NOVARTIS

Global Clinical Development - General Medicine

QVM149B (Indacaterol acetate/Glycopyrronium bromide/Mometasone furoate)

Clinical Trial Protocol CQVM149B1304 / NCT03100825

A multicenter, open-label, single arm, 52-week treatment study to assess the safety of QVM149 in Japanese patients with asthma

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List of abbreviations

ACQ	Asthma Control Questionnaire
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS/ERS	American Thoracic Society/European Respiratory Society
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CCV	Cardiovascular and cerebrovascular
CFR	US Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CPO	Country Pharma Organization
CRO	Contract Research Organization
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ePEF	electronic Peak Flow Meter
FDC	Fixed Dose Combination
FEV_1	Forced Expiratory Volume in 1 second
FPM	Fine Particle Mass
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intra Uterine System
JGL	Asthma Prevention and Management Guideline
LABA	Long-Acting β2 Agonist
LAMA	Long-Acting Muscarinic Antagonist
LFT	Liver Function Test
MDDPI	Multi Dose Dry Powder Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mometasone Furoate
OC/RDC	Oracle Clinical/Remote Data Capture
OCS	Oral Corticosteroids
o.d.	once a day

PC	Personal Computer
PEF	Peak Expiratory Flow
pMDI	pressurized Metered Dose Inhaler
RBC	Red Blood Cell
SABA	Short-Acting β2 Agonist
SAE	Serious Adverse Event
SAMA	Short-Acting Muscarinic Antagonist
SCS	Systemic Corticosteroids
SDDPI	Single Dose Dry Powder Inhaler
SUSAR	Suspected Unexpected Serious Adverse Reactions
ULN	Upper Limit of Normal range
WBC	White Blood Cell
WHO	World Health Organization

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
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
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)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
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.”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication.
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Premature study withdrawal (PSW)	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
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/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject number	A number assigned to each patient who enrolls into the study
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	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 01

Amendment rationale

Modification of inclusion criteria for duration of baseline ICS/LABA requirements from 6 months to 3 months. This is based on investigator feedback from real world asthma populations and intended to address evolving treatment patterns, whereby patient medications are more rapidly up-titrated in response to symptoms. This will help identify previously ineligible patients who may potentially benefit from treatment with LAMA as add-on therapy to existing ICS/LABA treatment.

Changes to the protocol

The described changes pertaining to the aforementioned amendment rationale are implemented throughout the protocol.

In addition, the following clarifications/additions are included in this protocol amendment:

- Change the required pre-treatment period of ICS/LABA to 3 months prior to Visit 1 in inclusion criteria 4 (Section 4.1)
- Add the guidance of washout period in inclusion criteria 6 (Section 4.1)
- Update the repeat spirometry test including reversibility in inclusion criterion 6, inclusion criterion 7, and exclusion criterion 21 (Section 4.1 and Section 4.2)
- Change the condition of spacer use for reversibility testing in inclusion 7 and excluding spacer use for rescue medication in exclusion criterion 30 (Section 4.1 and Section 4.2)
- Add a clarification of Myocardial Infarction in exclusion criteria 16 and 19 (Section 4.2)
- Correct the condition under antihistamines (except mizolastin) is permitted (Section 5.5.8)
- Enhance importance of alert to have appropriate actions taken (Section 6.4.4).
- Correct urinalysis item(Section 6.5.4.3)
- Clarify SAE reporting (Section 7.2.2)
- Remove ATC code for summarizing concomitant medication(Section 9.3)
- Update the definition of repeatability in the spirometry guidance (Appendix 3)

An opportunity was also taken to make smaller changes such as some minor editorial changes that include correction of typographical errors and some clarifications and rewording to ensure consistency between protocol sections.

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

IRBs/IECs

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

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

The changes herein do NOT affect the trial specific model ICF.

Protocol summary

Protocol number	CQVM149B1304
Full Title	A multicenter, open-label, single arm, 52-week treatment study to assess the safety of QVM149 in Japanese patients with asthma
Brief title	A long-term safety study of QVM149 in Japanese patients with asthma
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to provide long term safety data of QVM149 in Japanese patients with asthma for the registration of QVM149 in Japan.
Primary Objective(s)	To assess the safety/tolerability of 52 weeks of treatment with QVM149 (high dose) in Japanese patients with inadequately controlled asthma, by the incidence and severity of treatment emergent adverse events
Secondary Objectives	• To assess the safety of QVM149 over 52 weeks of treatment, in terms of ECG, Vital signs, laboratory parameters, and plasma cortisol • To assess the efficacy of QVM149 in terms of lung-function in Japanese patients with inadequately controlled asthma after 26 and 52 weeks of treatment • To assess the efficacy of QVM149 in terms of asthma control after 26 and 52 weeks of treatment • To assess the efficacy of QVM149 in terms of rescue medication use during 52 weeks treatment
Study design	52 weeks multi-center, open-label, single arm study
Population	The study population will consist of approximately 100 Japanese males and females aged ≥ 18 years with asthma.
Key Inclusion criteria	• Written informed consent must be obtained before any assessment is performed. • Male and female adult patient ≥ 18 years old. • Patients with a diagnosis of persistent asthma (GINA 2016) for a period of at least 1 year prior to Visit 1. • Patients who have used medium or high dose of ICS/LABA combinations for asthma for at least 3 months and at stable dose and regimen for at least 4 weeks prior to Visit 1. • An ACQ-7 score ≥ 1.5 at Visits 2. • Pre-bronchodilator FEV_1 of ≥ 40% and ≤ 85% of the predicted normal value for the patient after withholding bronchodilators at Visit 2. • Repeating is allowed once only. Repeating of percentage predicted FEV_1 should be done in an ad-hoc visit to be scheduled on a date that would provide sufficient time to receive confirmation from the spirometry data central reviewer of the validity of the assessment before Visit 99. • Patients must demonstrate reversibility defined as an increase in FEV_1 of ≥ 12% and 200 mL within 15 to 30 minutes after administration of 400 µg of salbutamol at Visit 2. Spacer devices are permitted during reversibility testing only. The Investigator or delegate may decide whether or not to use a spacer for the reversibility testing.

	• If reversibility is not proven at Visit 2, patients may be permitted to enter the study with historical evidence of reversibility that was performed within 5 years prior to Visit 1. • Alternatively, patients may be permitted to enter the study with a historical positive bronchoprovocation test (defined as a provoked fall in FEV_1 of 20% by bronchoconstriction agent e.g., methacholine, histamine) or equivalent test (e.g., astography) that was performed within 5 years prior to Visit 1. • If reversibility is not proven at Visit 2 and historical data is not available, reversibility should be repeated once in an ad-hoc visit scheduled as close as possible from the first attempt (but not on the same day).
Key Exclusion criteria	• Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6-weeks of Visit 1. • Patients who have ever required intubation for a severe asthma attack/exacerbation. • 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. • 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. • Patients who have had a respiratory tract infection or asthma worsening as determined by investigator within 4 weeks prior to Visit 1 or between Visit 1 and Visit 99. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening. • Patients with a history of chronic lung diseases other than asthma, including (but not limited to) COPD, sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis and active tuberculosis. • Patients with severe narcolepsy and/or insomnia • Pregnant or nursing (lactating) women • Women of child-bearing potential unless they are using highly effective methods of contraception during dosing and for 30 days after stopping of investigational medication
Study treatment	High dose QVM149 150/50/160 µg (indacaterol acetate/glycopyrronium bromide/MF) once daily delivered as powder in capsules via Concept1
Efficacy assessments	• Spirometry • Peak Expiratory Flow • ACQ-7 • Rescue Medication Use
Key safety assessments	• Adverse events and serious adverse events • ECG • Vital signs • Laboratory findings

	• Evening plasma cortisol
Other assessments	Not applicable
Data analysis	The primary variable is the number and percentage of patients who reported treatment emergent adverse events during the 52 weeks study period. Adverse events will be summarized with descriptive statistics for the Safety Set.
Key words	QVM149, asthma, Japanese

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 within the lung 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 2016).

Despite existing therapies there is 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 are lost annually due to asthma, representing 1% of the total global burden. Annual worldwide deaths have been estimated at 250 000 (Masoli et al 2004). In Japan, asthma death has been significantly decreased with the recent advance in asthma treatments and the widespread use of Asthma Prevention and Management Guideline (JGL). But then again, a nationwide survey conducted in Japanese adult asthma patients revealed that the proportion of patients with asthma control status of well-controlled, insufficiently-controlled and poorly-controlled were 9.1%, 73.6% and 17.3% respectively (Adachi et al 2015), indicating that there is still unmet needs for the new and better treatment option to improve asthma control.

GINA and JGL recommend similar diagnostic methods, treatment goals and treatment strategies and share the same treatment goal of long-term clinical asthma symptom control. The current mainstay of asthma treatment is LABA/ICS-based, and the LAMA is expected to be an add-on option for patients whose asthma symptoms are poorly controlled. A clinical study of a LAMA (tiotropium) added to ICS or LABA/ICS in poorly controlled moderate to severe persistent asthma patients showed significant respiratory function improvements (forced expiratory volume in 1 second (FEV_1) and peak expiratory flow (PEF)) without a particular safety issue (Befekdadu et al 2014). Tiotropium was approved for asthma indication in Japan in 2014.

Following tiotropium regulatory approval in asthma, GINA 2016 guideline recommends tiotropium as a new add-on option on top of the preferred controller choice for steps 4 and 5 in patients aged with a history of exacerbations. The preferred controller choice in asthma step 4 is med/high ICS/LABA and in step 5 add-on treatment e.g. anti-IgE.

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) in development for once-daily maintenance treatment of asthma GINA step ≥ 4. All three mono-components, indacaterol maleate, glycopyrronium bromide and MF have previously been developed as individual drugs for either COPD or asthma. 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 2016 Step ≥ 4).

