2: Reject H_1 and H_2 if $p_i<0.025$ for BOTH i=1, 2, stop here; otherwise go to step 3;

Step 3: If neither step 1 or 2 applies, perform Bonferroni test to H_1 and H_2.Thus reject H_1 if $p_1<0.0125$ and reject H_2 if $p_2<0.0125$ and stop.

For each of the two hypotheses, the corresponding testing statistics (estimated least square mean difference) follows normal distribution. Hence for H_1 and H_2, their corresponding testing statistics is assumed to follow jointly bivariate normal distribution. Therefore this testing procedure controls the overall type –I error rate at the 1-sided 0.025 level in the strong sense regardless if the bivariate normal distributions have positive or negative correlations as shown in Brannath et al (2009).

Other than the two analyses mentioned above for the primary endpoint, all other analyses will be performed at the nominal 2-sided 0.05 level (2-sided) without multiplicity adjustment.

9.4.5 Supportive analyses

Following supplementary analyses will be performed for primary.

The MMRM model used for the analysis of primary variables will be performed on the PPS.

Primary variables will be analyzed using the same MMRM model as that of primary analysis using the data from all time-points (i.e. on and available off treatment data) on FAS.

9.5 Analysis of secondary endpoints

All analyses will be performed on FAS.

9.5.1 Efficacy variables

9.5.1.1 AQLQ Score, domains, and responders at each visit

Change from baseline in each of the AQLQ domains (symptoms, emotions, exposure to environmental stimuli and activity limitation) as well as the change from baseline in total score at post-baseline visits will be analyzed using mixed model of repeated measurements (MMRM) similar to primary variable. Appropriate baseline AQLQ domain scores will be used as covariate instead of baseline AQLQ total score in the model. The between-treatment comparison will be carried out using the adjusted mean (least-square mean) difference corresponding to the respective visit. Adjusted mean (LS mean) will be displayed for each treatment group along with the estimated treatment differences and the 95% confidence intervals and the two sided p-values by visit.

The proportion of patients who achieve an improvement of at least 0.5 in the change from baseline in AQLQ total score (i.e. increase of AQLQ total score of at least 0.5 from baseline) at post-baseline visits will be analyzed using the same logistic regression model via GEE

specified for the ACQ-7 analysis except that baseline AQLQ will be used as the covariate in the model, instead of the baseline ACQ-7.

9.5.1.2 Spirometry

All spirometry efficacy variables will be analyzed for the FAS, unless otherwise specified. Spirometry measurements taken within 7 days of systemic corticosteroid used as acute treatment for exacerbation, or within 3 months of single depot corticosteroid injection, or within 6 hours of rescue medication, will be set to missing and not be imputed, unless specified otherwise.

Spirometry data at each visit

Change from baseline in trough FEV_1 at week 24 will be analyzed using a mixed model for repeated measure (MMRM) similar to the model used for primary variable on the FAS. Trough FEV_1 is calculated as average of 15 min and 45 min pre-dose measurements. The model will include baseline FEV_1 instead of baseline AQLQ score as covariate. The least squares means of the treatment differences, standard errors, 95% (two-sided) CI, and p-values (nominal) at week 24 of each dose QVM149 vs the combination of salmeterol/fluticasone 50/500 µg + tiotropium 5 µg will be presented.

Trough FEV_1 will also be analyzed using the same MMRM model as specified above, where the between-treatment comparison will be carried out using the adjusted mean (least-square mean) difference corresponding to the respective visit. Adjusted mean (LS mean) will be displayed for each treatment group along with the estimated treatment differences and the 95% confidence intervals and the two sided p-values by visit.

Similar analyses will be performed for FVC and FEF_{25-75}. Change from baseline in the spirometry values will be also analyzed using the same MMRM model.

9.5.1.3 ACQ-7 Score and responders at each visit

Change from baseline in ACQ-7 score at post-baseline visits will be analyzed using the mixed model of repeated measurements (MMRM) similar to primary variable. Baseline ACQ-7 score will be used as covariate instead of baseline AQLQ total score in the model.

The least squares means of the treatment differences, standard errors, 95% (two-sided) CI, and p-values at each visit of each dose QVM149 vs. the combination of salmeterol/ fluticasone 50/500 µg + tiotropium 5 µg, will be presented.

The proportion of patients who achieve an improvement of at least 0.5 in ACQ-7 (i.e. decrease of ACQ-7 score of at least 0.5 from baseline) at post-baseline visits will be analyzed using the logistic regression model via the generalized estimating equations (GEE). The model will include terms for treatment, region, visit, background ICS/LABA (medium or high dose), baseline-by-visit interaction and treatment-by-visit interaction as fixed effects, with baseline ACQ-7 as covariates. The within-patient correlation will be modeled using the unstructured covariance matrix in the GEE model. The estimated adjusted odds ratios of the treatment comparisons will be displayed along with the associated 95% (two- sided) confidence intervals and p-values.

9.5.2 Safety variables

Adverse events

All study emergent adverse events including asthma exacerbations will be listed. Adverse events starting on or after the time of the first inhalation of study drug but not later than 7 days (30 days in the case of a SAE) after the last administration 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 will be classified as a prior adverse event.

The following treatment emergent adverse event summaries will be produced, overall by system organ class and preferred term, overall by system organ class, preferred term and maximum severity, suspected drug-related adverse events by system organ class and preferred term, serious adverse events by system organ class and preferred term, and adverse events leading to permanent discontinuation of study-drug by system organ class and preferred term.

The number and percentage of patients with the most frequent AEs will be summarized by treatment.

Electrocardiogram (ECG) and vital signs

Data from the electrocardiogram will be summarized by treatment and visit.

Vital signs (blood pressure and radial pulse rate) data will be summarized by treatment and visit. Changes from baseline will also be summarized by treatment. Weight will be summarized by visit and treatment group.

All data will be included in the analysis regardless of rescue medication usage. The number (%) of patients with pulse rate of < 40 and > 90 bpm; systolic blood pressure of< 90 and $>$ 140mmHg; diastolic blood pressure of < 50 and > 90 mmHg will be summarized by treatment group.

Notable values for vital signs and change from baseline will be summarized. A notable value is defined as follows:

Systolic blood pressure

“Low” criterion: < 75 mmHg, or ≤ 90 mmHg and decrease from baseline ≥ 20 mmHg

“High” criterion: > 200 mmHg, or ≥ 180 mmHg and increase from baseline ≥ 20 mmHg

Diastolic blood pressure

“Low” criterion: < 40 mmHg, or ≤ 50 mmHg and decrease from baseline ≥ 15 mmHg

“High” criterion: > 115 mmHg, or ≥ 105 mmHg and increase from baseline ≥ 15 mmHg

Pulse rate

”Low” criterion: < 40 bpm, or ≤ 50 bpm and decrease from baseline ≥ 15 bpm

“High” criterion: > 130 bpm, or ≥ 120 bpm and increase from baseline ≥ 15 bpm

Notable QTc values and changes from baseline will be summarized. A notable value is defined as a QTc interval of greater than 450 ms (male), 460 ms (female) and 500 ms (both) at

baseline and the number of newly occurring or worsening notable QTc values for post baseline time points. The categories used for the change from baseline in QTc are less than 30 ms, 30 to 60 ms and greater than 60 ms. QTc will be calculated from the QT interval and RR (in seconds) using Fridericia's formula:

$QTc = QT / 3\sqrt{RR}$, where $3\sqrt{}$ denotes the cube root

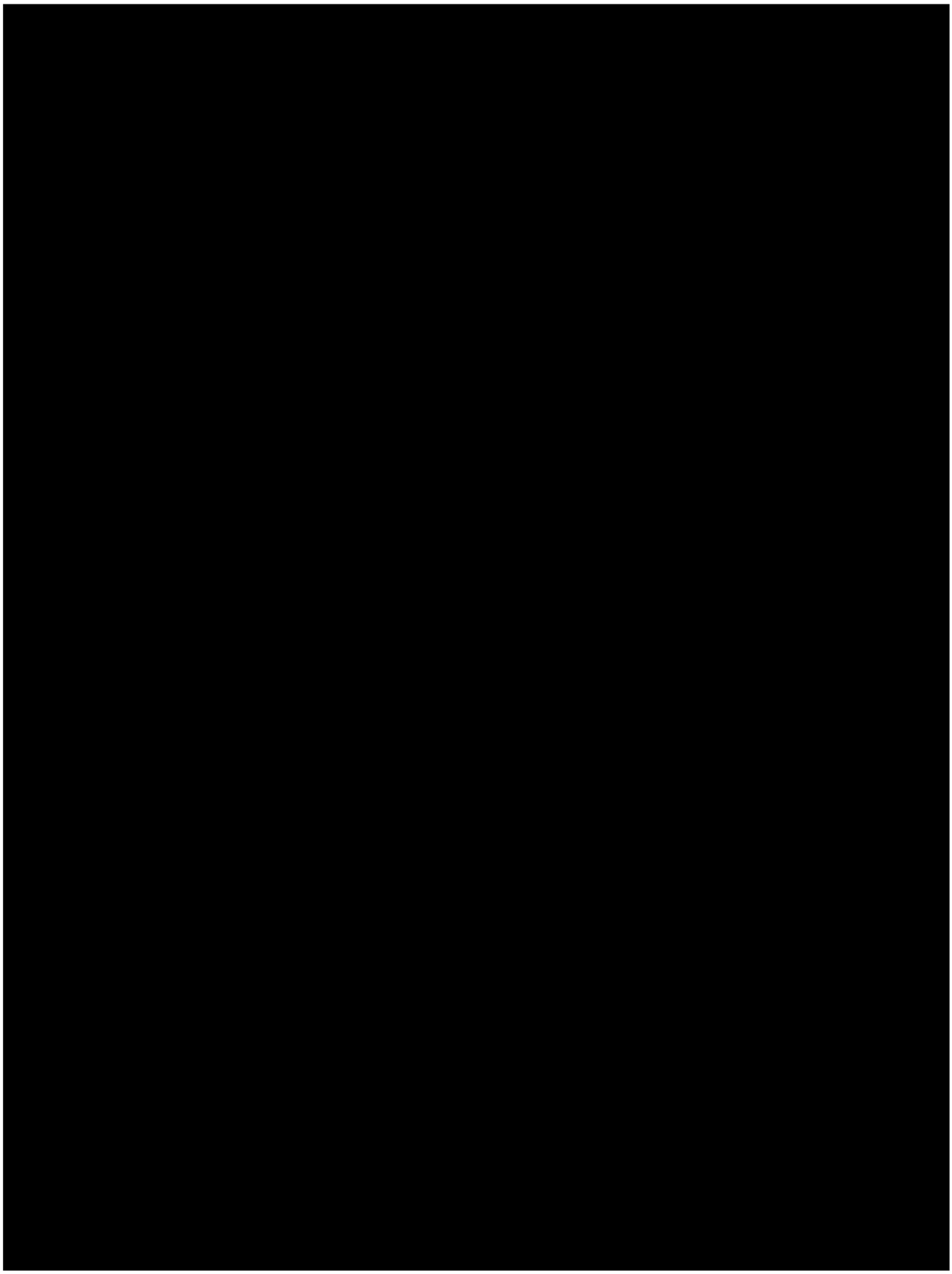
Vital signs and ECG data measured more than 7 days after last inhalation of study drug is regarded as post-treatment data and will not be summarized, only listed.