In parallel, Novartis is developing QMF149, which is a fixed dose combination of mometasone furoate (MF) and indacaterol, in the Concept1 device.

Data from QVM149 monocomponents:

QVM149 is being developed in parallel with QMF149 (indacaterol acetate/MF) and existing efficacy and safety data for the three mono-components of the QVM149 FDC as well as for the two combinations indacaterol/mometasone (QMF149) and glycoppyronium/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 2016). 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 26-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). Indacaterol acetate dilates the bronchi quickly and continuously over 24 hours when administered once daily at 150 µg in moderate to severe asthma patients (CQMF149E2203).

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 as Ultibro®, Breezhaler® in the EU and Japan (QVA149 110/50 µg with proven equivalent fine particle mass (FPM) of indacaterol maleate as obtained in indacaterol maleate 150 µg) with the same doses as proposed for QVM149 (150/50/80 µg). 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 world-wide for the treatment of asthma in adults and adolescents ≥ 12 years of age.

MF doses in QVM149

The MF doses in QMF149 program with Concept1 device are comparable to MF 200 µg, 400 µg and MF 800 µg (400 µg twice a day) in Twisthaler® device as demonstrated in study (CQMF149E2101, Vaidya et al 2012) and after in-vitro fine particle mass adjustment.

In a 4-week study in patients with persistent asthma (Study CQMF149E2201), MF doses of 80 µg and 320 µg delivered once daily via Concept1 showed comparable efficacy and systemic exposure to MF doses of 200 µg and 800 µg (2 x 400 µg) delivered once daily via Twisthaler® confirming the selected doses for MF Concept1 are appropriate for further QMF149 Concept1 development.

The nominal doses of MF are 80 µg and 160 µg in the QVM149 FDC to ensure that the FPM (in-vitro aerosol performance) in the lactose blend formulation for the triple FDC is similar to the nominal MF doses of 160 µg and 320 µg for QMF149 Concept1 program, respectively. In this current study the medium and high doses of MF taken forward in QVM149 are 80 µg and 160 µg which are comparable to the MF doses of 160 µg and 320 µg in the QMF149 products in QMF149B2301.

No adjustments to the doses of indacaterol acetate or glycopyrronium bromide in the FDC combinations were required.

Table 1-1 Comparison of nominal MF doses in Asmanex Twisthaler, QMF149 and QVM149 drug products delivered by Concept1 (Breezhaler)

MF dose level	MF in Asmanex delivered by Twisthaler	MF in QMF149 delivered by Concept1	MF in QVM149 delivered by Concept1
Mid	400 µg	160 µg	80 µg
High	800 µg	320 µg	160 µg

The role of long-acting anticholinergics on top of medium and high dose ICS and LABA (FDC) as controller medication (QVM149) is supported based on the asthma clinical trial data with tiotropium on top of ICS and LABA/ICS in patients with severe persistent asthma (Kerstjens et al 2012).

Given that literature suggests that many asthma patients have poorly controlled disease despite currently available controller medications and there is increasing evidence of lung function benefit and improved control with triple combination therapy, further investigation of QVM149 triple therapy is supported.

On-going CQVM149B2302 is the pivotal study for regulatory submission, in which the superiority of QVM149 to QMF149 is evaluated and Japanese subjects are involved. Efficacy and safety data of 1 year treatment in Japanese patients will be obtained from this study.

The regulatory requirement for the long term safety data is to collect data for at least 100 Japanese patients exposed to the study drug for one year. To comply with the requirement,

this study (CQVM149B1304) is intended to support the assessment of the long term safety and efficacy of QVM149 in Japanese population.

Additional information to QVM149 can be found in the QVM149 Investigator's brochure.

1.2 Purpose

The purpose of this study is to provide long term safety data of QVM149 in Japanese patients with asthma for the registration of QVM149 in Japan.

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	Endpoint(s) for primary objective(s)
• To assess the safety/tolerability of 52 weeks of treatment with QVM149 (150/50/160 µg, once daily) in Japanese patients with inadequately controlled asthma	• The incidence and severity of treatment emergent adverse events (AEs) over 52 weeks of treatment
Secondary Objective(s)	Endpoint(s) for secondary objective(s)
• To assess the safety of QVM149 over 52 weeks of treatment	• ECG, vital sign (blood pressure, pulse rate), laboratory parameters (hematology, clinical chemistry and urinalysis), plasma cortisol over 52 weeks of treatment
• To assess the efficacy of QVM149 in terms of lung-function in Japanese patients with inadequately controlled asthma	• Change from baseline of pre-dose FEV_1 measured after 26 and 52 weeks treatment • Change from baseline of morning and evening PEF during 52 weeks
• To assess the efficacy of QVM149 in terms of asthma control	• Change from baseline of ACQ-7 after 26 and 52 weeks treatment • Responder rate of patients achieving the minimal important difference (MID) of ACQ-7 ≥ 0.5 after 26 and 52 weeks treatment
• To assess the efficacy of QVM149 in terms of rescue medication use	• Change from baseline rescue medication use during 52 weeks treatment

[redacted]

3 Investigational plan

3.1 Study design

This study uses a 52-week treatment, multicenter, open-label, single-arm design in Japanese patients with asthma (Figure 3-1). One interim analysis is planned after the last patient completed the assessments at Week 26 (Visit 107).

Screening epoch

All patients must have used medium or high dose ICS/LABA for at least 3 months and been on stable dose and regimen for at least 4 weeks prior to Visit 1. A screening epoch of maximum of 4 weeks (from Visit 1 to 99) will be used to assess eligibility and to taper patients off prohibited medications (Section 5.5.8). At Visit 1, all patients will be given salbutamol to use as rescue medication throughout the screening and treatment epochs and will be given an electronic diary to record asthma symptoms and rescue medication use. In addition, patients will be given an electronic Peak Flow meter to record PEF. The last 2 weeks of screening epoch (from Visit 2 to 99) will be used to assess eligibility of the patients to enter the treatment epoch and to collect baseline values for some variables.

Screening epoch must have a minimum of 2 weeks prior to start taking study medication at Visit 101 (Day 1).

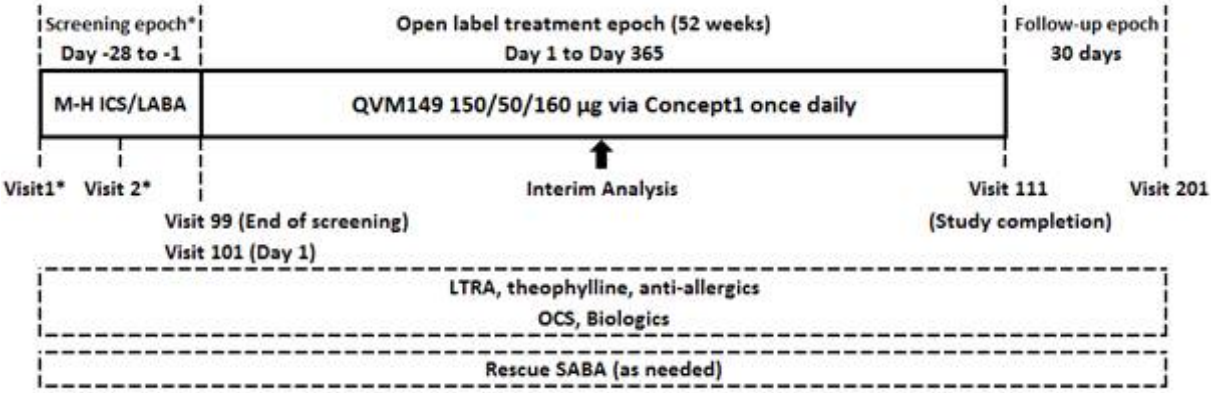
Treatment epoch

Visits 99 and 101 take place sequentially on the same date. The assessments at Visit 99 should be performed prior to administration of the first dose of investigational drug; eligible patients will be assigned to QVM149 150/50/160 µg o.d. (high ICS dose), and enter 52-week treatment epoch. Patients will be required to inhale QVM149 150/50/160 µg via Concept1 once daily in the evening throughout treatment epoch. The first dose of investigational drug will be administered at the clinic in the evening (between 4:00 and 8:00 pm) at Visit 101. Subsequent clinic visits will be scheduled so that patients will be reassessed as close as possible to the same time relative to the evening doses. Patients will be instructed not to take their evening dose of investigational drug on the days of the clinic visits, as these doses will be administered at the clinic under the supervision of study personnel. Clinic visits to assess safety and efficacy are scheduled at weeks 4, 12, 26, 36 and 52.

Follow-up epoch

A safety follow-up (telephone contact, Visit 201) will be conducted at 30 days after the last treatment date (Visit 111 or early discontinuation). Investigator will prescribe appropriate asthma controller medication to the patients and investigational drug will not be given after the last treatment date.

Figure 3-1 Study design



*Duration of screening epoch may vary from 2 to 4 weeks. Screening epoch must have a minimum of 2 weeks prior to start taking study medication at Day 1. Visit 1 and Visit 2 may occur on the same day depends on concomitant medication and appropriate washout prior to spirometry testing. Please refer to Table 5-1, Table 5-2, and Table 5-3 for details.

3.2 Rationale for study design

The patient population will be described in more detail in the Section 4 below.

As stated in Section 1.2, this study is planned to fulfil the Japanese regulatory requirement for a registration of QVM149 (indacaterol acetate/glycopyrronium bromide/mometasone furoate) in Japan. [redacted]

An open-label design without comparator arm is considered adequate to evaluate Japanese long term safety for asthma and accepted by Japanese Health Authority previously (Ohta et al 2010, Tohda et al 2013).