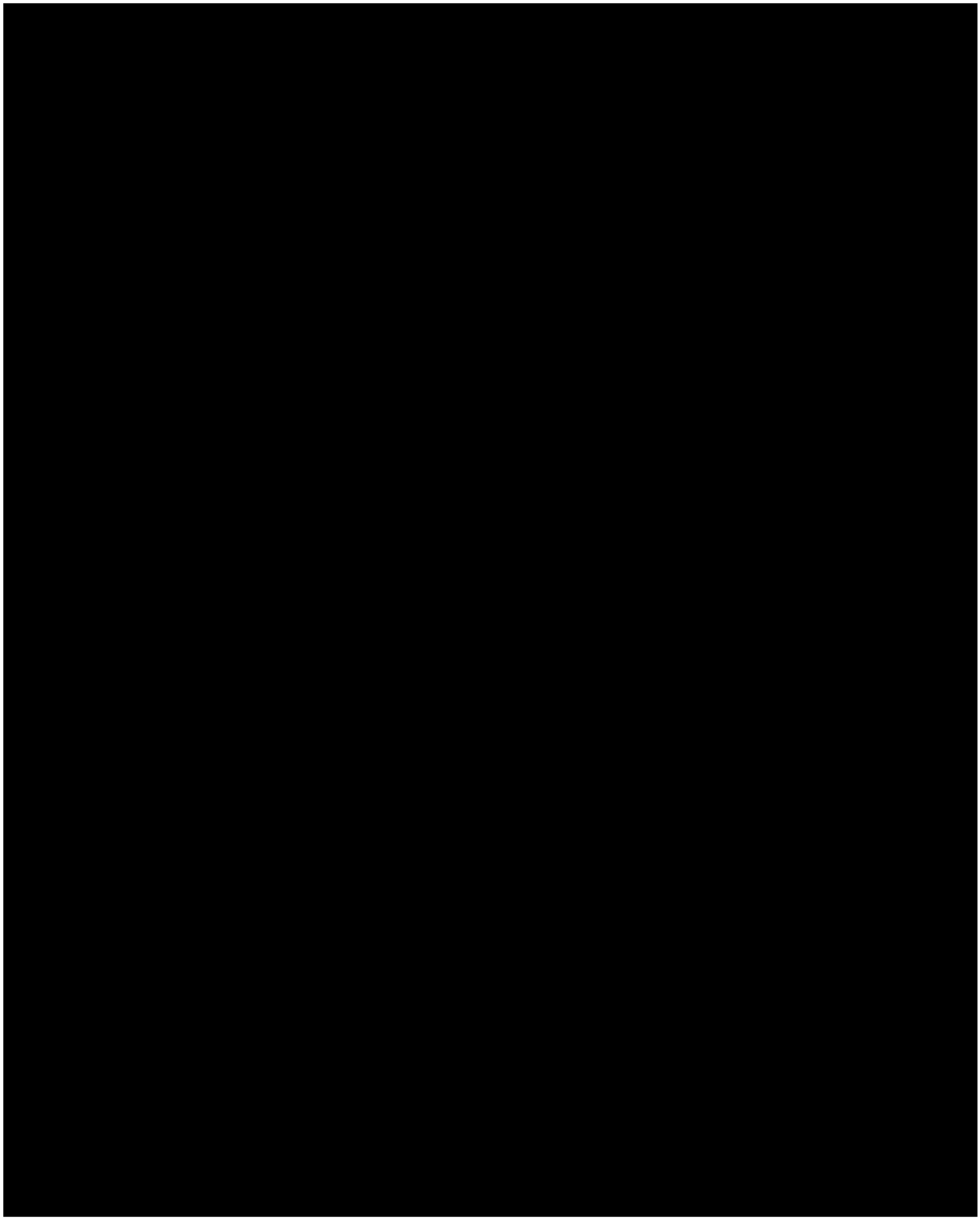
Laboratory data

All lab parameters will be summarized by treatment and visit. Changes from baseline will also be summarized by treatment. The baseline measurements are defined as last measurement prior to first dose of study drug.

All laboratory data will be listed with abnormal values flagged. The laboratory values and the change from baseline for continuous laboratory parameters will be summarized at each visit. A frequency table of results for categorical laboratory parameters will be produced by visit.

Shift tables relative to the normal reference ranges will be used to summarize the change from baseline to post-baseline by visit for each laboratory parameter. Laboratory data measured more than 7 days after last inhalation of study drug is regarded as post-treatment data and will not be summarized, only listed.





9.7 Interim analyses

No interim analysis is planned in this study.

9.8 Sample size calculation

The sample size calculation takes into account the following consideration:

- To achieve at least 90% power (with multiplicity adjustment) for primary endpoint, to demonstrate the non-inferiority of either of QVM149 dose vs. the free triple combination of salmeterol/fluticasone + tiotropium in patients with uncontrolled asthma for AQLQ at the week 24. With the assumption of 0.25 for the NI margin, zero as the point estimation of the treatment difference, one-sided alpha level of 0.025, and 0.8 of the standard deviation based on studies QMF149E2203 and Kerstjens (2012);

If 10% dropout rate is assumed, then the calculation shows that the sample size of 1251 patients (i.e 417/arm) will provide 99% power with multiplicity adjustment as given in Figure 9-1.

The sample size and power calculations are performed in R 3.1.2 with package gMCP.

10 Ethical considerations

10.1 Regulatory and ethical compliance informed consent procedures

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

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, only fully legal competent patients can be included The patient must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 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, informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/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.

10.4 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.

10.5 Quality Control and Quality Assurance

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

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

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

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/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 patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7, Safety Monitoring must be followed.

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13 Appendix 1: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 13-1 Liver Event and Laboratory Trigger Definitions

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

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

Table 13-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

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

14 Appendix 2: Spirometry Guidance

Equipment

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

Calibration

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

Preparing the test subject

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

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

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

Performing Spirometry

The subject's age, height and gender will be entered into the spirometer. It is important that the height is measured accurately at the study site. Spirometry, an effort-dependent test, requires careful instruction and cooperation of the subject. The technician should ensure a good seal around the mouthpiece, and confirm that the subject's posture is correct. The subject should be instructed to perform a maximal inspiration, followed by maximum forced expiration until no more air can be exhaled or for at least 6 seconds. Expiration must be rapid with exertion of maximal effort. The results of spirometry should meet the ATS/ERS criteria for acceptability and repeatability. Acceptability criteria should be applied before repeatability is determined.

Number of trials

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

Acceptability

An acceptable maneuver has the following characteristics:

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

Repeatability

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

Recording of data

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

Predicted normal

This study will utilize the spirometric predication equation standards for the European Community for Coal and Steel[2], Nhanes[3], ERS Global Lung Function Initiative (GLI)[2] or Japanese Respiratory Society[3].

Reversibility

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

Administer 400 µg of salbutamol 360 µg albuterol through a spacer following the completion of the baseline assessment. A second spirometry assessment is then performed 15 to 30 minutes after administration of the salbumatol/albuterol.

Reversibility is calculated as:

$$100 \times \frac{FEV_1 \text{ (post } \beta_2\text{-agonists)} - FEV_1 \text{ (baseline)}}{FEV_1 \text{ (baseline)}}$$

Subjects will be considered reversible if an increase of at least 12% (and 200 mL) is demonstrated after administration of the bronchodilator.

References

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

[2] Quanjer PH et al. ERS Global Lung Function Initiative. Multi ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. Report of the Global Lung Function Initiative (GLI). ERS Task Force to establish improved Lung Function Reference Values.

[3]Kubota, Kobayashi, Quanjer PH, et al. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous

values. Clinical Pulmonary Functions Committee of the Japanese Respiratory Society. Respiratory Investigations 2014: 242-250.

15 Appendix 3: Instruction for Use of Concept1

Instructions for using inhaler and capsules.

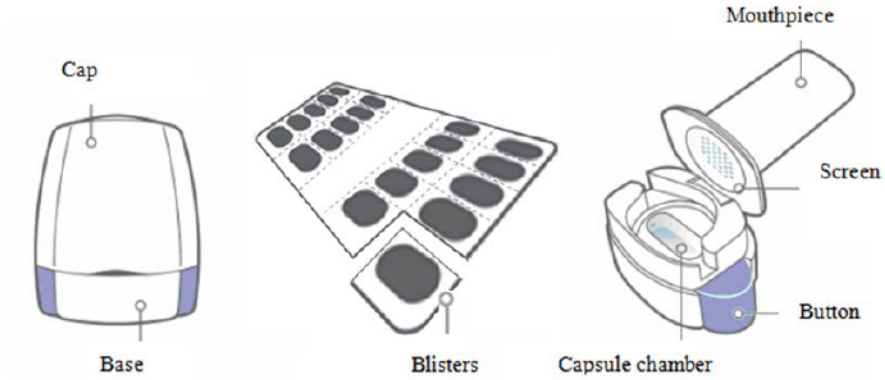
Do not swallow capsules.

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.

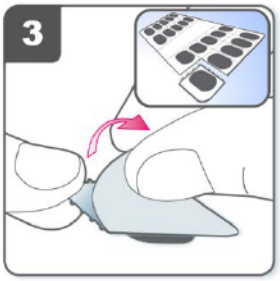
Do not use the study medication capsules with any other capsule inhaler, and do not use the inhaler to take any other capsule medicine.

How to use your inhaler

Pull off cap.

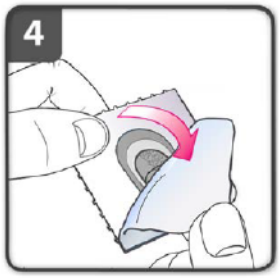
Open inhaler:

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



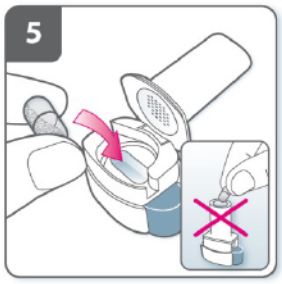
Prepare capsule:

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.



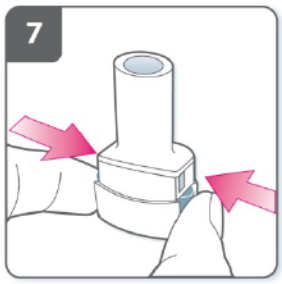
Insert capsule:

Place the capsule into the capsule chamber.

Never place a capsule directly into the mouthpiece.

Close the inhaler:

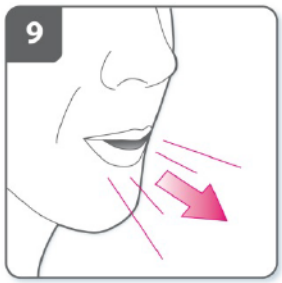
You should hear a “click” as the mouthpiece closes onto the inhaler base.



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.

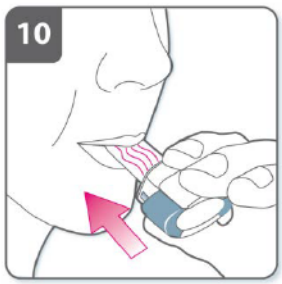
Release the side buttons fully.



Breathe out:

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

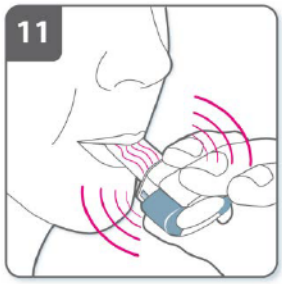
Do not blow into the mouthpiece.



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

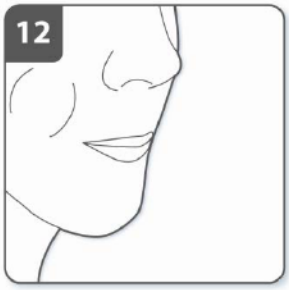
Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these

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.

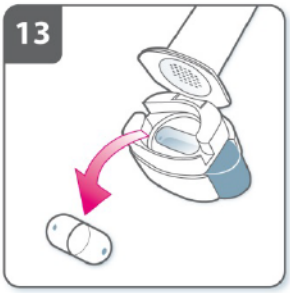
If there is powder left in the capsule:

- 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.
- The inhaler should be used for a maximum of 30 days, then replaced with a new inhaler
- Always use the new inhaler that comes with your new medication pack.
- 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

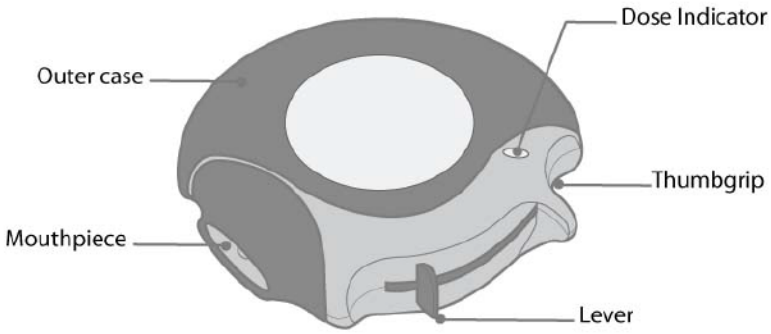
- Clean your inhaler once a week.
- Wipe the mouthpiece inside and outside to remove any powder with a clean, dry lint-free cloth.
- Do not wash your inhaler with water. Keep it dry.
- Do not take the inhaler apart.