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

On-going Phase III study CQVM149B2302 is evaluating two doses of QVM149 150/50/80 µg (medium ICS dose) o.d. inhalation and 150/50/160 µg once daily inhalation in asthma. The difference between the two doses of QVM149 is the dose of mometasone component (ICS). For the purpose of collecting additional long term safety data in Japanese patients, high dose of QVM149 150/50/160 µg o.d. is chosen on the basis that exposure of asthma patients to high (ICS) dose can generate supportive safety information for the lower/medium (ICS) dose in the fixed triple combination.

Treatment duration of 52 weeks is chosen to comply with Japanese regulatory requirement (Section 3.2).

3.4 Rationale for choice of comparator

Not applicable.

3.5 Purpose and timing of interim analyses/design adaptations

[redacted]

Details of statistical considerations are described in Section 9.6.

3.6 Risks and benefits

QVM149 is an orally inhaled fixed-dose combination of indacaterol acetate (a LABA), glycopyrronium bromide (a LAMA), and mometasone furoate (an ICS). All three mono-components of QVM149, indacaterol maleate, glycopyrronium bromide and mometasone furoate have previously been developed and approved as individual drugs for COPD or asthma, respectively. QVM149 as a lactose-blended inhalation powder is delivered via Concept1 (Breezhaler®), a single dose dry powder inhaler (SDDPI). The favorable benefit-risk ratio of a fixed-dose combination of indacaterol acetate and mometasone furoate (QMF149, in the Phase III development worldwide) in asthma and glycopyrronium bromide in COPD as well as the so far acquired knowledge about LAMA (tiotropium) on top of LABA/ICS in asthma (Kerstjens et al 2012) is a rationale to conduct this study.

Dual bronchodilation with ICS controller would be expected to achieve good symptom control, minimize airflow obstruction, minimize risk of exacerbations, and hospitalizations in asthma patients inadequately controlled on medium- or high-dose LABA/ICS. 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 efficacy by improved adherence and convenience. Based on available data of components, it is expected that QVM149 will have a favorable benefit to risk profile in patients with asthma.

In line with current medical treatment guidelines, all patients participating in the study will receive active “controller” treatment for their asthma throughout the screening epoch and 52-week treatment epoch. In addition, the patients will be provided with rescue medication for use as needed throughout study. At no time, will any patient be without treatment for asthma.

QVM149 is under development and therefore it is possible that unexpected safety issues may be identified. The risk will be minimized by compliance with the eligibility criteria and close clinical monitoring of patients. In addition, safety monitoring (e.g. symptom collection and rescue medication use via electronic diary) and daily PEF 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. The risks of side effects from the study medication are those known for the individual compounds indacaterol acetate,

glycopyrronium bromide and mometasone furoate. Up to now 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 (IB).

There are concerns that LABA treatment used alone in asthma might cause severe asthma exacerbations. To address this safety concern all patients are treated with a FDC of LABA/LAMA/ICS in this study so LABA alone will not be allowed.

Potential risk of inappropriate use of inhaler devices will be mitigated by detailed instructions and trainings provided by the Investigators to patients.

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

In summary, based on available data of components, it is anticipated that QVM149 150/50/160 µg once daily will have an acceptable benefit to risk profile in patients with asthma.

4 Population

The study population will consist of approximately 100 Japanese males and females aged ≥ 18 years with asthma, who are currently treated with or qualify for treatment with LABA/LAMA/ICS triple therapy. Since a 25% screening failure rate and a 10% dropout rate are expected, approximately 134 patients will be screened in order to collect a total of approximately 90 completed patients. Dropouts will not be replaced. This study is a single national trial to be conducted in Japan.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female adult patient ≥ 18 years old.
3. Patients with a diagnosis of persistent asthma (GINA2016) for a period of at least 1 year prior to Visit 1.
4. Patients who have used medium or high dose of ICS/LABA combinations for asthma for at least 3 months and at stable dose and regimen for at least 4 weeks prior to Visit 1.
5. An ACQ-7 score ≥ 1.5 at Visit 2.
6. Pre-bronchodilator FEV_1 of ≥ 40% and ≤ 85% of the predicted normal value for the patient after withholding bronchodilators at Visit 2.
    - Withholding period of bronchodilators prior to spirometry:
        - SABA for ≥ 6 hrs,

- LABA (or FDC of ICS/LABA) for ≥ 24 hrs,
- Tiotropium for ≥ 7 days,
- SAMA for ≥ 8 hrs,
- Short acting xanthines for ≥ 12 hrs,
- Long acting xanthines for ≥ 24 hrs.

- Washout period of each drug should be kept as close as possible as above and should not be longer. If longer washout period is needed due to scheduling issues, please contact Novartis Medical monitor.
- Repeating is allowed once only. Repeating of percentage predicted FEV_1 should be done in an ad-hoc visit to be scheduled on a date that would provide sufficient time to receive confirmation from the spirometry data central reviewer of the validity of the assessment before Visit 99.

7. Patients must demonstrate reversibility defined as an increase in FEV_1 of ≥ 12% and 200 mL within 15 to 30 minutes after administration of 400 µg of salbutamol at Visit 2. Spacer devices are permitted during reversibility testing only. The Investigator or delegate may decide whether or not to use a spacer for the reversibility testing.
   - If reversibility is not proven at Visit 2, patients may be permitted to enter the study with historical evidence of reversibility that was performed **within 5 years** prior to Visit 1.
   - Alternatively, patients may be permitted to enter the study with a historical positive bronchoprovocation test (defined as a provoked fall in FEV_1 of 20% by bronchoconstriction agent e.g., methacholine, histamine) or equivalent test (e.g., astography) that was performed within 5 years prior to Visit 1.
   - Where patient is assessed as eligible based on historical evidence, a copy of the original printed report must be available as source documentation.
   - If reversibility is not proven at Visit 2 and historical data is not available, reversibility should be repeated once in an ad-hoc visit scheduled as close as possible from the first attempt (but not on the same day).
   - If reversibility is not demonstrated at Visit 2 (or after repeated assessment at ad-hoc visit) and historical evidence of reversibility/bronchoprovocation/astography is not available, patients must be screen failed.

4.2 Exclusion criteria

Patients/subjects 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/subjects.

1. Use of other investigational drugs within 30 days or 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
2. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof (including lactose).

3. 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.
4. Patients with evidence upon visual inspection (laboratory culture is not required) of clinically significant (in the opinion of investigator) oropharyngeal candidiasis at Visit 99 or earlier, with or without treatment. Patients may be re-screened once their candidiasis has been treated and has resolved.
5. Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia (BPH patients who are stable on treatment can be considered) or bladder-neck obstruction or severe renal impairment or urinary retention.
6. Patients who have smoked or inhaled tobacco products within the 6 month period prior to Visit 1, or who have a smoking history of greater than 10 pack years *(Note:1 pack is equivalent to 20 cigarettes. 10 pack years = 1 pack/day x 10 yrs., or ½ pack/day x 20 yrs)*. This includes nicotine inhalers such as e-cigarettes at time of Visit 1.
7. 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 99 they may be re-screened 6 weeks after recovery from the exacerbation.
8. Patients who have ever required intubation for a severe asthma attack/exacerbation.
9. Patients who have had a respiratory tract infection or asthma worsening as determined by investigator within 4 weeks prior to Visit 1 or between Visit 1 and Visit 99. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening.
10. 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.
11. Patients with a history of chronic lung diseases other than asthma, including (but not limited to) chronic obstructive pulmonary disease, sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis and active tuberculosis.
12. 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.
13. Patients with Type I diabetes or uncontrolled Type II diabetes.
14. Patients who, either in the judgment of the investigator or the responsible Novartis personnel, have a clinically significant condition such as (but not limited to) unstable ischemic heart disease, New York Heart Association (NYHA) Class III/IV left ventricular failure arrhythmia, uncontrolled hypertension, cerebrovascular disease, psychiatric disease, neurodegenerative diseases, or other neurological disease, uncontrolled hypo- and hyperthyroidism and other autoimmune diseases, hypokalemia, hyperadrenergic state, or ophthalmologic disorder or patients with a medical condition that might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study.

15. 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 2 with a resting ventricular rate < 100/min. At Visit 2 the atrial fibrillation must be confirmed by central reading.
16. Patients with a history of myocardial infarction (this should be confirmed clinically by the investigator) within the previous 12 months.
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 2 (Fridericia method) is prolonged (> 450 msec for males and > 460 msec for females) and confirmed by a central assessor (these patients should not be rescreened).
19. Patients who have a clinically significant ECG abnormality at Visit 2. ECG evidence of myocardial infarction at Visit 2 (via central reader) should be clinically assessed by the investigator with supportive documentation.
20. Patients who have a clinically significant laboratory abnormality at Visit 2.
21. Patients who have not achieved an acceptable spirometry result at Visit 2 in accordance with ATS/ERS criteria for acceptability and repeatability. A one-time repeat spirometry is allowed in an ad-hoc visit scheduled as close as possible from the first attempt (but not on the same day) if the spirometry did not qualify due to ATS/ERS criteria. If the patient fails the repeat assessment, the patients may be rescreened, provided the patient returns to the required treatment as per inclusion criteria 4.
22. Patients taking any asthma-related prohibited medications in the classes specified in Table 5-1 unless they undergo the required washout period.
23. Patients in need of any prohibited medications listed in Table 5-2.
24. Patients taking medications listed in Table 5-3 should be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met.
25. Patients on Maintenance Immunotherapy (desensitization) for allergies or less than 3 months prior to Visit 1 or patients on Maintenance Immunotherapy for more than 3 months prior to Visit 1 but expected to change throughout the course of the study.
26. Patients with severe narcolepsy and/or insomnia.
27. Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers).
28. History of alcohol or other substance abuse.
29. Patients who are directly associated with any members of the study team or their family members.
30. Patients unable to use the Concept1 dry powder inhaler or a metered dose inhaler. Spacer devices are not permitted for rescue medication.
31. Patients with a known history of non-compliance to medication or who were unable or unwilling to complete a patient diary or who are unable or unwilling to use Electronic Peak Flow with e-Diary device.