16 Appendix 4: Instruction for Use of Accuhaler®/Diskus®

Instructions for use

Follow the instructions below for using your Accuhaler® inhalation device. **You will breathe in (inhale) the medicine from the Accuhaler®.** Do not use the Accuhaler® 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 Accuhaler®



Take the Accuhaler® out of the medication pack given to you. The Accuhaler® will be in the closed position. The **dose indicator** on the top of the Accuhaler® tells you how many doses are left. The dose indicator number will decrease each time you use the Accuhaler®. After you have used 55 doses from the Accuhaler®, 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 Accuhaler®

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

1. OPEN

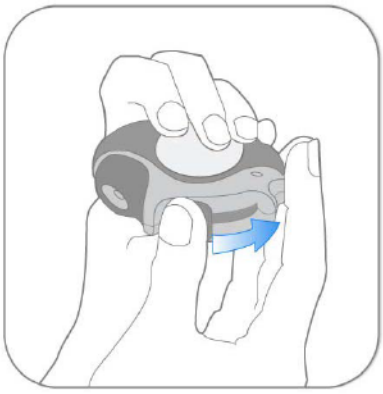
Hold the Accuhaler® in one hand and put the thumb of your other hand on the **thumbgrip.** Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position (see Figure 3).

Figure 3 Opening the Mouthpiece Cover

2. CLICK

Hold the Accuhaler® 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 Accuhaler® is now ready to use.

Figure 4 Sliding the Lever Until It Clicks



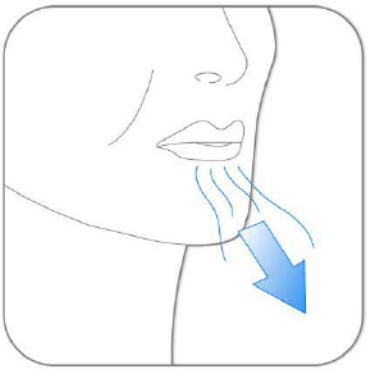
Every time the **lever** is pushed back, a dose is ready to be inhaled. This is shown by a decrease in numbers on the dose counter. **To avoid releasing or wasting doses once the Accuhaler® is ready:**

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

3. INHALE

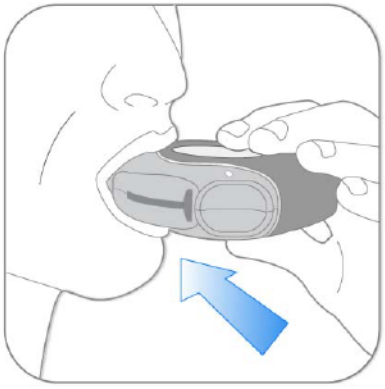
Before inhaling your dose from the Accuhaler®, breathe out (exhale) fully while holding the Accuhaler® level and away from your mouth (see Figure 5). **Remember, never breathe out into the Accuhaler® mouthpiece.**

Figure 5 Exhaling



Put the mouthpiece to your lips (see Figure 6). Breathe in quickly and deeply through the Accuhaler®. Do not breathe in through your nose.

Figure 6 Inhaling



Remove the Accuhaler® from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly. The Accuhaler® 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 Accuhaler® if you do not feel or taste the medicine.

4. CLOSE

Close the Accuhaler® when you are finished taking a dose so that the Accuhaler® 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 Accuhaler® will click shut. The lever will automatically return to its original position. The Accuhaler® is now ready for you to take your next scheduled dose, due in about 12 hours. (Repeat steps 1 to 4 at that time).

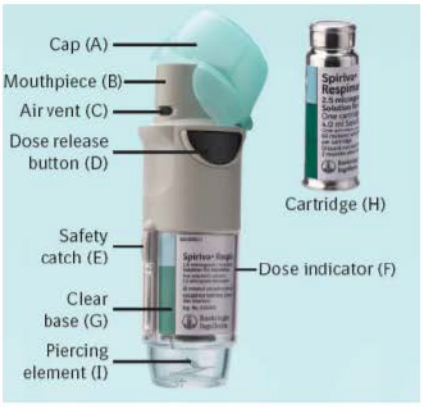
Figure 7 Closing the Mouthpiece Cover

Remember:

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

17 Appendix 5: Instructions for Use of the Respimat®

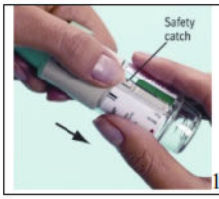
Patient's instructions for use and handling



Spiriva Respimat inhaler and Spiriva Respimat cartridge

1) Inserting the cartridge

The following steps 1-6 are necessary before first use:

 1	**1** With the green cap (A) closed, press the safety catch (E) while pulling off the clear base (G).
 2a  2b	**2** Take the cartridge (H) out of the box. Push the **narrow** end of the cartridge into the inhaler until it **clicks** into place. The cartridge should be pushed **firmly** against a firm surface to ensure that it has gone all the way in (2b). The cartridge will not be flush with the inhaler, you will still see the silver ring of the lower end of the cartridge. Do not remove the cartridge once it has been inserted into the inhaler.
 3	**3** Replace the clear base (G). Do not remove the clear base again.

2) To prepare the Spiriva Respimat inhaler for first-time use

 4	**4** Hold the Spiriva Respimat inhaler upright, with the green cap (A) closed. Turn the base (G) in the direction of the red arrows on the label until it **clicks** (half a turn).
 5	**5** Open the green cap (A) until it snaps fully open.
 6	**6** Point the Spiriva Respimat inhaler towards the ground. Press the dose release button (D). Close the green cap (A). **Repeat steps 4, 5 and 6 until a cloud is visible.** **Then repeat steps 4, 5 and 6 three more times to ensure the inhaler is prepared for use.** **Your Spiriva Respimat inhaler is now ready to use.** These steps will not affect the number of doses available. After preparation your Spiriva Respimat inhaler will be able to deliver your 60 puffs (30 medicinal doses).