32. 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.
33. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 30 days after stopping of investigational medication. 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, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
    - Use of oral, (estrogen and progesterone), injected* or implanted* hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception*.

    * Not approved in Japan.

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

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The investigational drug is as follows:

- QVM149 (indacaterol acetate/glycopyrronium bromide/mometasone furoate) 150/50/160 µg o.d. delivered as powder in hard capsules via Concept1 (Appendix 5)

There is no control drug for this trial.

5.1.2 Additional treatment

Starting at Visit 1, patients will receive short-acting β2 agonist (salbutamol) inhaler to use as rescue medication on an "as needed" basis.

More details regarding rescue medication are in Section 5.5.6.

5.2 Treatment arms

All eligible patients will be assigned to the investigational drug (Section 5.1.1) at Visit 101.

5.3 Treatment assignment and randomization

This study is a single-arm, non-randomized trial. For the purpose of the investigational drug accountability and tracking, Interactive Response Technology (IRT) will be used.

At Visit 101, 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 unique number to the patient, which will be used to link the patient to a unique medication number for the first package of study drug to be dispensed to the patient.

5.4 Treatment blinding

Not applicable.

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. The site must select the CRF book with a matching Subject Number from the EDC system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening epoch Study Disposition eCRF.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to a specific visit. 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.

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 CPO 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/subjects 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

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

The investigator should promote compliance by instructing the patient to take the study treatment (Section 5.1) 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.

At Visit 1 all patients will be instructed how to use a pMDI to administer rescue salbutamol correctly. At Visit 99 all patients will be fully trained in the correct use of the Concept1 to administer QVM149. Patients who are unable to use Concept1 correctly at Visit 99 will not be eligible to enter the treatment epoch. For this training purpose, training kits (placebo capsules of QVM149 and Concept1 inhalers) will be supplied to the investigator site. At each clinic visit 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 if required.

Starting at Visit 101, all eligible patients will be instructed to take QVM149 150/50/160 µg via Concept1 once daily in the evening at approximately the same time of day. Patients will be instructed to rinse their mouth (e.g., 2 times with approximately 30 mL water) after

inhalation of QVM149. Water used for mouth rinsing should be spat out and should NOT be swallowed.

The study treatment can be taken without regard to sleep, meals, and other activities. On days of scheduled clinic visits, patients should take QVM149 at the clinic (approximately between 4:00 to 8:00 pm) under the supervision of investigator or his/her delegate.

The duration of treatment epoch is 52 weeks, with the last dose of study treatment occurring in the evening of Day 365 (Visit 111).

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

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

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

Dose adjustments and/or interruptions of QVM149 are not permitted unless the investigator considers an interruption is necessary for the treatment of an adverse event. Any interruption of QVM149 should be for the shortest time period possible and must be recorded on the Dosage Administration Record CRF.

5.5.6 Rescue medication

At Visit 1, all patients will be provided with a short-acting β2 agonist (100 µg salbutamol via pMDI) which they will be instructed to use throughout the screening and treatment epoch as rescue medication on an 'as needed' basis. Patients will be advised that between visits they can take their rescue medication for symptoms. The rescue salbutamol will be provided to the patients by the investigator site and reimbursed locally by Novartis or supplied to the investigator sites locally by Novartis. Nebulized salbutamol is not allowed as rescue medication and use of a spacer for rescue medication is not allowed at any time throughout the study.

In order to standardize measurements, patients will be instructed to abstain from taking rescue salbutamol within 6 hours of the start of each spirometry visit 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.

Bronchodilator medications that the patients used prior to Visit 1 must be recorded in the asthma-related prior/concurrent medication page of the CRF, with the stop date for these bronchodilators recorded as the date of Visit 1. The rescue salbutamol provided at Visit 1 for use during the study should NOT be recorded on the asthma-related prior/concurrent medication page of the eSource. From Visit 1, daily use of rescue medication (number of puffs taken in the previous 12 hours) will be recorded each morning and evening throughout the 52 week treatment epoch by the patient using their electronic diary.

5.5.7 Concomitant medication

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' and 'Surgical and Medical Procedures' CRF.

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 entering the treatment epoch or allowing a new medication to be started.

5.5.8 Prohibited medication

The class of medications listed in Table 5-1 and Table 5-2 are not permitted to be taken during the study. The medications in Table 5-3 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 Novartis before allowing a new medication to be started.

If indicated for the treatment of an asthma exacerbation, any treatment deemed necessary by 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. Patients may NOT self-medicate (other than administration of rescue medication) or adjust therapy without permission/guidance from treating physician.

Table 5-1 Prohibited Asthma-related medications[1]

Medication	Minimum cessation prior to Screening (Visit 1) and Baseline (Visit 99)
Long-acting anticholinergics (LAMA)	Must not be used from 7days prior to Visit 2 onwards.
Short-acting anticholinergics (SAMA)	Must not be used from 8 hours prior to spirometry at Visit 2 onwards.
Fixed dose combinations of β_2-agonists and inhaled corticosteroids	Must be discontinued 24 hours prior to Visit 99. Must be withheld 24 hours prior to spirometry at Visit 2.
Long-acting β_2-agonists (LABA)	Must be discontinued 24 hours prior to Visit 99. Must be withheld 24 hours prior to spirometry at Visit 2.
Inhaled corticosteroid	Must be discontinued one day prior to Visit 99 (after the evening dose).
Short acting β2-agonists (SABAs) (other than Salbutamol provided at Visit 1 for rescue medication)	Must be discontinued at Visit 1
Salbutamol/albuterol (SABA) provided at Visit 1	Must be withheld 6 hours prior to spirometry[2]
Parenteral corticosteroids (systemic corticosteroids are permitted for the treatment of asthma exacerbations)	Must be discontinued 4 weeks prior to Visit 1
Intra-muscular depot corticosteroids	Must be discontinued 3 months prior to Visit 1

1 These tables are not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria. These medications are also prohibited if administered for other indications.

2 Clinic visits may be rescheduled if rescue medication were taken less than 6 hours prior to the spirometry assessments.

Table 5-2 Prohibited Medications[1]

Medication	Minimum cessation prior to Visit 2
Other investigational drugs	30 days or 5 half-lives, whichever is longer (Biologics and/or monoclonal antibody need to have a 6 month wash out period)
Non-selective systemic beta-blocking agents	7 days
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug)	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	14 days or 5 half-lives, whichever is longer
Mizolastin	5 days
Tricyclic antidepressants (Please note that tetracyclics, which are similar in class with regards to drug interaction are also to be excluded)	14 days
All antipsychotic agents (first, second and third generation, inclusive of atypical antipsychotics). Combinations of antipsychotic agents with antidepressants are prohibited	14 days
Strong inhibitors of cytochrome P450 3A (e.g. ketoconazole) (may depend on compound)	7 days
Serotonin Noradrenaline Reuptake Inhibitors	14 days
Monoamine-oxidase inhibitors	14 days
Noradrenaline reuptake inhibitors	7 days
Systemic anticholinergics	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. The washout of these prohibited medications is not to be encouraged.

Table 5-3 Medications allowed under certain conditions[1]

Medication	Condition under which medication is permitted
Topical Corticosteroids for treatment of eczema	Recommended doses and dosage regimens
Maintenance Immunotherapy for allergies	Stable dose for at least 3 months prior to screening (Visit 1) and unchanged throughout the study.

Medication	Condition under which medication is permitted
Pure Selective Serotonin Reuptake Inhibitors (they must have no documented effect on any other neurotransmitters or other biological pathways. e.g. muscarinic pathway)	Stable regimen for at least 30 days prior to screening (Visit 1).
Intra-nasal corticosteroids	Stable dose for at least 4 weeks prior to screening (Visit 1) In the case of as needed, provided an established pattern of use has been documented.
Antihistamines (except mizolastin) (e.g. loratadine, cetirizine)	Stable dose/regimen for at least 4 weeks prior to the screening (Visit 1). In the case of as needed, provided an established pattern of use has been documented.
Mucolytic agents not containing bronchodilators	Stable dose/regimen for at least 4 weeks prior to the screening (Visit 1) and unchanged throughout the study.
Systemic mast cell stabilizers	Stable dose/regimen for at least 4 weeks prior to the screening (Visit 1) and unchanged throughout the study.
Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine	Not administered within 48 hours prior to a study visit
Rescue Short-acting β2 agonists	Not used within 6 hours prior to spirometry
Leukotriene Antagonist and leukotriene synthesis inhibitors	Stable dose/regimen for at least 4 weeks prior to the screening (Visit 1) and unchanged throughout the study.
Long-acting theophylline	Stable dose/regimen for at least 4 weeks prior to the screening (Visit 1) and unchanged throughout the study. Not administered within 24 hours prior to spirometry.
Short-acting theophylline	Stable dose/regimen for at least 4 weeks prior to the screening (Visit 1) and unchanged throughout the study. Not administered within 12 hours prior to spirometry.
Monoclonal antibodies for the treatment of asthma (e.g., omalizumab, mepolizumab)[2]	Stable dose for at least 3 months prior to screening (Visit 1)
Oral corticosteroids[3]	Stable dose for at least 30 days prior to screening (Visit 1) and throughout the study at prednisone equivalent dose of 5 mg daily to 10 mg every other day

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

2 Omalizumab or mepolizumab may be discontinued at the investigator's discretion. Once discontinued, resuming omalizumab or mepolizumab is not permitted during the study. Omalizumab dosing should be guided by Japanese labelling.

3 Oral corticosteroids may be continued at a low stable dose after a course of steroid taper for exacerbations at the discretion of the investigator (in doses not to exceed equivalent of prednisone 5 mg daily). If steroids are continued beyond 7 to 10 day taper, the stable low dose (≤ prednisone 5 mg daily) should be maintained for at least 3 months prior to stopping. Otherwise patient must be discontinued from study treatment.

5.5.9 Emergency breaking of assigned treatment code

Not applicable for this open-label study.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit (Visit 111, Week 52) planned in the protocol.

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

For all patients a safety follow-up visit (Visit 201) should be conducted (e.g. by telephone) 30 days after last visit (Visit 111, Week 52). The information to be collected at this follow up visit includes serious adverse events, asthma exacerbations, and survival status.

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. Patients may voluntarily discontinue study treatment for any reason at any time. In the case the patients would want to discontinue the treatment, it is particularly important to ask the reason and if they would be willing to remain in the trial to share their safety and vital status information (e.g., via telephone contact) until 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 would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Adverse events for which continued inhalation of the investigational drug would be detrimental
- Abnormal test procedure results indicating risk for the patient on continued inhalation of the investigational drug
- Pregnancy (see Section 6.5.7 and Section 7.6)
- If a patient develops a medical condition that requires use of prohibited treatment as per Section 5.5.8 or if patient exhibits a behavior of non-compliance regarding prohibited medications
- Patients who experience 5 or more asthma exacerbations during the treatment epoch that required treatment with systemic corticosteroids
- Patients with > 50% decrease in FEV_1 from baseline (Visit 101) during treatment epoch
- Any situation in which study participation 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. The patient should return to the clinic as soon as possible, after discontinuation of investigational drug, for a study treatment discontinuation visit. If the

patient fails to return for the study treatment discontinuation visit for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact him/her as specified in Section 5.6.4. Treatment discontinuation visit assessments detailed in the "unscheduled treatment discontinuation visit" (UNS) in Table 5-4 and 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 on the Dosage Administration eCRF.

The investigator and study staff must discuss with the patient the continued participation in the study by maintaining regular telephone contact with him/her or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule. After study treatment discontinuation, the following data should to be collected via telephone visits:

- Asthma exacerbation
- Serious Adverse Events

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

Table 5-4 Table of assessment for the patients who discontinue investigational drug prematurely

Assessment	Early study treatment discontinuation visit	Unscheduled safety follow-up visit	At time of scheduled clinic visit[1]	Early Study discontinuation (Premature study withdrawal)[2]	Follow-up Visit 201
Visit type	**Clinic visit**	**Telephone**	**Telephone**	**Telephone**	**Telephone**
Week	**Discontinuation date**	**Discontinuation date + 4 weeks**			**56**
Day	**Discontinuation date**	**Discontinuation date + 30 days**			**395**
IRT treatment discontinuation call	X				
Vital signs	X				
Physical exam	S				
Oropharyngeal examination	S				
Pregnancy test (serum)	X				
Collect study medication	X				
Record asthma/non-asthma related concomitant medication	X	X			
Record interruption/changes in drug administration to assess compliance	X				
Download/review e-Diary	S				
Review rescue medication use	S				
Review AEs	X	X			
Review SAEs	X	X	X*	X*	X*
Review asthma exacerbations	X	X	X	X	X
Review surgery and procedures	X	X			
Safety lab assessments (hematology, clinical chemistry, urinalysis)	X				
Spirometry[3]	X				
ECG[3]	X				
ACQ-7[3, 4]	X				
Evening plasma cortisol[3]	X				
Survival status		X	X	X	X
Record Healthcare visit for asthma worsening	X			X	
Record end of treatment epoch disposition page (Study Phase Completion)	X			X	

S These assessments are source documentation only and will not be entered into the eCRF

X assessment to be reported in the clinical database

* If a subject experienced a serious adverse event (SAE), complete a corresponding AE CRF.

1 Refer to Table 6-1.

2 Refer to Section 5.6.3 and Section 5.6.5

3 Details of timed assessments are provided in Table 6-2.

4 ACQ assessed at clinic should be completed before any other assessment.

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 from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the Table 5-4.

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A 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 by Novartis at any time for any reason. This may include reasons related to the benefit-risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as 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 of the assessments and indicates with an "x" when the visits are performed.

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

Patients will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

Table 6-1 Assessment schedule

Epoch	Screening			Treatment													Follow-up[1]
Visit number	1	2	99	101	102	103	104	105	106	107	108	109	110	111	EOT Early treatment discontinuation	PSW Early Study Discontinuation	201
Clinic (C)/Telephone (T)	C	C	C	C	C	T	C	T	T	C	T	C	T	C	C	T	T
Week	-4 to -2	-2	0	0	4	8	12	16	20	26	32	36	44	52			56
Obtain informed consent	X																
Relevant Medical History/Demographics	X																
History of Asthma exacerbation	X																
Smoking History	X																
Current asthma medication review	X																
Inclusion/Exclusion criteria	X	X	X														
Central pregnancy test (Serum)		X												X	X		
Local pregnancy test (urine)			X							X							
Urinalysis (dipstick)			S							S				S	S		
Hematology/biochemistry		X		X						X				X	X		
Evening plasma cortisol				X						X				X	X		
Inhalation device training			S														
Drug dispensing				X	X		X			X		X					
Administer study drug at the visit				X			X			X				X			
Reversibility test		X															
Spirometry (centralized)		X		X			X			X				X	X		
Issue and training on patient e-Diary	S			S													
e-Diary, ePEF device training	S	S	S														
Concomitant medication review (for asthma & for non-asthma)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Epoch	**Screening**			**Treatment**													**Follow-up[1]**
Visit number	1	2	99	101	102	103	104	105	106	107	108	109	110	111	EOT Early treatment discontinuation	PSW Early Study Discontinuation	201
Clinic (C)/Telephone (T)	C	C	C	C	C	T	C	T	T	C	T	C	T	C	C	T	T
Week	-4 to -2	-2	0	0	4	8	12	16	20	26	32	36	44	52			56
Review and upload patient e-Diary			S		S		S			S		S		S	S		
ACQ-7		X		X			X			X				X	X		
Physical examination		S		S	S		S			S		S		S	S		
Oropharyngeal examination		S		S	S		S			S		S		S	S		
Vital sign: BP and pulse		X		X	X		X			X		X		X	X		
Record height and weight		X															
ECG		X		X						X				X	X		
SAE recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review surgery and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record healthcare visits for asthma worsening					X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]																	
Survival status																X	X
Study Disposition (Screening)		X	X														
Study Disposition (Study Phase Completion)														X	X	X	
Record End of Treatment page														X	X	X	
Study Disposition (Follow-up)																	X

Early Study Discontinuation Visit should be used for Premature study withdrawal (PSW, please refer to Section 5.6.2)

X = assessment to be recorded on clinical data base
S = these assessments are source documentation only and will not be entered into the eCRF

[1] Information about patients' survival will be obtained by a telephone call during the study treatment period and 30 days after the patient's last dose of study drug for completed patients. For patients who withdraw early, please refer to discontinuation of study treatment and premature patient withdrawal section.

Table 6-2 Timing of clinic visit procedures

	Time Point[1]	ACQ-7	ECG	Vital Signs[2]	Hematology Chemistry /Plasma cortisol/ Urinalysis[3]	Spirometry[4]
Visit 99/ Visit 101 Day 1	-50 min	X				
	-45 min					X
	-30 min		X	X	X	
	-15 min					X
	30 min		X			
Visit 104 Week 12	-50 min	X				
	-45 min					X
	-30 min			X		
	-15 min					X
Visit 107 Week 26	-50 min	X				
	-45 min					X
	-30 min		X	X	X	
	-15 min					X
Visit 111 Week 52 Day 365	-50 min	X				
	-45 min					X
	-30 min		X	X	X	
	-15 min					X

1: Time relates to the dose given from the device at visit. When multiple measurements are scheduled at a single time-point, they should wherever possible be done in the following order: ECG, vital signs and then samples for hematology/clinical chemistry/plasma cortisol and urinalysis.

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

3: Urine analysis at central laboratory is to be done only if the urine dipstick is abnormal, and only done pre-dose.

4: A minimum 10 min rest period from the end of spirometry maneuvers and the beginning of ECG assessments must be observed at all times.

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

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

- Year of birth
- Age
- Sex
- Race and ethnicity

- Height and Weight
- BMI (calculated)
- Baseline physical examination (not databased 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
- ACQ-7
- Prior concomitant medication (Both asthma related and non-asthma related)
- Pre and post-bronchodilator spirometry (screening spirometry and reversibility testing).
- Baseline PEF

6.3 Treatment exposure and compliance

The time of study treatment administration at each in-office dosing visit will be collected on the eCRF as well as any dosing interruptions. For assessments where spirometry is performed, the time of dosing is to be taken from the spirometer. While at home, the time of study treatment administration will be recorded by the patient in the e-Diary once a week. The data from the e-Diary will be reviewed at each visit.

Study treatment compliance should be assessed by the investigator and/or center personnel at all visits. In order to ensure compliance and safety follow-up, the patients will be requested to record once per week in the e-Diary whether he/she missed any dosage in the evening from Visit 101 to 111. Where necessary, the Investigator will discuss compliance/documentation issues with the patient. The Investigator or designee will collect, from the patient, the used/unused investigational medication and packaging (unused capsules/blister strips and SDDPIs) at Visits 102, 104, 107, 109, 111 (or at Early Treatment Discontinuation/end of treatment (EOT) Visit or Study Withdrawal visit if applicable). Study treatment compliance will be assessed from the capsule count from previously dispensed blister strips for the Concept1.

6.4 Efficacy

6.4.1 Spirometry

The following spirometric assessments will be made:

- Forced expiratory volume in one second (FEV_1)
- Forced Vital Capacity (FVC)

Spirometric assessments will be measured at Visits 2, 101, 104, 107, 111 and EOT if applicable as indicated in Table 6-1.

Pre-dose FEV_1 is defined as the mean of the two FEV_1 values measured at -45 min and -15 min prior to evening dose taken at the site.

All clinic visits must occur in the evening. Please refer to Table 6-2 for full details of the scheduling of spirometry measurements. Equipment for spirometry assessments will be provided to all study sites by a Central Spirometry vendor, and all measurements will be reviewed by trained spirometry technicians at the central vendor.

Please refer to the latest version of Spirometry Guidance in Appendix 3 for full details on performing spirometry.

6.4.2 Electronic Diary

All patients will be provided with a patient electronic diary (referred to as e-Diary or e-Diary/ePEF) to record daily clinical symptoms, peak flow or rescue medication (salbutamol) use. The patients will be instructed to routinely complete the patient diary twice daily at the same time morning or evening (before taking the study drug) and approximately 12 hours apart. The e-Diary is to be reviewed at each clinic visit until study completion. Sites and patients will receive appropriate training and guidance on the use of the e-Diary device (see Appendix 4 for questions).

6.4.2.1 Number of inhalations of Rescue Medication

The total number of inhalation used of rescue medication (number of puffs taken in the previous 12 hours) will be recorded morning and evening by the patient, in the e-Diary.

The patient will input the number of puffs of rescue medication they have used during the 12 hours previous. The patients mean evening and morning recue medication usage will be automatically be calculated by the e-Diary. This SABA data collected by the patient during the last 7 days of screening will be used to set alerts to the patient to contact the investigator in case of worsening asthma (see Section 6.4.4 Asthma worsening criteria).

6.4.2.2 Peak expiratory flow (PEF)

An electronic Peak Flow Meter (ePEF) will be given to each patient at Visit 1 for the measurement of morning and evening PEF from Visit 1 until the end of the treatment epoch.

PEF will be measured at consistent times for a patient, in the morning and evening each day during the study from Visit 1 to 111. The measurements will be performed using an ePEF provided to the patients at Visit 1. PEF will be measured twice a day; in the evening just prior to taking study medication and again 12 hours later and as soon as possible after waking in the morning. Patients should be encouraged to perform morning and evening PEF measurements BEFORE the use of any rescue medication. At each time point, the patient should be instructed to perform 3 consecutive maneuvers within 10 minutes. These PEF values are captured in the e-Diary/ePEF. The best of 3 values will be used.

6.4.3 Asthma Control Questionnaire 7 (ACQ-7)

In this study, the ACQ-7 will be used to assess improvements in asthma symptom control. The ACQ-7 (Juniper et al 1999, Juniper et al 2005, Juniper et al 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 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 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 Master Scope spirometer. The ACQ-7 should be completed at the investigators site at Visits 2, 101, 104, 107, 111 and EOT if applicable.

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 will also be used to alert the patient and/or investigator to possible signs of worsening asthma. The investigator must provide the patient with written instructions to contact the investigator if at any time during the trial from the screening onwards one or more of the following criteria of worsening asthma develops:

Asthma Worsening Criteria

1. > 20% decrease in FEV_1 from the baseline value (Criteria only be applicable to the investigator review at the time of study visit or possibly an alert setting if device is structured to capture)
2. > 50% increase in SABA use and > 8 puffs on 2 out of any 3 consecutive days compared to baseline
3. ≥ 20% decrease in AM or PM PEF from baseline on 2 out of any 3 consecutive days compared to baseline
4. < 60% of 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 screening epoch would be the FEV_1 and PEF taken at Visit 1 (Screening). The Baseline FEV_1 for the treatment epoch is taken at treatment Day 1 (Visit 101). The Baseline PEF (morning and evening) for the treatment epoch is calculated at Visit 99 and is the mean of the best of the three daily PEF measurements over the last 2 weeks of screening epoch (Visit 2 to 99).

If any of the above criteria (including the alert from e-Diary) are met while a patient is in the screening or treatment epoch, the investigator should assess the patient condition. If this occurs during screening epoch and it is considered a clinically significant asthma worsening in the investigator's opinion, the patient should be treat as appropriate and screen failed. Once the condition is resolved, if eligibility criteria are met, the patient may be reconsidered for rescreening.

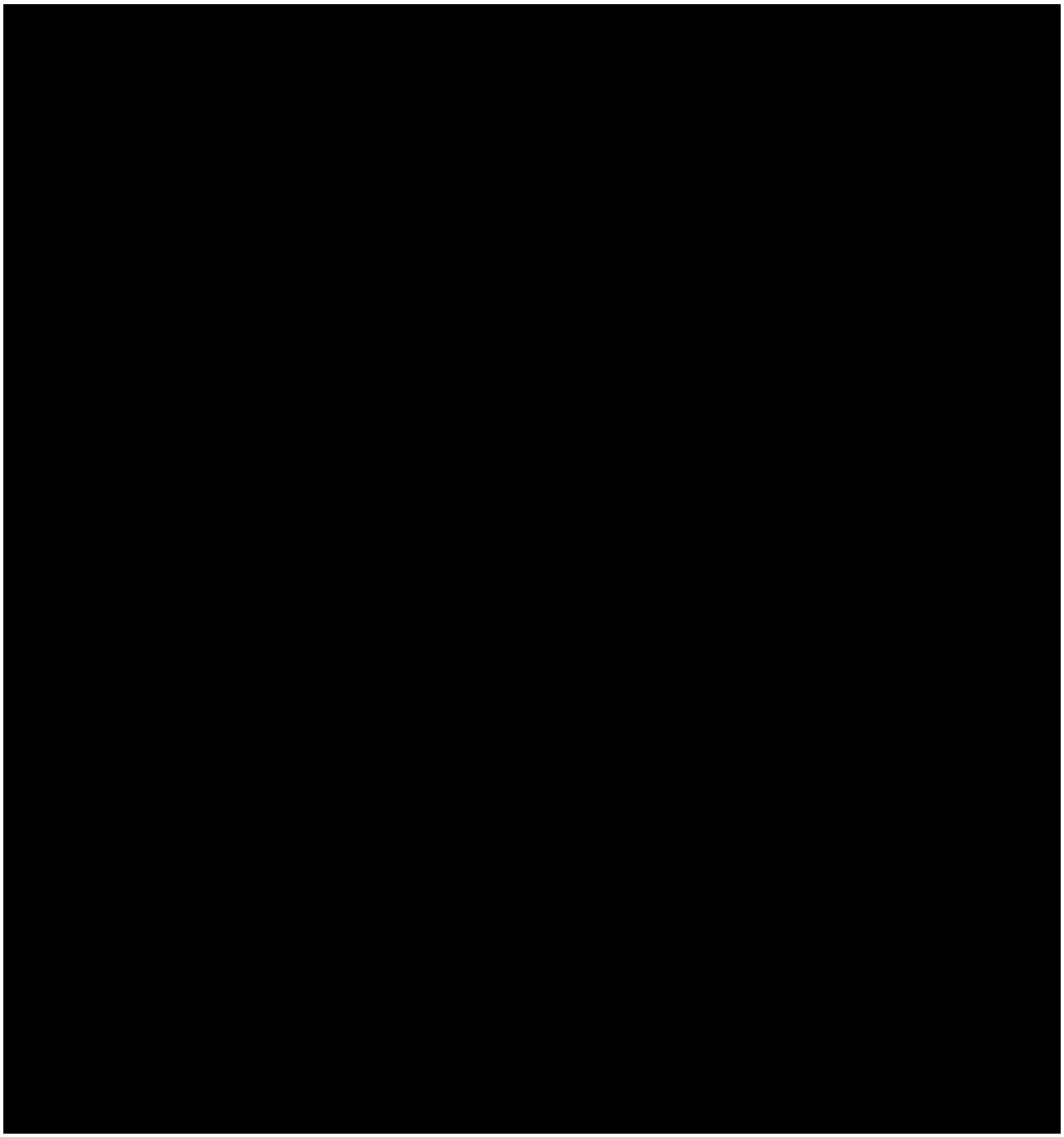
The alerts, which are trigged by above criteria, are in place to detect early onset of asthma worsening at any time during the study and to help direct early intervention. Therefore the investigator should do the following when alerts are received:

- Reviewing alert trends over time, in particular PEF decreases
- Calling the patient promptly when alerts are received when any one specific alert type (e.g. PEF < 60%) is received on consecutive days to further assess the clinical status. This may include urgent clinic visits as appropriate and/or immediate treatment.
- Implementing prompt treatment as necessary

If patients believe their symptoms are worsening and/or receive alerts as outlined above, the patient should also notify the investigator and be evaluated by the investigator and treated as clinically appropriate.

Patients should also be withdrawn for safety reasons if, in the opinion of the investigators, it is appropriate to do so.

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.



6.4.6 Appropriateness of efficacy assessments

The measures described above are standard outcome measures in asthma trials.

6.5 Safety

The following safety assessments will be performed:

- Medical history and physical examination including oropharyngeal examination
- Vital signs

- Hematology, chemistry, Urinalysis
- Evening plasma cortisol
- 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)

ECG and Laboratory assessments will be centralized.

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 at Visits 2, 107, 111 and in case of early study treatment discontinuation visit as described in Table 6-1. A short physical examination, including the examination of general appearances and vital signs (see Section 6.5.2), will be performed at all other clinic visits.

An oropharyngeal examination will be performed at each clinic visit.

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 Medical History 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 screen of the patient's 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 Table 6-1. At Visits 2, 101, 102, 104, 107, 109, 111, or EOT if applicable, vital signs should be measured directly after the ECG assessments.

6.5.3 Height and weight

Height in centimeters (cm) will be measured at Visit 2. Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at Visit 2. 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) will be performed at Visits 2, 101, 107, 111 and EOT if applicable.

6.5.4.1 Hematology

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

6.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, AST (SGOT), ALT (SGPT), bilirubin, creatinine, γGT, 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 (ULN), total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

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 study medication has discontinued.

6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, pH, protein, glucose and blood will be performed at Visits 99, 107, 111, and EOT if applicable. Dipsticks are provided to investigators from the central laboratory.

If dipstick test is abnormal, the sample will be sent to central laboratory for additional testing, including assessment of microscopy and WBC and RBC sediments. The Central Laboratory will provide detailed procedures for the preparation and collection of these samples in the laboratory manual.

6.5.4.4 Plasma Cortisol

Evening plasma cortisol will be measured at Visits 101, 107, 111 and EOT (if applicable). The sampling point is as shown in Table 6-2.

6.5.5 Electrocardiogram (ECG)

Electrocardiograms (ECGs) must be recorded *after 10 minutes rest in the supine position to ensure a stable baseline.* When the ECG recording time coincides with vital signs, spirometry, and blood draws, the ECG must be performed first, followed by vital signs and the blood draws but with enough time planned to ensure the spirometry is performed at the planned time point outlined in Table 6-2. Spirometry must be performed as close to the scheduled time point as possible.

Centralized ECG equipment

At Visit 2, a screening ECG will be measured to test for eligibility for trial inclusion. (Patients whose ECG is abnormal at screening due to technical/mechanical faults may be re-screened.) At Visit 101, ECGs will be measured at 30 min pre-dose (evening dose) and 30 min post dose, at Visits 107, 111, and EOT if applicable, ECG will be measured pre-dose only as indicated in Table 6-2. All electrocardiograms should include 12 standard leads. An ECG tracing will be taken for those patients who prematurely discontinue from the study.

For each ECG performed original traces should be printed. Each ECG will be sent electronically for central review directly from the ECG machine. The 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 number 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. In the event that the central cardiologist reports that an ECG is abnormal, the investigator must assess whether the ECG abnormality is clinically significant or not. 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/AE eCRF page as appropriate.

New cases (not present during screening) 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 Serious Asthma outcomes

Asthma-related hospitalizations, asthma-related intubations and asthma-related deaths over the 52 week treatment epoch will be recorded and will all be reviewed by the Adjudication Committee. Hospitalization is defined as an inpatient stay or a ≥ 24 hour stay in an observation area in an emergency department or other equivalent facility.

6.5.7 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. A serum or urine pregnancy test will be performed (tests provided by the Central Laboratory) per Assessment Schedule Table 6-1. If the urine pregnancy test at Visit 99 and Visit 107 is positive, a plasma testing is to be done to confirm the pregnancy. A positive pregnancy test at Visits 2 (Week -2), 99 (Week 0), 107 (Week 26), 111 (Week 52), EOT or at any time during

the study requires the patient to be discontinued from the study treatment. Refer to Section 5.6.2 and Section 7.6 for more details.

6.5.8 Appropriateness of safety measurements

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

6.6 Other assessments

No additional tests will be performed on patients/subjects entered into this study.

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

- its relationship to the study treatment
  - Yes
  - No
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding investigational treatment

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

- no action taken (e.g. further observation only)
- investigational treatment dosage increased/reduced
- investigational treatment interrupted/withdrawn
- concomitant medication 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's Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the 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

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (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 (please refer to 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 (please refer to 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 patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs

experienced after the 30 days period 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. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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, 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 Pneumonia Reporting

Pneumonia will be defined as an event characterized by increased respiratory symptoms (e.g. increased cough, dyspnea, wheezing, purulent sputum), fever (i.e. body temperature greater than 38°C) or pleuritic chest pain or leukocytosis or other clinical signs consistent with pneumonia considered relevant in the opinion of the investigator and confirmed by X-ray. Any reported pneumonia will have to be confirmed by either X-ray or radiologist reading report of the X-ray (to be kept in the source documents). If not confirmed by X-ray, it should be reported as lower respiratory tract infection.

7.4 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 Table 13-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 13-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 13-2 in Appendix 2.

For the liver laboratory trigger:

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

These LFT repeats 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. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event 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 CRF pages, including the liver event overview CRF pages.

7.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

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
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.6 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 3 months after the birth, 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 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 eCRF must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

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

8.2 Data collection

The trial will be conducted in a fully validated Data Capture system which conforms to US CRF 21 Part 11 requirements. Investigator site staff will not be given access to the system until they have been trained. Designated investigator staff will enter the data required by the protocol into the Data Capture system. Automatic validation programs within the system check for data discrepancies in the CRFs and by generating appropriate error messages, allow the data to be confirmed or corrected by the investigator staff. The investigator staff must certify that the data entered are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff 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. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

ECG readings will be processed centrally and the results will be sent electronically to Novartis.

Spirometry readings will be processed centrally and the results will be sent electronically to Novartis.

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

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 Novartis IRT, who will also manage the database. The database will be sent electronically to 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 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 treatment start 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 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. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

The Safety Set will consist of all patients who received at least one dose of study medication during this study.

Full Analysis Set (FAS) will consist of all patients who entered in this study and received at least one dose of study medication during this study.

Note that the Safety Sets and FAS are the same except that the Safety Set allows the inclusion of patients who are not intended to enter in this study but received study drug in error.

The Safety Set will be used in the analysis of all safety variables. The efficacy analysis population will be the FAS.

9.2 Patient demographics and other baseline characteristics

Demographic and baseline characteristics including age, sex, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, screening spirometry parameters: (FEV_1, FVC, and FEV_1/FVC), FEV_1 reversibility, percentage of predicted FEV_1, baseline PEF, 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 ACQ-7, will be summarized.

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 Safety Set.

Baseline is defined as the last measurement before first dose of study drug.

9.3 Treatments

Study drug administration and concomitant medication data will be listed and summarized using the Safety Set.

The duration of exposure and the number of patients who completed the study medication and who discontinued from the study medication will be summarized.

Medications started and stopped prior to study drug, and taken concomitantly will be summarized for 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 screening epoch will be summarized.

Treatment compliance with study medication over the study period will be summarized.

9.4 Analysis of the primary variable(s)

9.4.1 Primary Variable(s)

The primary objective of this study is to assess the safety/tolerability of 52 weeks of treatment with QVM149 (150/50/160 µg, once daily), particularly with regard to treatment emergent adverse event reporting in Japanese patients with inadequately controlled asthma.

The primary variable is the number and percentage of patients who reported treatment emergent adverse events during the 52 week study period.

Adverse events will be summarized with descriptive statistics for the Safety Set.

All study emergent adverse events including asthma exacerbations will be summarized and 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 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.

9.4.2 Statistical model, hypothesis, and method of analysis

The number and percentage of patients who reported treatment emergent adverse events will be summarized by primary system organ class, preferred term for

- All adverse events
- Serious adverse events
- Adverse events by maximum severity
- Adverse events suspected to be related to study drug
- Adverse events leading to permanent study drug discontinuation
- Adverse events of special interest

In addition, all adverse events reported in the study will be listed.

9.4.3 Handling of missing values/censoring/discontinuations

No imputation will be done for missing data. All available data will be summarized.

9.4.4 Sensitivity analyses

Not applicable.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The efficacy measurements during the study will be summarized for the FAS.

Baseline is defined as the last measurement before first dose of the study drug, unless otherwise specified. No imputation will be done for missing data.

Spirometry

Spirometry measurements taken within 7 days of systemic corticosteroid use and/or 6 hours of rescue use will be set to missing and not be imputed, unless specified otherwise.

For FEV_1 and FVC, the baseline is defined as the mean of the values taken in the clinic at 45 and 15 min prior to first dose at Visit 101.

Pre-dose FEV_1 and FVC at Weeks 12, 26 and 52

The pre-dose FEV_1 is defined as the mean of the pre-dose 45 and 15 min FEV_1 values.

The pre-dose FEV_1 and the change from baseline at 12, 26 and 52 weeks of the study treatment will be summarized with descriptive statistics. Summaries will be repeated for pre-dose FVC.

In addition, the means in pre-dose FEV_1 and FVC for each visit will be displayed graphically.

Peak Expiratory Flow Rate (PEF)

The morning/evening PEF (liters/min) will be averaged over the first 26 weeks and over the 52 weeks.

e-Diary data recorded during the screening period will be used to calculate the baseline value.

The mean morning/evening PEF and the mean change from baseline will be summarized.

Rescue medication

The total number of puffs of rescue medication per day over the first 26 weeks and over the 52 weeks will be calculated and divided by the total number of days to derive the mean daily number of puffs of rescue medication taken for the patient.

e-Diary data recorded during the screening period will be used to calculate the baseline value.

The mean daily number of puffs of rescue medication use over the first 26 weeks and over the 52 weeks of treatment and the mean change from baseline will be summarized.

In addition, the mean number of puffs of rescue medication in the morning and in the evening, and the percentage of 'rescue medication free days' (defined from diary data as any day where the patient did not use any puffs of rescue medication) will be summarized.

Asthma Control Questionnaire 7 (ACQ-7) at Weeks 26 and 52

ACQ-7 and the change from baseline at 26 and 52 weeks of the study treatment will be summarized.

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 summarized.

9.5.2 Safety variables

All safety variables will be summarized with descriptive statistics for the Safety Set.

Baseline is defined as the last measurement before first dose of the study drug, unless otherwise specified. No imputation will be done for post-baseline missing data.

Electrocardiogram (ECG) and vital signs

Data from the ECG (including QT interval, RR interval, PR interval, QRS duration, heart rate, Fridericia's QTc and Bazett's QTc) will be summarized at 30 min pre-dose, and at 30 min post-dose by visit. The baseline measurement will be the 30 min pre-dose measurement at Visit 101.

Vital signs (blood pressure, radial pulse rate) will also be summarized by visit.

The maximum (QTc, systolic blood pressure, radial pulse rate) or minimum (diastolic blood pressure) post first dosing (i.e., post-baseline) value will be summarized. The changes from baseline will also be summarized by visit.

All data will be included in the analysis regardless of rescue medication usage.

The number and percentage of patients by the following classifications will be presented for each visit.

The number (%) of patients with pulse rate of < 40 and > 90 bpm; systolic blood pressure of < 90 and > 140 mmHg; diastolic blood pressure of < 50 and > 90 mmHg will be summarized.

Notable values for vital signs and the 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 the 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) by two methods:

1. using Fridericia's formula: $QTc = QT / 3\sqrt{RR}$, where $3\sqrt{}$ denotes the cube root
2. using Bazett's formula: $QTc = QT / \sqrt{RR}$

ECG and vital signs 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:

Evening plasma cortisol will be summarized by visit. The maximum evening plasma cortisol post first dosing (i.e. post baseline value) will be summarized. The changes from baseline will also be summarized by visit.

All other 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.

All data will be included in the analysis regardless of rescue medication usage.

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.

9.5.3 Resource utilization

Not applicable.

9.5.4 Pharmacokinetics

Not applicable.

9.5.5 DNA

Not applicable.

9.5.6 Biomarkers

Not applicable.

9.5.7 PK/PD

Not applicable.

[redacted]

9.7 Interim analyses

An interim analysis for 6-month data will be performed for the initial New Drug Application submission in Japan (Section 3.2). This analysis will be performed after all patients have been enrolled and completed Visit 107 (Week 26) or discontinued the study.

The cut-off date for each patient is defined as the Visit 107 date or study discontinuation date prior to Visit 107. All protocol specified analyses will be performed for all data on or prior to this cut-off date.

9.8 Sample size calculation

Since asthma is a chronic disease, and QVM149 is expected to be administered over a long period, safety in long-term treatment needs to be confirmed. “Regarding sample size and treatment period required to assess safety at the clinical study stage of a new drug anticipated to be administered for a non-fatal disease over a long period” (Notification No. 592 of the Pharmaceuticals and Cosmetics Division, Pharmaceutical Affairs Bureau, MHLW, dated 24-May-1995), this notification requires to collect safety data of at least 100 patients who receive the drug over one year. CQVM149B2302 study was planned to collect efficacy and safety data of about 10 Japanese Asthma patients exposed to QVM149. Therefore this study, CQVM149B1304, is designed to obtain safety data of approximately 90 Japanese asthma patients exposed to QVM149. Since a 25% screening failure rate and a 10% dropout rate are expected, approximately 134 patients will need to be screened in order to collect approximately 100 patients who enter the treatment epoch and to collect a total of approximately 90 completed patients.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US 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, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators 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, written 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 is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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

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.

12 References

References are available upon request

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13 Appendices

13.1 Appendix 1: Clinically notable laboratory values and vital signs

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory reports. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate CRF.

Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

See Appendix 2 for specific liver event and laboratory test trigger definitions and follow-up requirements.

For ECGs, a notable QTc value is defined as a QTcF (Fridericia) interval of ≥ 450 msec for males or ≥ 460 msec for females – all such ECGs will be flagged by the Central CRO and require assessment for clinical relevance and continuance of the patient by the Investigator.

For vital signs, 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

Investigators are responsible for reviewing these abnormal values for clinical relevance and reporting adverse events considered clinically significant in the appropriate CRF.

13.2 Appendix 2: 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.

13.3 Appendix 3: 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 greatest FEV_1 and FVC from any of the acceptable curves are recorded. (The greatest FEV_1 and FVC may not necessarily result from the same acceptable curve).

Predicted normal

This study will utilize the spirometric predication equation standards from the ERS Global Lung Function Initiative[2] or Japanese Respiratory Society[3] for Japanese subjects 17 years of age or greater.

Reversibility

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing[1]. A pre-bronchodilator spirometry assessment should be performed after a washout period of at least:

- 6 h for short-acting β2-agonists
- 8 h short-acting anticholinergics
- 24 h for long-acting β2-agonists
- 7 days long-acting anticholinergic
- 7 days indacaterol
- 12 h for short-acting xanthines
- 24 h for long-acting xanthines

Administer 400 µg of salbutamol/albuterol (or equivalent) following the completion of the pre-bronchodilator assessment. Post-bronchodilator spirometry assessment is then performed within 15 to 30 minutes after administration of the salbutamol/albuterol.

Reversibility is calculated as:

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

FEV_1 (pre-bronchodilator)

Subjects will be considered reversible if an increase of at least 12% (and 200 ml) is demonstrated after administration of the salbutamol/albuterol.

Following the reversibility testing assessment for post-bronchodilator FEV_1, if patient has not met the above reversibility criteria after administration salbutamol/albuterol, then the patient may be rescreened or allow one spirometry retest.

References

[1] Miller MR, Crapo R, Hankinson J, et al. (2005) Standardization of Lung Function Testing. Eur Resp J; 26:153-61.

[2] Quanjer PH, Stanojevic S, Cole TJ, et al. (2012) 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. Eur Resp J; 40(6):1324-43.

[3] Kubota M, Kobayashi H, Quanjer PH, et al. (2014) 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 Investigation; 52:242-50.

13.4 Appendix 4: Patient Asthma Control e-Diary

The following information will be captured:

In the MORNING	**In the EVENING**
Peak expiratory flow rate	
How did you sleep last night?	
Did you have asthma symptoms upon awakening in the morning?	
Number of puffs of rescue medication during the past 12 hours	
	Peak expiratory flow
	Did your respiratory symptoms stop you from performing your usual daily activities?
	How severe was your shortness of breath today?
	How was your wheeze during the past 12 hours?
	How was your cough during the past 12 hours?
	Did you have Chest tightness during the past 12 hours?
	Number of puffs of rescue medication during the past 12 hours

13.5 Appendix 5: Instruction for Use of Concept1

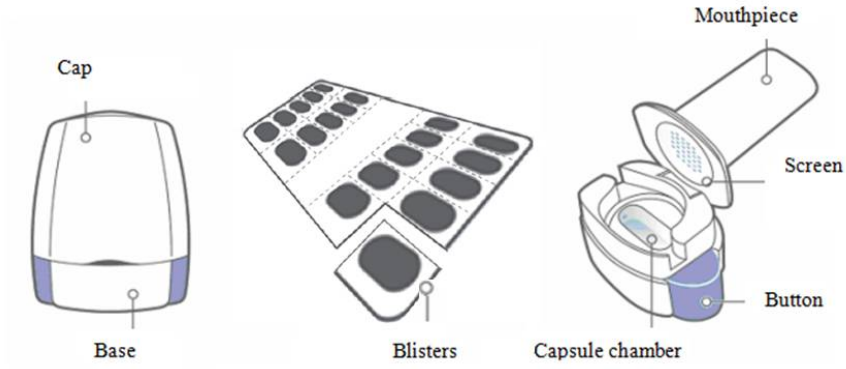
Instructions for using inhaler and capsules.

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

- 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.

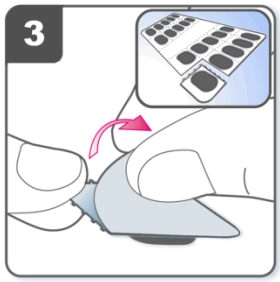
Do not use the study medication capsules with any other capsule inhaler, and do not use the inhaler to take any other capsule medicine.

How to use your inhaler

Pull off cap.

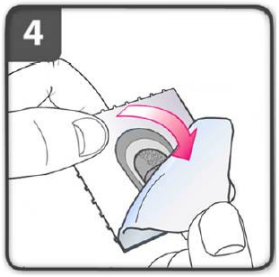
Open inhaler:

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



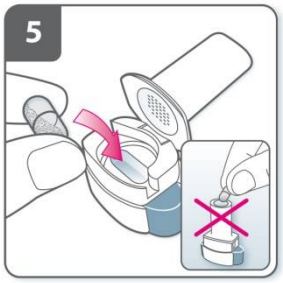
Prepare capsule:

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.



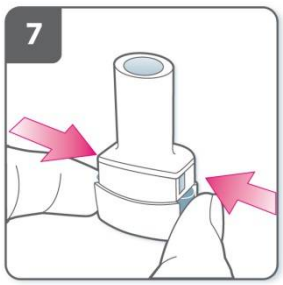
Insert capsule:

Place the capsule into the capsule chamber.

Never place a capsule directly into the mouthpiece.

Close the inhaler:

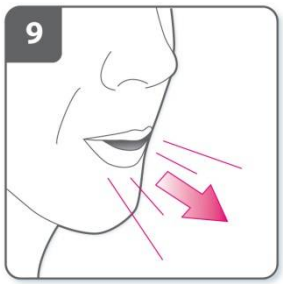
You should hear a “click” as the mouthpiece closes onto the inhaler base.



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.

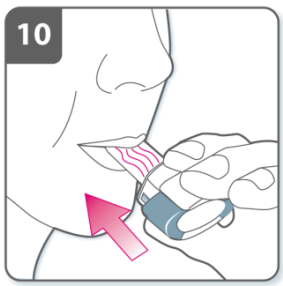
Release the side buttons fully.



Breathe out:

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

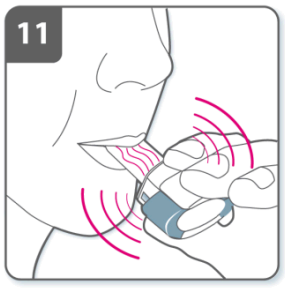
Do not blow into the mouthpiece.



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

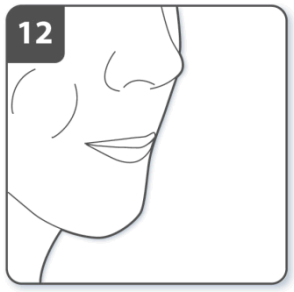
Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed. The chances of the capsule breakage will be increased if the capsule is accidentally pierced 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.

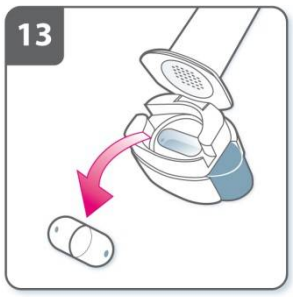
If there is powder left in the capsule:

- 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.