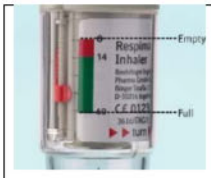
Daily use of your Spiriva Respimat inhaler

You will need to use this inhaler ONLY ONCE A DAY. Each time you use it take TWO PUFFS.

 I	**I** Hold the Spiriva Respimat inhaler upright, with the green cap (A) closed, to avoid accidental release of dose. Turn the base (G) in the direction of the red arrows on the label until it clicks (half a turn).
 II	**II** Open the green cap (A) until it snaps fully open. Breathe out slowly and fully, and then close your lips around the end of the mouthpiece without covering the air vents (C). Point your Spiriva Respimat inhaler to the back of your throat. While taking in a slow, deep breath through your mouth, press the dose release button (D) and continue to breathe in slowly for as long as you can. Hold your breath for 10 seconds or for as long as comfortable. **III Repeat steps I and II so that you get the full dose.** **You will need to use this inhaler only ONCE A DAY.** **Close the green cap until you use your Spiriva Respimat inhaler again.**

	If Spiriva Respimat inhaler has not been used for more than 7 days release one puff towards the ground. If Spiriva Respimat inhaler has not been used for more than 21 days repeat steps 4 to 6 until a cloud is visible. Then repeat steps 4 to 6 three more times.

When to get a new Spiriva Respimat inhaler

	The Spiriva Respimat inhaler contains 60 puffs (30 medicinal doses). The dose indicator shows approximately how much medication is left. When the pointer enters the red area of the scale, there is, approximately, medication for 7 days left (14 puffs). This is when you need to get a new Spiriva Respimat inhaler prescription. Once the dose indicator has reached the end of the red scale (i.e. all 30 doses have been used), the Spiriva Respimat inhaler is empty and locks automatically. At this point, the base cannot be turned any further. At the latest, three months after use the Spiriva Respimat inhaler should be discarded even if not all medication has been used.

How to care for your inhaler

Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week.
Any minor discoloration in the mouthpiece does not affect your Spiriva Respimat inhaler performance.

If necessary, wipe the outside of your Spiriva Respimat inhaler with a damp cloth.

19 Appendix 7: AQLQ-S

(The sample provided here is for illustrative purposes only)

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE _____

Page 1 of 5

Please complete all questions by circling the number that best describes how you have been during the last 2 weeks as a result of your asthma.

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK-RELATED ACTIVITIES (tasks you have to do at work*)	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.

5. SLEEPING	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE _____

Page 2 of 5

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE _____

Page 3 of 5

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE _____

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IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have a feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Severely Limited Most Not Done	Very Limited	Moderately Limited Several Not Done	Slightly Limited	Very Slightly Limited Very Few Not Done	Hardly Limited At All	Not Limited Have Done All Activities
31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE _____

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HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

20 Appendix 8: ACQ-7

(The sample provided here is for illustrative purposes only)

ASTHMA CONTROL QUESTIONNAIRE© PATIENT ID:_____

DATE:_____

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Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1.	On average, during the past week, how often were you woken by your asthma during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the past week, how limited were you in your activities because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4.	In general, during the past week, how much shortness of breath did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal

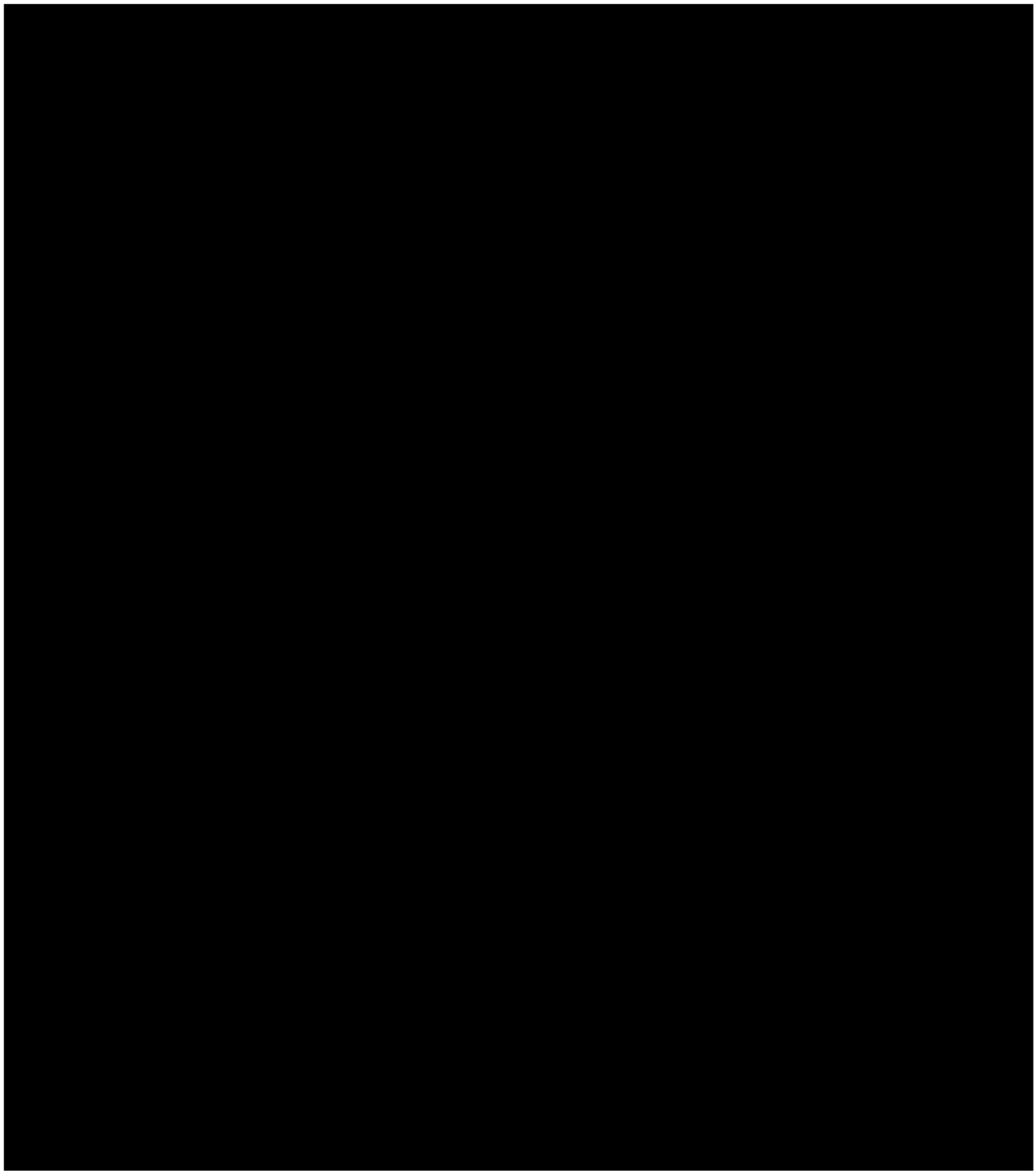
ASTHMA CONTROL QUESTIONNAIRE© PATIENT ID:_____

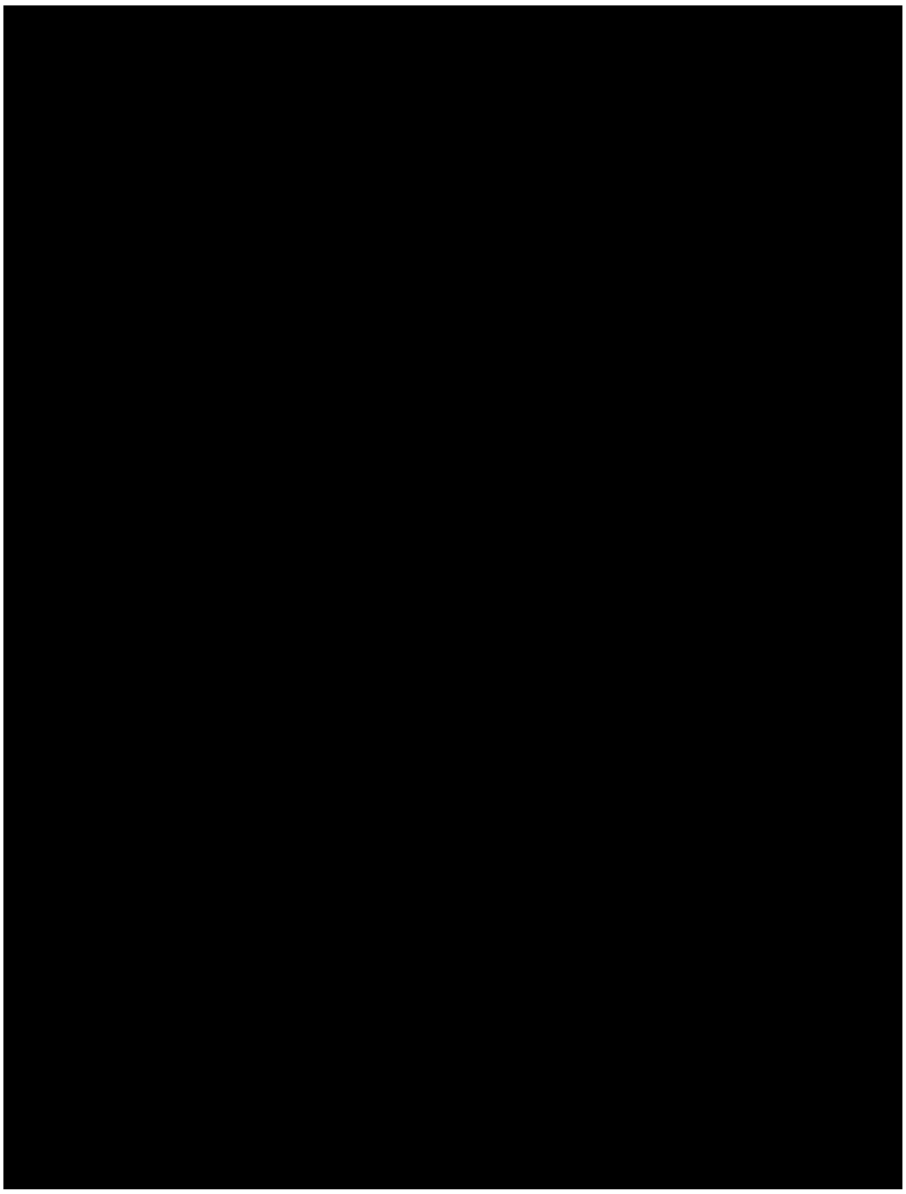
DATE:_____

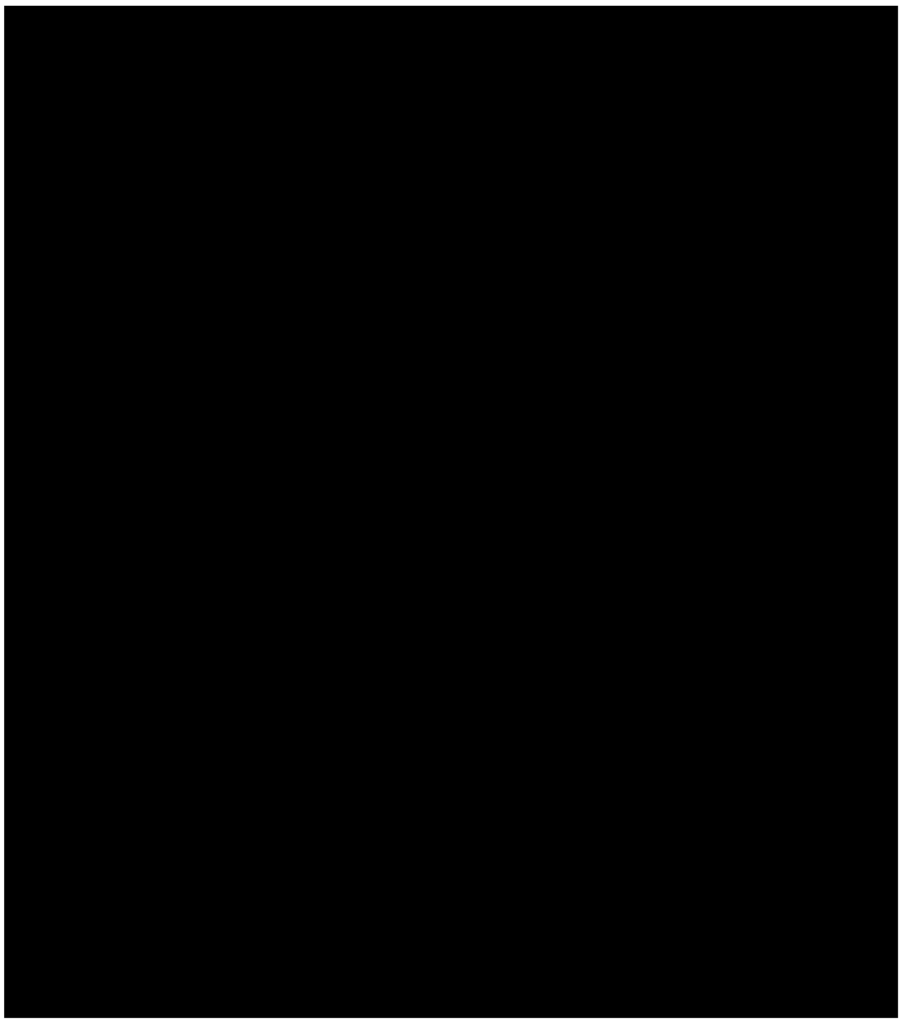
5.	In general, during the past week, how much of the time did you wheeze?	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time
6.	On average, during the past week, how many puffs/inhalations of short-acting bronchodilator (e.g. Ventolin/Bricanyl) have you used each day? *(If you are not sure how to answer this question, please ask for help)*	0 None 1 1 - 2 puffs/inhalations most days 2 3 - 4 puffs/inhalations most days 3 5 - 8 puffs/inhalations most days 4 9 - 12 puffs/inhalations most days 5 13 - 16 puffs/inhalations most days 6 More than 16 puffs/inhalations most days

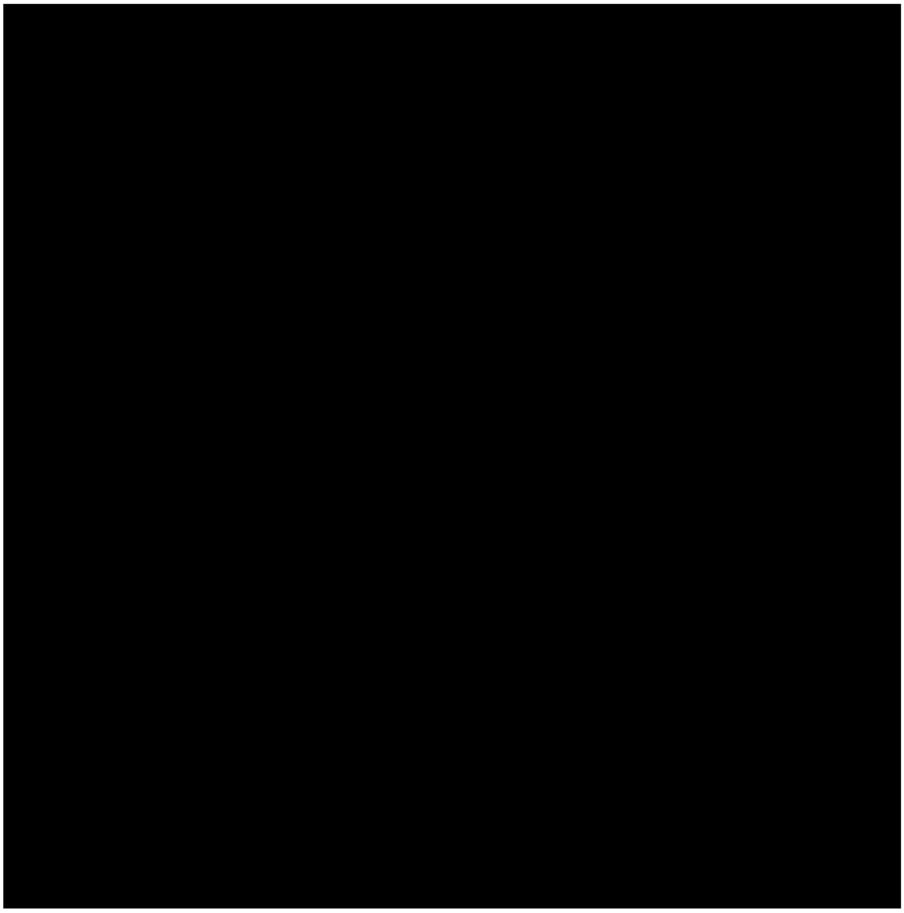
To be completed by a member of the clinic staff

7.	FEV_1 pre-bronchodilator: …… FEV_1 predicted:… …… FEV_1 % predicted:…… …… (Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)	0 > 95% predicted 1 95 - 90 % 2 89 - 80 % 3 79 - 70 % 4 69 - 60 % 5 59 - 50 % 6 < 50% predicted









22 Appendix 10: Low, medium and high Daily Doses of Inhaled Glucocorticosteroids for Adults[1]

Drug	Total Daily Dose (µg/day)		
	Low	Medium	High
Beclomethasone dipropionate – CFC[2]	200-500	> 500 – 1000	> 1000
Beclomethasone dipropionate – HFA	100-200	> 200 – 400	> 400
Budesonide- DPI	200-400	> 400 – 800	> 800
Ciclesonide – HFA	80-160	> 160 – 320	> 320
Fluticasone Furoate – DPI[3]	NA	100	200
Fluticasone propionate – DPI	100-250	> 250 – 500	> 500
Fluticasone propionate – HFA	100-250	> 250 – 500	> 500
Mometasone furoate	110-220	>220-440	≥ 440
Triamcinolone acetonide	400-1000	> 1000 – 2000	> 2000

[1,3] Categories based on GINA 2017 with exception of Fluticasone Furoate which is based on the Summary of Product Characteristics of Relvar® Ellipta®

[2]Beclomethasone dipropionate CFC is included for comparison with older literature.

CFC: chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant.