NOVARTIS

Global Clinical Development - General Medicine

QVM149B (Indacaterol acetate / Glycopyrronium bromide /Mometasone furoate)

Full Protocol CQVM149B2302 / NCT02571777

A multicenter, randomized, 52-week, double-blind, parallel-group, active controlled study to compare the efficacy and safety of QVM149 with QMF149 in 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 classification
ATS/ERS	American Thoracic Society/European Respiratory Society
AQLQ	Asthma Quality of Life Questionnaire
b.i.d.	Twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CCV	Cardio-/Cerebro-vascular
CFR	US Code of Federal Regulations
CDS	Core Data Sheet (for marketed drugs)
eCRF	Case Report/Record Form (electronic)
COPD	Chronic Obstructive Pulmonary Disease
CPO	Country Pharma Organization
CRO	Contract Research Organization
CSR	Clinical Study Report
DALYS	Disability–adjusted life years
DMC	Data Monitoring Committee
DPI	Dry powder inhaler
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOT	Early Treatment Discontinuation
FAS	Full analysis set
FDC	Fixed dose combination
FEF	Forced expiratory flow
FEV_1	Forced expiratory volume in 1 second
FPM	Fine particule mass

[redacted]

FVC	Forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HV	Healthy volunteer
[redacted]	[redacted]
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
i.v.	Intravenous
IQS	Integrated quantitative drug development sciences.
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra uterine device
IUS	Intra uterine system
LABA	Long acting beta-2 agonist
LAMA	Long acting muscarinic antagonist
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
MDDPI	Multi dose dry powder inhaler
MF	Mometasone furoate
MedDRA	Medical dictionary for regulatory activities
OC/RDC	Oracle Clinical/Remote Data Capture o.d. once a day
OCS	Oral Corticosteroids
Pbo	Placebo
PEF	Peak expiratory flow
PI	Post inhalation
PPS	Per protocol set
PRO	Patient reported outcome
p.o.	Oral (ly)
RAN	Randomization set
SABA	Short acting beta-2 agonist

[redacted]

SAE	Serious adverse event
SCS	Systemic corticosteroids
SDDPI	Single dose dry powder inhaler
SUSAR	Suspected Unexpected Serious Adverse Reactions
[redacted]	[redacted]
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	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
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Premature subject/patient withdrawal	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
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
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), 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

[redacted]

Amendment 6

Amendment rationale

Conduct primary analysis after all patients have completed at least 26 weeks treatment (Visit 207):

The primary and key secondary endpoints of CQVM149B2302 study are trough FEV_1 and ACQ-7, respectively after 26 weeks of treatment, while the entire study treatment period is 52 weeks. Novartis has decided to perform primary analysis (see CSR I below) once **all** patients have completed 26 weeks of treatment (Visit 207) or prematurely withdrawn from the study. The analysis will be used for internal decision making prior to study completion at 52 weeks. Importantly, the study will continue as originally planned in a blinded manner, for full 52 weeks period (plus 30 days of safety follow-up). This will be conducted by a distinct and separate study team who are not involved in the primary analysis.

In terms of reporting, two separate CSRs will be written:

- CSR I: will be completed for the primary analyses once all patients have completed the assessments after 26 weeks of treatment (Visit 207) or prematurely withdrawn from the study. This will consist of primary and key secondary objectives as well as other pre-specified objectives up to and including Week 26. The CSR will be based on variable duration of exposure with minimum of 26 weeks and maximum of 52 weeks. It will consist of:
  - All data in all patients up to 26 weeks (Visit 207)
  - Data for the subset of patients who have completed 52 weeks treatment plus follow up (Visit 214 and 301) or prematurely withdrawn from the study.
  - Data up to last available visit for patients who have already completed 26 weeks (Visit 207) but have not yet completed 52 week treatment plus follow up (Visit 214/301)
- CSR II: will be completed once **all** patients have completed 52 weeks of treatment (Visit 214) plus 30 day follow up (Visit 301) or prematurely withdrawn from the study. CSR II will consist of primary and secondary objectives analyzed in CSR I in addition to all other objectives evaluated after 26 weeks and up to 52 weeks (plus follow up).

Since the primary analysis (CSR I) will be performed prior to all patients completing the study, a dedicated unblinded team will be involved in CSR I related activities. In order to maintain the integrity of the study data, a separate blinded team will continue the study until its completion. The details outlining this process including appropriate firewalls will be maintained in a separate charter.

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:

[redacted]

- Add an explanation for primary analysis when all patients have completed 26 weeks of treatment as above (Section 3.5, Section 5.3, Section 8.2 and Section 9.6)
- Add an additional explanation for the treatment of asthma exacerbation (Section 5.4.8, Section 6.4.5)
- Add the clarification that the treatment for adverse events (including asthma exacerbations) is permitted (Section 5.4.8)
- Add the importance of eDiary/PEF data and also reporting asthma events on CRF (Section 6.4.4)
- Change the requirement for duplicate trace of ECG. Duplicated trace was printed out as a back-up (e.g. in case of data transmission error). However currently ECG central vendor accepts an electronic back up only (Section 6.5.5)
- Clarify the handling of missing data in terms of the duration of post-dosing spirometry with respect to b.i.d. regimen (Section 9.4.3, Section 9.4.6)
- Align to the analysis plan for the analysis of glucose and potassium value (Section 9.5.2). This was mentioned in the last version of amendment (Amendment 5, 08-Feb-2017); however, the text deletion was not done
- Add further clarification to ICS/LABA Standard of Care prior to the study. A patient who has been treated with FDC (ICS/LABA) plus ICS monotherapy should be avoided because his/her ICS treatment would be higher than the ones in the study treatment (Appendix 10)

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 the specific sections of the protocol are shown by track changes in the track changes version of the protocol using strike through (for deletions) and underlining (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.

[redacted]

Summary of amendments issued before this amendment:

Amendment 5 (08-Feb-2017)

Amendment rationale

1. Modification of inclusion criteria for duration of baseline ICS/LABA requirements from 1 year 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.
2. Revision of the sample size based on the re-estimation of drop-out rate at Week 26 at which time the primary and key secondary objectives are evaluated.

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:

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- Update the required sample size based on the new estimate in terms of drop-out rate at Week 26 (Section 4 and Section 9.8)
- 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 7 (Section 3.1, Section 4.1)
- Update the repeat spirometry test including reversibility in inclusion criterion 7, inclusion criterion 8, and exclusion criterion 22 (Section 3.1, Section 4.1 and Section 4.2)
- Change the condition of spacer use for reversibility testing in inclusion 8 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)
- Enhance importance of alert to have appropriate actions taken (Section 6.4.4).
- Remove ATC code for summarizing concomitant medication(Section 9.3)
- Align to the analysis plan for the analysis of glucose and potassium value (Section 9.5.2)
- Update the definition of repeatability in the spirometry guidance (Appendix 3)
- Add fluticasone furoate in the table of the ICS dose (Appendix 10)

[redacted]

Amendment 4 (08-Sep-2016)

Amendment rationale

1. Recent approval of tiotropium Respimat® 5 µg o.d. for asthma in September 2014 as well as changes to GINA guidelines in 2015 are expected to result in a progressive increase in use of tiotropium (LAMA) as add on to ICS/LABA therapy in GINA ≥Step 4 patients. This has already been observed, where the uptake in LAMA use has been higher than anticipated based on initial expectations at time of protocol development and initial feasibility.
   To mitigate this issue, in consultation with leading experts in the field of asthma treatment and based on real-world evidence on asthma treatment, a protocol amendment will be implemented to reduce the exclusion period for LAMA use **from 12 months to 3 months prior to Visit 1.** This will broaden the pool of eligible patients and help better reflect rapidly evolving medical practice in GINA ≥Step 4 asthma patients. The modified criteria will maintain the rigor of the study design including assessment of endpoints in a population that may benefit from LAMA in a fixed triple combination, QVM149. A 3 month timeframe will help ensure there is no carryover effect from recent LAMA use, and will NOT require washout at the time of Visit 1. To help ensure continued safety, all patients must be free of asthma exacerbations within 6 weeks of Visit 1 or asthma worsening within 4 weeks of Visit 1, respectively.
   The Protocol Summary, Section 4.2 exclusion criteria and Table 5-2 Prohibited asthma-related medications were updated accordingly.
2. E-Diary Alert handling during run-in epoch due to asthma worsening (Section 6.4.4). Currently, if an asthma worsening alert is observed during the run-in epoch, the patients must be discontinued regardless of clinical context and the investigator's judgment. This amendment will allow investigator's discretion in determining the clinical significance of asthma worsening e-diary alerts during the run-in epoch and allow the investigator to make the most appropriate decision as to whether patients may continue in the study or be discontinued. If asthma worsening is confirmed as clinically significant by investigator, patients should be discontinued. A combination of e-diary alerts and investigator's judgment will help ensure that the most appropriate patients are enrolled in the study, while maintaining rigorous monitoring and assessment of patient safety.
   The Protocol Summary, Section 4.2 exclusion criteria and Section 6.4.4 Worsening of asthma were updated accordingly.

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:

- Section 4.1 Inclusion criteria:
  - Clarify the definition and documentation of asthma exacerbations in the inclusion criteria #6.
  - Align washout period of LABAs and xanthines with Table 5-2 and Table 5-4 in the inclusion criteria #07.

[redacted]

  - Clarify that repeat spirometry is permitted in cases where the spirometry did not meet percent predicted FEV1 and/or ATS/ERS criteria at Visit 101 in the inclusion criteria #07 and the exclusion criteria #22.
- Section 4.2 Exclusion criteria:
  - Clarify that smoking exclusion also pertains to the use of e-cigarettes in the exclusion criteria #01.
  - Change prohibited period of LAMA use from 12 months to 3 months in the exclusion criteria #05 (Table 5-2 as well).
  - Clarify the exclusion criteria #07 and Section 6.4.4 that the discontinuation is **at investigator's discretion** when the e-diary asthma worsening alert criteria are met during run-in epoch in accordance with Section 6.4.4. The current text states that discontinuation is mandatory regardless of investigators discretion. This amendment will allow the investigator to incorporate clinical judgment into the context of e-diary alerts during run-in epoch to assess clinical significance of the asthma worsening alert and decide on best course of treatment for patient.
  - Clarify the ECG prior to randomization (Visit 102) in the exclusion criteria #15 and #19, although no ECG is scheduled at Visit 102, any clinically significant abnormal ECG before Visit 102 (including unscheduled ECG) should lead to exclusion.
  - Include lactose as an example of hypersensitivity in the exclusion #21 since study drug is formulated using lactose blended dry powder.
  - Specify "severe" narcolepsy and/or insomnia in the exclusion criteria #26.
  - Exclusion criteria #35
    - Adjust the wording from "effective" to "highly effective" because the listed methods are actually "highly effective" contraception methods.
    - Under 'total abstinence', the following text has been added. "if allowed as effective method of contraception by local regulations".
    - Clarify that contraception requirement includes both treatment epoch and 30 days follow-up epoch after end of study treatment.
- Specify that time between Visit 1 and Visit101 can be adapted according to the required wash-out from previous medication as per Table 5-2.
- Add IL-5 inhibitor (e.g., mepolizumab) in Table 5-4.
- Clarify the conditions in which anti-histamine use is permitted in Table 5-4.
- Clarify the timing of urinalysis in Table 6-2.
- Align the visit number where pregnancy test is required in Section 6.5.7.
- Update of Section 7.2.2 for Serious Adverse Event reporting.
- Update the follow-up period "up to 3 months after birth" in case that the female patient is pregnant while the patient is on the study treatment in Section 7.4.
- Add the maximum duration of device usage in Appendix 1.
- As Visit 299 does not have a specific e-CRF visit page, but only summary pages to fill in, the numbering was replaced by the term Early Study Discontinuation to avoid misunderstanding.
- The word masterscope was replaced with "equipment provided by spirometry vendor".

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 the specific sections of the protocol are shown by track changes in the track changes version of the protocol using strike through (for deletions) and underlining (for insertions).

Amendment 3 (08-Oct-2015)

Amendment rationale

The purpose of this amendment is to modify the ACQ score inclusion criteria from ACQ ≥ 2 to ACQ ≥1.5 based on recent feedback from an external expert advisory board in September 2015. Initial threshold of ≥ 2 was defined based on internal modelling and simulation data as well as published literature (Barnes 2014). However, expert advisory board members suggested that a threshold of 1.5 is more clinically meaningful for this patient population. Additionally, there is precedent for this threshold in recent asthma studies (Kerstjens 2015)

The Protocol Summary, Section 3.3 Rationale for dosing, Section 4. Inclusion criteria and Section 9.4.6 Supportive analysis were updated accordingly.

Changes to the protocol

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

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

- Clarify that asthma worsening criteria in Section 6.4.4 as defined by PEF is based on a decrease of more than 60% of PEF compared to baseline. The terms ‘predicted’ and ‘personal best’ to describe PEF measurements have been removed to avoid confusion. This is also reflected in the asthma exacerbation definition in Section 6.4.5.
- Baseline PEF definition for the treatment period is added as being calculated at visit 102 as the mean value of the best of the three daily PEF efforts over the past 14 days.
- Add footnote on Table 6-1 Table of Assessment to specify that historical reversibility or bronchoprovocation are acceptable as inclusion criteria.
- Clarify on Section 6 the order of the PROs completion
- Remove the visit window between Visit 102 to Visit 201 Day 1 in Section 3.1 and Table 6-1
- Add clarification on number of days of hospitalization to number of hospitalization due to asthma exacerbation. [redacted]
- Update the analysis method for the duration of asthma exacerbation in Section 9.5.1.6 Asthma exacerbations

[redacted]

Amendment 2 (31-Aug-2015)

Amendment rationale

The purpose of this administrative Amendment was to replace the Appendix 1 - Instruction for use of Concept1 (picture 3 and 5 were missing and a black field was covering the text describing Concept1 picture) and the Appendix 5 - AQLQ-S (questions 26-31 of the questionnaire were missing and the page was blank and a black field was covering part of the question 32) which were incomplete due to a technical issue during protocol publication.

The opportunity was taken to also clarify that:

- additional pregnancy testing might be performed if requested by local requirements (added on the footnote of Table 6-1 Table of Assessment, Section 6.5 Safety and Section 6.5.7 Pregnancy and Assessment of Fertility)
- at Visit 102 spirometry does not include reversibility test (change in the Table 6-1 Table of Assessment)

[redacted]

Amendment 1 (03-Aug-2015)

Amendment rationale

The purpose of this Amendment is to clarify how the data for the ACQ7 instrument will be collected. Questions 1-6 of the ACQ7 will be completed by the patients based on one week recall. Item 7 will be completed by the investigator using the MasterScope spirometer at the study site. Derivation of rescue medication from the e-diary (6^{th} item on ACQ7) will not be performed. The rationale is that the ACQ7 will be administered to patients in the manner in which it has been validated. The update was done on Table 5-5, Table 6-1, Section 6.4.2.1 and Section 9.5.1.2.

The opportunity was taken to also:

- Add the ACQ-7 in Appendix 4 and AQLQ-S questionnaire in Appendix 5
- Update the asthma control e-diary questions in order to align to the exacerbations definitions in Appendix 7
- Specify on Section 6.4.3 and Section 6.4.3.1 from which visit the measurements of rescue medication use, PEF, asthma symptoms and study medication compliance start.
- Specify in Section 6.3 that the patient will have to enter on the e-diary the timing of study drug once a week.
- Correct Table 6-1 as the peak flow meter is given on the same time than the e-diary at Visit 1 as it is part of the same device
- Make a few edit corrections.

[redacted]

Protocol summary

Protocol number	CQVM149B2302
Title	A multi-center randomized 52-week treatment, double-blind, parallel group controlled study to compare the efficacy and safety of QVM149 with QMF149 in patients with asthma
Brief title	Safety and Efficacy study of QVM149 in asthmatic patients
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the trial is to evaluate the efficacy and safety of two different doses of QVM149 (QVM149 150/50/80 µg and QVM149 150/50/160 µg via Concept1) over two respective QMF149 doses (QMF149 150/160 µg and QMF149 150/320 µg via Concept1 in poorly controlled asthmatics as determined by pulmonary function testing and effects on asthma control.
Primary Objective(s)	The primary objective of this study is to demonstrate superiority of either QVM149 150/50/80 µg o.d. to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. to QMF149 150/320 µg o.d. all delivered via Concept1 in terms of trough FEV_1 after 26 weeks of treatment in patients with asthma.
Secondary Objectives	The key secondary objective is to demonstrate the superiority of either QVM149 150/50/80 µg o.d. to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. to QMF149 150/320 µg o.d., all delivered via Concept1, in terms of ACQ-7 after 26 weeks of treatment in patients with asthma.
Study design	52 weeks multi-center, randomized, double-blind, double-dummy, parallel-group, active controlled study
Population	The study population will consist of approximately 2980 males and females with asthma.
Inclusion criteria	1. Male and female adult patient ≥ 18 years old and ≤ 75 years. 2. Written informed consent must be obtained before any study-related assessment is performed. 3. Patients with a diagnosis of asthma, (GINA 2015) for a period of at least 1 year prior to Visit 1 (Screening). 4. Patients who have used medium or high dose of ICS/LABA combinations (Appendix 10) for asthma for at least 3 months and at stable medium or high doses of ICS/LABA for at least 1 month prior to Visit 1. 5. Patients must be symptomatic at screening despite treatment with mid or high stable doses of ICS/LABA. Patients with ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (before randomization). • In case that the spirometry is repeated due to a failure of meeting criterion 7, ACQ-7 should be repeated as well. 6. Patients with documented history of at least one asthma exacerbation which required medical care from a physician, ER visit (or local

	equivalent structure) or hospitalization in the 12 months prior to Visit 1, and required systemic corticosteroid treatment. • Previous asthma exacerbation in this context is based on patient´s recall of unplanned need for medical care at any primary care physician, pulmonologist, emergency room or hospital AND requiring treatment with systemic corticosteroids due to asthma exacerbation. • Investigator must use appropriate means to ensure the accuracy of the patient's exacerbation history (e.g., patient history at Visit 1 documented in source notes, pharmacy records, hospital records, or chart records are acceptable). 7. Pre-bronchodilator FEV_1 of < 80 % of the predicted normal value for the patient according to AST/ERS guidelines after withholding bronchodilators (Table 5-2) at both Visits 101 and 102. • Withholding period of bronchodilators prior to spirometry: • SABA for ≥ 6 hrs • twice daily LABA (or fixed dose combination (FDC) of ICS/LABA) for ≥ 12 hrs • once daily LABA (or FDC of ICS/LABA) for ≥ 24 hrs, • SAMA for ≥ 8 hrs • short acting xanthines for ≥ 12 hrs • long acting xanthines for ≥ 24 hrs. • A one-time repeat of percent predicated FEV1 (Pre-bronchodilator) at Visit 101 and/or Visit 102 is allowed. Repeat spirometry should be done in an ad-hoc visit to be scheduled on a date that would provide sufficient time to receive confirmation from the spirometry data central reviewer of the validity of the assessment before randomization in case of repeat Visit 101. • A one time rescreening is allowed provided the patient returned to the required treatment as per inclusion criteria 4. 8. Patients who demonstrate an increase in FEV_1 of ≥ 12% and 200 mL within 15 to 30 minutes after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at Visit 101. All patients must perform a reversibility test at Visit 101. If reversibility is not demonstrated at Visit 101 then one of the following criteria need to be met : • Reversibility should be repeated once. • Patients may be permitted to enter the study with historical evidence of reversibility that was performed according to ATS/ERS guidelines within 2 years prior to Visit 1. • Alternatively, patients may be permitted to enter the study with a historical positive bronchoprovocation test that was performed within 2 years prior to Visit 1. If reversibility is not demonstrated at Visit 101 (or after repeated/re-tested assessment in an ad-hoc visit) and historical evidence of reversibility/bronchoprovocation is not available (or was not performed according to ATS/ERS guidelines) patients must be screen failed. Spacer devices are permitted during reversibility testing only. The Investigator or delegate may decide whether or not to use a spacer for the

[redacted]

	reversibility testing.
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 (Screening). • 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 treated with a LAMA for asthma within 3 months prior Visit 1 (Screening). • 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 (Screening) or between Visit 1 and Visit 102. 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 • Patients on Maintenance Immunotherapy (desensitization) for allergies for less than 3 months prior to Visit 101 or patients on Maintenance Immunotherapy for more than 3 months prior to Visit 101 but expected to change throughout the course of the study.
Investigational and reference therapy	The Investigational treatments are as follows: • QVM149 (indacaterol acetate/ glycopyrronium bromide/MF) 150/50/80 µg o.d. delivered as powder in capsules via Concept1 • QVM149 (indacaterol acetate/glycopyrronium bromide/MF) 150/50/160 µg o.d. delivered as powder in capsules via Concept1 The Comparative treatments are: • QMF149 (indacaterol acetate/MF) 150/160 µg o.d. delivered as powder in capsules via Concept1 • QMF149 (indacaterol acetate/MF) 150/320 µg o.d. delivered as powder in capsules via Concept1 • salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d. delivered as powder via Accuhaler® In addition the following placebo will be provided to enable the double-dummy design of the study: • Placebo delivered as powder in capsules via Concept1 Placebo delivered as powder via Accuhaler®
Efficacy assessments	• Spirometry • Health Status (PROs)

[redacted]

	• e-Diary • Peak Expiratory Flow • Rescue Medication Use • Asthma Exacerbation
Safety assessments	• Medical history and physical examination including oropharyngeal examination • Vital signs • Hematology, Blood chemistry, Urinalysis • Evening plasma cortisol • ECG • Adverse events and serious adverse events • Pregnancy (female patients) • Serious asthma outcomes (asthma-related hospitalizations, intubations or deaths) • CCV events and new onset of atrial fibrillation
[redacted]	
Data analysis	**The primary objective** of this study is to demonstrate superiority of either QVM149 150/50/80 µg o.d. to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. to QMF149 150/320 µg o.d. all delivered via Concept1 in terms of trough FEV_1 after 26 weeks of treatment in patients with asthma. The comparisons of QVM149 150/50/80 µg o.d. vs. QMF149 150/160 µg o.d. and QVM149 150/50/160 µg o.d. vs. QMF149 150/320 µg o.d., all delivered via Concept1, will be evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a): H_0: QVM149 treatment group is equal to QMF149 treatment group in trough FEV_1 at Week 26 H_a: QVM149 treatment group is not equal to QMF149 treatment group in trough FEV_1 at Week 26 The primary variable will be analyzed using a mixed model for repeated measure (MMRM) on the FAS. The model will contain treatment, region, visit (Days 2, 184 and 365), and treatment-by-visit interaction as fixed effects with baseline FEV_1 measurement, baseline-by-visit interaction, FEV_1 prior to inhalation and FEV_1 within 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates, and center nested within region as a random effect. The estimated adjusted treatment difference (QVM149-QMF149) will be displayed along with the associated standard error, 2-sided 95% confidence interval (CI), and p-value (2-sided). **The key secondary objective** of this study is to demonstrate superiority of either QVM149 150/50/80 µg o.d. to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. to QMF149 150/320 µg o.d. all delivered via Concept1. in terms of ACQ-7 after 26 weeks of treatment in patients with asthma. The key secondary endpoints will be analyzed using the same MMRM model (including all available visits) on the FAS as used for the primary

[redacted]

	analysis but will include baseline ACQ-7 score instead of baseline FEV_1. **Multiplicity Adjustment** To control the family-wise type-I error rate at the two-sided 5% significance level, a graphic testing procedure based on the generalized Simes test in Maurer et al (2011) is used. The family for the overall type-I error rate control contains total four hypotheses including: two hypotheses for the primary endpoint trough FEV_1, and two hypotheses for the key secondary endpoint ACQ-7. Denote the two hypotheses for the primary endpoint as H1 and H2 for comparing QVM149 150/50/80 µg o.d. versus QMF149 150/160 µg o.d. and QVM149 150/50/160 µg o.d. versus QMF149 150/320 µg respectively. Similarly, denote the two hypotheses for the key secondary endpoint ACQ-7 as H3 and H4, for comparing QVM149 150/50/80 µg o.d. versus. QMF149 150/160 µg o.d. and QVM149 150/50/80 µg o.d. versus. QMF149 150/320 µg o.d. respectively. Below is a brief description of the testing procedure based on the generalized Simes test in Maurer et al (2011). Let p_1, p_2, p_3, p_4 be the corresponding p-values (2-sided) of the four hypotheses of H1, H2, H3, and H4. Step 1: Retain all four hypotheses if $p_i<=0.05$ **AND** the observed treatment difference for the corresponding p_i is in the wrong direction (i.e. QMF149 is performing better than QVM149) for **ANY** i=1, 2, 3, 4, stop here; otherwise go to step2; Step 2: Reject all four hypotheses if $p_i<0.05$ for **ALL** i=1, 2, 3, 4 and stop here; otherwise go to step 3; Step 3: If neither step 1 or 2 applies, perform a closed successive weighted Bonferroni test as given in Figure 9-1. The initial weights of 0.5 to H1 (corresponding to 0.025 alpha level, 2-sided) and 0.5 to H2 (corresponding to 0.025 alpha level, 2-sided) were assigned. Here is a brief summarization of the successive weighted Bonferroni test based on Bretz et al (2011): If null H1 is rejected at the initial significance level of 0.025, then H3 can be tested at the significance level of 0.025. Similarly, if null H2 is rejected at the initial significance level of 0.025, then H4 can be tested at the significance level of 0.025. If neither primary null hypothesis can be rejected at the initial significance levels, then the testing stops and efficacy cannot be claimed for neither of the doses and endpoints. Otherwise the graph is sequentially updated with reallocated weights after each hypothesis is rejected. In addition, if efficacy can be shown for one of the doses on both the primary and key secondary endpoint at the initial significance level, the associated weight is passed on to the other dose for further testing.
Key words	QVM149, QMF149, asthma

[redacted]

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 2015).

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 (DALYs) are lost annually due to asthma, representing 1% of the total global burden. Annual worldwide deaths have been estimated at 250,000 (Masoli, 2004).

Recently, tiotropium (Spiriva® Respimat®) has been approved in EU as an add-on maintenance bronchodilator treatment in adult patients (≥ 18 years) with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥ 800µg budesonide/day or equivalent) and long-acting beta2-agonists and who experienced one or more severe exacerbations in the previous year.

Following tiotropium regulatory approval in asthma, GINA 2015 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-Ig E.

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 2015 Step ≥ 4).

In parallel, Novartis is developing QMF149, which is a fixed dose combination of mometasone furoate (MF) and indacaterol, in the Concept 1 device.

Data from mono-components:

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.

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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 2015). 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).

Glycopyrronium bromide (50 µg once daily in a lactose-based formulation) is registered in the EU since 2012 as Seebri® Breezhaler® (Concept1) for the treatment of COPD. Glycopyrronium bromide 50 µg has demonstrated clinically meaningful and statistically significant improvements in lung function in COPD patients which is sustained over 24 hours and provides significant symptomatic benefits with a favorable safety and tolerability profile. The fixed dose combination of indacaterol maleate and glycopyrronium bromide is also registered in the EU as Ultibro®, Breezhaler® (QVA149) with the same doses as proposed for QVM149. 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.

QVM149:

The MF doses in QMF149 program with Concept1 device are comparable to MF 200 µg, 400 µg and MF 800 µg (400 µg b.i.d.) in Twisthaler® device as demonstrated in study (CQMF149E2101, Vaidya S 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 fine particle mass (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

[redacted]

program, respectively. In this current study the mid and high doses of MF (see Appendix 10) 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 mid 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 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.

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

1.2 Purpose

The purpose of the trial is to evaluate the efficacy and safety of two different doses of QVM149 (QVM149 150/50/80 µg and QVM149 150/50/160 µg via Concept1) over two respective QMF149 doses (QMF 150/160 µg and QMF 150/320 µg via Concept1 in poorly controlled asthmatics as determined by pulmonary function testing and effects on asthma control.

2 Study objectives

The primary and key secondary objectives will consider the following 2 comparison groups:

- QVM149 150/50/80 µg o.d. compared with QMF149 150/160 µg o.d. both delivered via Concept1
- QVM149 150/50/160 µg o.d. compared with QMF149 150/320 µg o.d, both delivered via Concept1

The secondary objectives will consider the following 4 comparison groups:

- QVM149 150/50/80 µg o.d. compared with QMF149 150/160 µg o.d. both delivered via Concept1
- QVM149 150/50/160 µg o.d. compared with QMF149 150/320 µg o.d. both delivered via Concept1
- QVM149 150/50/80 µg o.d. compared with salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. via Accuhaler®

[redacted]

- QVM149 150/50/160 µg o.d. compared with salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. via Accuhaler®

2.1 Primary objective

The primary objective of this study is to demonstrate superiority of either QVM149 150/50/80 µg o.d. to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. to QMF149 150/320 µg o.d, all delivered via Concept1 in terms of trough Forced Expiratory Volume in 1 second (FEV_1) after 26 weeks of treatment in patients with asthma.

2.2 Key Secondary objectives

The key secondary objective of this study is to demonstrate superiority of either QVM149 150/50/80 µg o.d. to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. to QMF149 150/320 µg o.d. all delivered via Concept1 in terms of asthma control as assessed by the Asthma Control Questionnaire (ACQ-7) after 26 weeks of treatment in patients with asthma.

2.3 Secondary Objectives

The secondary objectives will consider the 4 comparison groups explained above and will evaluate the following efficacy endpoints:

- Trough FEV_1 after 52 Weeks treatment
- Pre-dose FEV_1 and FVC (defined as the mean of -45 min and -15min FEV_1 values pre-evening dose) at Week 4 and Week 12
- FEV_1, Forced Vital Capacity (FVC) and Forced Expiratory Flow between 25% and 75% of FVC (FEF_{25-75}) over 52 weeks
- Morning and Evening Peak Expiratory Flow Rate (PEF) over 26 and 52 weeks of treatment
- Asthma control as assessed by the Asthma Control Questionnaire (ACQ-7) over 52 weeks
- Percentage of days with no symptoms, the percentage of days with no awakenings and the percentage of mornings with no symptoms on rising over 52 weeks of treatment
- Percentage of days without rescue medication usage (salbutamol(albuterol) as recorded by e-diary over 26 and 52 weeks of treatment,
- Percentage of patients achieving the minimal important difference (MID) ACQ $\geq$ 0.5 at Week 26 and Week 52
- To evaluate the efficacy in terms of asthma exacerbation-related parameters described here further during 52 weeks of treatment. The analysis will be performed by exacerbation category wherever specified. The exacerbation categories are: mild, moderate, severe and moderate or severe:
  - Time to first hospitalization for asthma exacerbation
  - Time to first asthma exacerbation by exacerbation category
  - Annual rate of asthma exacerbations excluding measurements in patients requiring chronic corticosteroid use after an exacerbation (beyond permitted steroid taper for exacerbation) by exacerbation category
  - Duration in days of asthma exacerbations by exacerbation category
  - Percentage of patients with at least one asthma exacerbation by exacerbation category

[redacted]

  - Time in days to permanent discontinuation of study medication due to asthma exacerbations
  - Percentage of patients who permanently discontinued study medication due to asthma exacerbations
  - Total amounts of systemic corticosteroids (in doses) used to treat asthma exacerbations.
- % of rescue medication free days over 26 and 52 weeks of treatment
- Quality of life as assessed by Asthma Quality of Life Questionnaire (AQLQ) over 52 weeks.
- Furthermore, as an additional secondary comparison, QVM149 150/50/80 µg o.d. and QVM149 150/50/160 µg o.d. delivered via Concept1 will be compared with salmeterol xinafoate /fluticasone propionate 50/500 µg via Accuhaler® for all the listed secondary endpoints above as well as the following ones:
  - Trough FEV_1 measured after 26 weeks of treatment
  - Asthma control as assessed by the Asthma Control Questionnaire (ACQ-7) after 26 weeks treatment

The following safety and tolerability endpoints will be evaluated for all treatment comparison groups:

- Cumulative incidence of the composite endpoint of serious asthma outcomes (i.e. asthma-related hospitalization, asthma-related intubation, or asthma-related death) and CCV events/atrial fibrillation over 52 weeks of treatment
- Adverse events, vital signs, ECG and laboratory analysis (haematology, blood chemistry including glucose and potassium, urinalysis) and treatment discontinuation due to adverse event over 52 weeks of treatment.
- Plasma evening cortisol over 52 weeks of treatment

3 Investigational plan

3.1 Study design

This study uses a 52 week treatment, randomized, double-blind, double-dummy, parallel-group design. There is a screening visit (Visit 1) where informed consent is obtained and current asthma and other non-asthma medications are reviewed. Where appropriate, concurrent asthma and other medications are adjusted at this visit and prohibited medications are replaced with permitted asthma medications for use throughout the study.

All patients must have used inhaled LABA/ICS for at least 3 months and been on stable mid or high dose LABA/ICS for at least 1 month prior to Visit 1. Once patient's concurrent medications comply with the requirements of the study (Table 6-1), patients will enter a Run-In epoch at Visit 101. At Visit 101 all patients will receive an open-label "medium" dose of ICS combined with LABA, salmeterol xinafoate/fluticasone propionate 50/250 µg b.i.d., which will be used throughout the Run-In epoch and stopped at Visit 102 (Figure 3-1).

The screening epoch between Visit 1 and Visit 101 is used to ensure wash-out of prior asthma medication according to the protocol. Depending on prior asthma medications at the time of Visit 1, the time period between Visit 1 and Visit 101 may be shorter than 2 weeks. At Visit 1, all patients will be given salbutamol/albuterol to use as rescue medication throughout the study and will be given an electronic diary combined with Peak Flow (PEF) meter to record asthma symptoms and rescue medication use. After the end of the screening epoch (maximum 2 weeks after Visit 1)/starting in the Run-In epoch (Visit 101), patients will be record PEF.

The Run-In epoch is of 2 weeks duration and will be used to assess eligibility of the patients to enter the treatment epoch and to collect baseline values for some variables. Run-in medication should be dispensed once spirometry assessments meet inclusion criteria (ATS/ERS quality criteria, FEV1 % predicted normal value, and reversibility) as per equipment.

At Visit 102 patients whose eligibility is confirmed will be randomized to one of the five treatment groups with an equal (1:1:1:1:1) ratio:

- QVM149 150/50/80 µg o.d. delivered via Concept1
- QVM149 150/50/160 µg o.d. delivered via Concept1
- QMF149 150/160 µg o.d. delivered via Concept1
- QMF149 150/320 µg o.d. delivered via Concept1
- Salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. delivered via Accuhaler®.

Visits 102 and 201 take place sequentially on the same date. The assessments at Visit 102 should be performed prior to administration of the first dose of study medication. Randomized patients will enter the 52 week treatment epoch during which they will be required to inhale study medication via Concept1 once daily in the evening (between 5:00 and 8:00 pm) and twice daily via Accuhaler® once in the morning (between 5:00 and 8:00 am) and once in the evening 12 hours after the morning dose (between 5:00 and 8:00 pm).

Patients will be followed at regular intervals throughout the 52 weeks treatment epoch to assess the safety and efficacy of treatment, either by telephone or at clinic visits. Clinic visits are scheduled to take place after 4, 12, 26, 36 and 52 weeks. All clinic visits should occur as scheduled on the Table 6-1. For Visit 214 (Week 52), in case of logistical issues, the visit is allowed to take place within a 4 days window. All patients will be required to attend the clinic to perform trough measurements of lung function (24 hours post dosing) after the first dose of study medication (Visit 201) and after the dose of study medication administered at the clinic after 26 and 52 weeks of treatment (Clinic Visits 207 and 214). Telephone reviews of patients' status will be conducted after 8, 16, 20, 28, 32, 40, 44 and 48 weeks of treatment. Telephone contacts with patients may indicate that a clinic visit is necessary, in which case an unscheduled clinic visit should be arranged as soon as possible and should include safety assessment (AEs/asthma exacerbation, safety laboratory exams as needed, concomitant medication)

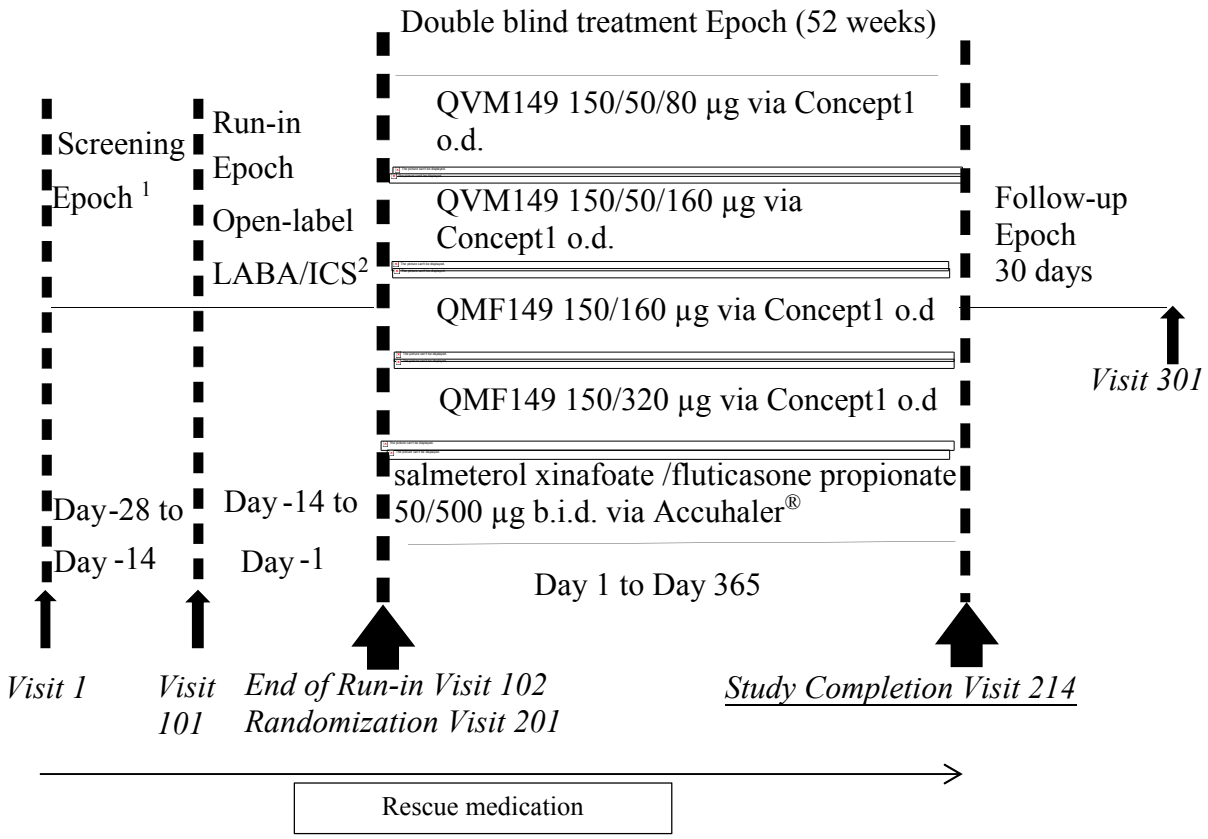
A final telephone contact must be conducted at 30-days after last treatment date (telephone Visit 301). Clinic Visit 214 Day 365 (in the morning) is the last dosing day of the treatment period. Day 365 the second part of the Visit 214 will take place for trough measurements to be made.

The first dose of study medication will be administered at the clinic in the evening (between 5:00 and 8:00 pm) at Visit 201 (Day 1). 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 study medication on the days of the clinic visits, as these doses will be administered at the clinic under the supervision of study personnel. Patients will also be reminded to take the morning dose of study medication on the morning of the Clinic Visit appointment at home.

[redacted]

[redacted] Evening plasma cortisol will be measured on all patients only at Visits 201, 207 and 214.

Figure 3-1 Study design



[1] Please refer to Table 5-2 for details of adjustments to concomitant asthma medication and appropriate washout times prior to spirometry testing

[2] Open-label salmeterol xinafoate/fluticasone propionate 50/250 µg b.i.d. via Accuhaler®

3.2 Rationale of study design

This study is a pivotal, multi-center, randomized, double-blind, double-dummy, parallel-group, phase III study with a 52 week treatment epoch. In order to preserve the integrity of the study, a randomized, double-blind study design is used. This design is well-established in respiratory clinical trials and enables the study treatments to be given for an appropriate and practical length of time to assess the efficacy and safety of the treatments. The study design does not include a placebo control, as this would not be considered ethical in this population of asthmatic patients, GINA step ≥ 4, whose symptoms are inadequately controlled with mid or high ICS/LABA doses (GINA, 2015).

The primary objective of the trial is to evaluate the efficacy and safety of two different doses of QVM149 (QVM149 150/50/80 µg and QVM149 150/50/160 µg via Concept1) over two respective QMF149 doses (QMF149 150/160 µg and QMF149 150/320 µg via Concept1) in poorly controlled asthmatics as determined by pulmonary function testing, effects on asthma

[redacted]

control and rescue medication use. In addition secondary endpoints will provide data on asthma exacerbations, quality of life, [redacted] will establish the long term safety of the two QVM149 doses in this specific asthma patient population.

The analyses will be performed in a sample size of approximately 2980 patients to ensure the adequacy and reliability of the data.

An independent semi-blinded Data Monitoring Committee is planned to evaluate the safety data during the trial to ensure patients' safety throughout the study. Details are given in Section 8.4

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

QVM149 will be in a similar lactose-based formulation and the same inhalation device as QMF149 and selection of the QVM149 combination product doses (150/50/80 µg o.d. and 150/50/160 µg o.d.) for evaluation in Phase III for asthma is based on the doses of the constituent monotherapies which have been approved for either COPD or asthma.

Indacaterol acetate:

Indacaterol maleate at a dose of 150 µg o.d. is marketed for the maintenance treatment of COPD. A dose-ranging study of indacaterol maleate in asthmatic patients demonstrated that a dose of 150 µg o.d. was safe and effective (Study CQAB149B2357). The acetate salt of indacaterol was found to result in a lower incidence of the post-inhalation cough, observed for indacaterol maleate, without impact on efficacy or safety CQAB149D2301. The dose of indacaterol acetate 150 µg was also confirmed in Study CQMF149E2203 in adult asthma patients where indacaterol acetate 150 µg and 75 µg delivered via Concept1 to placebo were investigated. Indacaterol acetate 150 µg showed positive trends in terms of trough FEV_1, PEF and rescue medication use compared with indacaterol acetate 75 µg. In study QMF149A2210, QMF149 150/160 µg o.d. showed beneficial effects on asthma exacerbations in terms of the time to first exacerbation and the cumulative incidence of serious asthma exacerbations. Therefore, a dose of indacaterol acetate 150 µg o.d. has been selected for use in the QVM149 program.

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

Mometasone furoate:

Since available data for the MF component exists in the Twisthaler® device, a 3 step bridging approach was conducted to determine MF dose for Concept1 which is comparable to each of the registered daily doses of Asmanex® Twisthaler® (mometasone furoate, inhalation powder). This is due to difference in device performance characteristics between the Twisthaler® and Concept1 devices. Step 1: pharmacokinetic bridging utilizing pharmacokinetic characterization in study CQMF149E2101 (Vaidya S et al, 2012) followed by in-vitro fine particle mass adjustment (step 2) and finally pharmacodynamic evaluation of efficacy in asthma patients in study CQMF149E2201 (step 3).

[redacted]

For Step 1 and 2, the data of study CQMF149E2101 (Vaidya S et al, 2012), along with in-vitro fine particle mass adjustments have led to the selection of 80, 160 and 320 µg as doses of MF in Concept1 device that are comparable to the approved doses 200 µg, 400 µg and 800 µg (2x400 µg) MF in Twisthaler®.

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

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

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

Glycopyrronium bromide:

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

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

Tiotropium 5ug once daily has recently been approved in Europe for treatment of asthma as add on to high dose LABA/ICS in patients with a history of exacerbations. It is recommended by GINA guideline (GINA 2015) as an add-on option (on top of the preferred controller choice) for Steps 4 and 5 in patients aged ≥ 18 years with a history of exacerbations.

[redacted]

It is expected that glycopyrronium bromide 50 µg once-daily will provide similar efficacy in an asthma population.

The two LAMAs, glycopyrronium and tiotropium both demonstrate similar kinetic selectivity for M3 over M2 receptors, which is important for their similar long and sustained bronchodilator effects (Testi 2014).

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

This current study will compare two doses of QVM149 150/50/80 µg and 150/50/160 µg with the respective two doses of QMF149 150/160 µg and QMF149 150/320 µg. The purpose is to investigate the additional benefit of glycopyrronium bromide 50 µg on top of mid and high ICS/LABA doses (FDCs) in this population of patients whose asthma is inadequately controlled with mid/high ICS/LABA (symptomatic patients with an ACQ ≥ 1.5).

This study is designed to provide efficacy and safety data over a 52 week treatment epoch which is considered to be sufficient duration to demonstrate treatment differences of the two QVM149 doses, QVM149 150/50/80 µg and QVM149 150/50/160 µg o.d. delivered via Concept1 vs the two QMF149 doses, QMF149 150/160 µg as well as QMF149 150/320 µg o.d. delivered via Concept1 in terms of lung function, symptom control and other endpoints.

3.4 Rationale for choice of comparator

QMF149 was selected as the comparator in this study in order to demonstrate the additional benefit of glycopyrronium bromide on top of QMF149 medium and high dose of MF in patients whose asthma is inadequately controlled with mid/high dose ICS/LABA.

Two doses of QMF149 (150/160 µg and 150/320 µg via Concept1) as comparator will be used based on previous available data.

The early QMF149 development program in Twisthaler® consisted of two dose-ranging studies of indacaterol maleate Twisthaler® (one in asthma and one in COPD) and eight clinical studies of FDC QMF149 Twisthaler® to assess the efficacy, safety tolerability and pharmacokinetics of multiple doses of indacaterol and QMF149 via Twisthaler®.

In study CQMF149A2210, 1508 asthmatic patients including 4.4% of adolescents were treated. In this study QMF149 500/400 µg o.d. via Twisthaler® (comparable to QMF149 150/160 µg o.d. via Concept1) was compared with MF alone 400 µg o.d. via Twisthaler®. The findings of this safety study demonstrated that both QMF149 and MF had beneficial effects on asthma exacerbations in terms of the time to first exacerbation and the cumulative incidence of serious asthma exacerbations (with treatment differences in favor of QMF149 over MF). Furthermore, the differences between treatments for efficacy parameters, in terms of lung function and asthma symptoms were all statistically significant in favor of QMF149 throughout the treatment period, with treatment differences in trough FEV_1 between the QMF149 and MF treatment groups of 100 to 140 mL in favor of QMF149 throughout the study period (Beasley R et al, 2012).

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

3.5 Purpose and timing of interim analyses/design adaptations

It is planned that the independent data monitoring committee (DMC) will review semi-blinded (i.e., treatment group named as A, B, C, D or E) safety data.

The details of the information flow, confidentiality and specific analyses required for the safety monitoring analysis will be documented in the DMC Charter.

[redacted]

For Primary Analysis at Week 26

The primary and key secondary endpoints of CQVM149B2302 study are trough FEV_1 and ACQ-7 after 26 weeks of treatment, respectively while the entire study treatment period is 52 weeks. Novartis has decided to perform primary analysis once all patients have completed 26 weeks of treatment (Visit 207) or prematurely withdrawn from the study which will be used for internal decision making prior to study completion. The study will continue as planned in a blinded manner for full 52 weeks period (plus 30 days of safety follow-up).

In terms of reporting, two separate CSRs will be written:

- CSR I: To support analyses once all patients have completed the assessments after 26 weeks of treatment (Visit 207) or prematurely withdrawn from the study. This will consist of primary and key secondary objectives as well as other pre-specified objectives up to and including Week 26. The CSR will be based on variable duration of exposure with minimum of 26 weeks (Visit 207) and maximum of 52 weeks (Visit 214)
- CSR II: To support analysis once all patients have completed 52 weeks of treatment (Visit 214) plus follow up (Visit 301) or prematurely withdrawn from the study. CSR II will consist of primary and secondary objectives analyzed in CSR I and all other objectives evaluated after 26 weeks and up to 52 weeks (plus follow up).

Since the primary analysis (CSR I) will be performed prior to all patients completing the study, a dedicated unblinded team will be involved in CSR I related activities. In order to maintain the integrity of the study data, a separate blinded team will continue the study until its completion. The details outlining this process including appropriate firewalls will be maintained in a separate charter.

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3.6 Risks and benefits

The favorable benefit-risk ratio based on QMF149 in asthma and glycopyrronium bromide (NVA237) in COPD as well as the so far acquired knowledge about LAMA (tiotropium) on top of LABA/ICS in asthma is the rationale to conduct this study with glycopyrronium bromide on top of QMF149 as a FDC in asthma.

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

Kerstjens et al showed that tiotropium on top of high dose ICS/LABA improved lung function and significantly prolonged time to first severe exacerbation (Kertjens 2012).

The benefit of adding a muscarinic antagonist in the treatment of poorly controlled asthma is supported by two replicate studies which compared tiotropium to placebo (Kertjens 2012). The addition of tiotropium increased the time to the first severe exacerbation (282 days vs. 226 days), with an overall reduction of 21% in the risk of a severe exacerbation.

The available asthma clinical trial data suggest that a LAMA may confer bronchodilator effects in terms of improved lung function when used in addition to ICS alone or in conjunction with LABA/ICS (i.e., “free combination” or “loose” triple therapy) (Fardon 2007, Peters 2010, Bateman 2011, Kerstjens 2011, Kerstjens 2012, Guyer 2013). A review evaluating the efficacy profile of a LAMA (tiotropium) as add-on therapy to ICS or LABA/ICS in patients with uncontrolled moderate to severe persistent asthma concluded that the addition of a LAMA resulted in significant improvements in lung function (FEV_1 and peak expiratory flow) (Befekadu 2014).

Thus, triple therapy could provide an alternative treatment option to theophylline, systemic corticosteroids or biologics for GINA Step ≥ 4 asthma patients inadequately controlled on medium- or high-dose LABA/ICS.

There is an extensive evidence of the efficacy and safety of the two dual combinations indacaterol acetate/mometasone furoate (QMF149) and indacaterol maleate/glycopyrronium bromide (Ultibro®) which is part of the FDC triple QVM149 components. A QMF149 Twisthaler® program in phase II along with further phase II studies in Concept1 suggest a favorable efficacy and safety of the QVM149 compound.

In one large phase II event driven trial with a duration up to 68 weeks in over 1500 asthma adults and adolescent patients, QMF149 (indacaterol acetate/mometasone furoate 500/400 µg delivered by Twisthaler® comparable to indacaterol acetate/mometasone furoate 150/160 µg delivered by Concept1) a favorable efficacy and safety profile of QMF149 over MF was shown (Beasley et al 2015). Further efficacy and safety trials in phase II included different indacaterol doses on background of MF in Concept1 in moderate to severe asthma (CQMF149E2203), a device bridging study with MF from Twisthaler® to Concept1 (CQMF149E2201) and an efficacy and safety study with QMF149 in Concept1 in moderate to very severe COPD (CQMF149F2202). The studies showed statistically significant

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improvements in lung function and symptomatic endpoints including exacerbations and confirmed a favorable and robust efficacy and safety profile in phase II.

Glycopyrronium bromide 50 µg is approved for the maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Evidence for the efficacy and safety of glycopyrronium bromide has been extensively provided via studies in 5,489 healthy subjects and COPD patients across 22 completed studies.

Addition of LAMA (tiotropium 5 µg Respimat®) to ICS/LABA is now a recommended treatment option in GINA 2015 guideline for step 4 onwards. As glycopyrronium and tiotropium (HandiHaler®) demonstrated comparable efficacy and safety in COPD, it is reasonable to expect that both drugs would show similar risk/benefit profiles in asthma.

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

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

In this current Phase III pivotal study, two QVM149 doses will be compared to two QMF149 doses and to salmeterol xinafoate/fluticasone propionate (Seretide®) during 52 weeks of treatment period. Participating patients in this study will be randomized to receive either one of the two doses of QVM149 or one of the two doses of QMF149 or salmeterol xinafoate/fluticasone propionate. The use of other controller medications, i.e. sustained release theophylline, leukotriene modifiers and monoclonal antibody (IgE inhibitor, IL-5 inhibitor) in stable doses will be permitted due to the severity of the disease and as treatment guideline (GINA 2015). The expected potential benefit for the patient include an improvement in the pulmonary function, a potential translation into better asthma control like reductions in symptoms, rescue medication use and lower frequency/ severity of asthma exacerbations, and an improved quality of life. A thorough medical evaluation of the patients' disease and close clinical monitoring for the duration of the study will provide additional benefit to the patient care.

Frequent and regular contacts will occur in terms of clinic visits and telephone contacts to each patient throughout the 52-week treatment epoch**. In addition, safety monitoring (e.g. symptom collection and rescue medication use via electronic diary), assessment of compliance with the study medication regimen, and PEF (daily) measurements at regular intervals throughout the study will help assess status of the patient's asthma symptom control.** Therefore, investigators may have an early indication of worsening symptoms and will be able to monitor the patient closely throughout the study.

[redacted]

In line with current medical treatment guidelines, all patients participating in the study will receive active "controller" treatment (minimum of ICS/LABA) for their asthma throughout the 52-week treatment period. In addition, providing the patients with rescue medication for use as needed to treat any breakthrough constriction throughout study mitigates these risks. At no time, will any patient be without treatment for asthma.

The risk to the patients in the study is that QVM149 and QMF149 are both under development and therefore it is possible that unexpected safety issues may be identified (Section 5.4.9) and the risk will be minimized by compliance with the eligibility criteria and close clinical monitoring of patients. The risks of side effects from the study medication are those known for the individual compounds indacaterol acetate, glycopyrronium bromide and MF. 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 and QMF149 Investigator's Brochure.

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

Guidance to manage potential worsening of asthma symptoms will be provided to investigators consistent with guideline recommendations (GINA 2015). 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 150/50/80 µg and QVM149 150/50/160 µg will have a favorable benefit to risk profile in patients with asthma.

4 Population

The study population will consist of approximately 2980 male and female patients with asthma.

It is anticipated that approximately 4967 patients will need to be screened in order to randomize approximately 2980 patients into the five treatment groups of the study with a randomization ratio of 1:1:1:1:1, (i.e. approximately 596 patients in each of the treatment groups). It is intended that at least 2680 patients (536 patients per treatment group) will have completed 26 weeks of treatment for analysis of primary and key secondary objectives.

Drop-outs after randomization will not be replaced. This study will enroll multi-nationally and patients will be stratified by region to achieve improved homogeneity within each stratum.

[redacted]

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4.1 Inclusion criteria

1. Male and female adult patient ≥ 18 years old and ≤ 75 years.
2. Written informed consent must be obtained before any study-related assessment is performed.
3. Patients with a diagnosis of asthma, (GINA 2015) for a period of at least 1 year prior to Visit 1 (Screening).
4. Patients who have used medium or high dose of ICS/LABA combinations (Appendix 10) for asthma for at least 3 months and at stable medium or high doses of ICS/LABA for at least 1 month prior to Visit 1.
5. Patients must be symptomatic at screening despite treatment with mid or high stable doses of ICS/LABA. Patients with ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (before randomization).
   - In case that the spirometry is repeated due to a failure of meeting criterion 7, ACQ-7 should be repeated as well.
6. Patients with documented history of at least one asthma exacerbation which required medical care from a physician, ER visit (or local equivalent structure) or hospitalization in the 12 months prior to Visit 1, and required systemic corticosteroid treatment.
   - Previous asthma exacerbation in this context is based on patient´s recall of unplanned need for medical care at any primary care physician, pulmonologist, emergency room or hospital, AND treatment with systemic corticosteroids due to asthma exacerbation.
   - Investigator must use appropriate means to ensure the accuracy of the patient's exacerbation history (e.g., patient history at Visit 1 documented in source notes, pharmacy records, hospital records, or chart records are acceptable).
7. Pre-bronchodilator FEV_1 of < 80 % of the predicted normal value for the patient according to ATS/ERS guideline after withholding bronchodilators (Table 5-2) at both visits 101 and 102.
   - Withholding period of bronchodilators prior to spirometry:
     - SABA for ≥ 6 hrs
     - Twice daily LABA (or FDC of ICS/LABA) for ≥ 12 hrs
     - Once daily LABA (or FDC of ICS/LABA) for ≥ 24 hrs
     - 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.
   - A one-time repeat of percentage predicated FEV1 (Pre-bronchodilator) at Visit 101 and/or Visit 102 is allowed in an ad-hoc visit. Repeat of Visit 101 spirometry should be scheduled on a date that would provide sufficient time to receive confirmation from the spirometry data central reviewer of the validity of the assessment before randomization. **Run-in medication should be dispensed once spirometry assessment met inclusion criteria (ATS/ERS quality criteria, FEV_1 % predicted normal value, and reversibility) as per equipment.**

[redacted]

- A one-time rescreening is allowed in case the patient fails to meet the criteria at the repeat, provided the patient returned to the required treatment as per inclusion criteria 4

8. Patients who demonstrate an increase in FEV_1 of ≥ 12% and 200 mL within 15 to 30 minutes after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at Visit 101. All patients must perform a reversibility test at Visit 101. If reversibility is not demonstrated at Visit 101 then one of the following criteria need to be met:
   - Reversibility should be repeated once
   - Patients may be permitted to enter the study with historical evidence of reversibility that was performed according to ATS/ERS guidelines within 2 years prior to Visit 1.
   - Alternatively, patients may be permitted to enter the study with a historical positive bronchoprovocation test that was performed within 2 years prior to Visit 1.
   - If reversibility is not demonstrated at Visit 101 (or after repeated assessment in an ad-hoc visit) and historical evidence of reversibility/bronchoprovocation is not available (or was not performed according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines patients must be screen failed.
   - 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.

4.2 Exclusion criteria

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

1. Patients who have 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.
2. 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 102 they may be re-screened 6 weeks after recovery from the exacerbation.
3. Patients who have ever required intubation for a severe asthma attack/exacerbation.
4. 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.
5. Patients treated with a LAMA for asthma within 3 months prior to Visit 1 (Screening).
6. 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.
7. Patients who have had a respiratory tract infection or asthma worsening as determined by investigator within 4 weeks prior to Visit 1 (Screening) or between Visit 1 and Visit 102. Patients may be re-screened 4 weeks after recovery from their respiratory tract infection or asthma worsening.

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8. Patients with evidence upon visual inspection (laboratory culture is not required) of clinically significant (in the opinion of investigator) oropharyngeal candidiasis at Visit 102 or earlier, with or without treatment. Patients may be re-screened once their candidiasis has been treated and has resolved.
9. Patients with any chronic conditions affecting the upper respiratory tract (e.g. chronic sinusitis) which in the opinion of the investigator may interfere with the study evaluation or optimal participation in the study.
10. Patients with a history of chronic lung diseases other than asthma, including (but not limited to) chronic obstructive pulmonary disease, sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis and active tuberculosis.
11. Patients with Type I diabetes or uncontrolled Type II diabetes.
12. Patients who have a clinically significant laboratory abnormality at Visit 101.
13. Use of other investigational drugs within 30 days or 5 half-lives of enrollment, until the expected pharmacodynamics effect has returned to baseline, whichever is longer.
14. Patients who, 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 the run-in visit (Visit 101) with a resting ventricular rate < 100/min. At Visit 101 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 101 (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 101 (Start of Run-In epoch) and any time between Visit 101 and Visit 102 (including unscheduled ECG). ECG evidence of myocardial infarction at Visit 101 (via central reader) should be clinically assessed by the investigator with supportive documentation.
20. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.

[redacted]

21. Patients with a history of hypersensitivity to lactose, any of the study drugs or to similar drugs within the class including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof.
22. Patients who have not achieved an acceptable spirometry result at Visit 101 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 at Visit 101 and/or Visit 102. If the patient fails the repeat assessment, the patient may be rescreened once, provided the patient returns to the required treatment as per inclusion criteria 4.
23. Patients receiving any medications in the classes listed in Table 5-3.
24. Patients receiving any asthma-related medications in the classes specified in Table 5-2 unless they undergo the required washout period prior to Visit 101 and Visit 201 and follow the adjustment to treatment program.
25. Patients receiving medications in the classes listed in Table 5-4 should be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met.
26. Patients with severe narcolepsy and/or insomnia.
27. Patients on Maintenance Immunotherapy (desensitization) for allergies for less than 3 months prior to Visit 101 or patients on Maintenance Immunotherapy for more than 3 months prior to Visit 101 but expected to change throughout the course of the study
28. Patients who are serving a custodial sentence, do not have a permanent residence or who are detained under local mental health legislation/regulations.
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, Accuhaler® or a metered dose inhaler. Spacer devices are not permitted for rescue medication.
31. History of alcohol or other substance abuse.
32. 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.
33. Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers).
34. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
35. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 30 days after stopping of study treatment.

    Only the following highly effective contraception methods will be permitted:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject) if allowed as effective method of contraception by local regulations. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking

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study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

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

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

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

The Comparative treatments are:
- QMF149 (indacaterol acetate/MF) 150/160 µg o.d. delivered as powder in hard capsules via Concept1
- QMF149 (indacaterol acetate/MF) 150/320 µg o.d. delivered as powder in hard capsules via Concept1
- Salmeterol xinafoate/fluticasone propionate 50/500 µg b.i.d. delivered as powder via Accuhaler®

In addition the following placebo will be provided to enable the double-dummy design of the study:
- Placebo delivered as powder in capsules via Concept1
- Placebo delivered as powder via Accuhaler®

Under no circumstances is an alternative inhalation device to be used for the administration of the investigational or reference therapies during the treatment period.

[redacted]

5.1.2 Additional study treatment

Starting with Visit 1 (Screening, Day -21) patients will receive short acting beta agonist (salbutamol or albuterol) inhaler to use as rescue medication on an "as needed" basis. The rescue medication will be provided by the sponsor to the patients for the duration of the study. More details regarding rescue medication are in Section 5.4.6

Salbutamol (100 µg) or albuterol (90 µg) will either be supplied to the investigator sites locally by Novartis or provided by the study center and reimbursed by Novartis.

5.1.3 Treatment arms

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

- QVM149 150/50/80 µg o.d. delivered via Concept1, placebo to salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler®
- QVM149 150/50/160 µg o.d. delivered via Concept1, placebo to salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler®
- QMF149 150/160 µg o.d. delivered via Concept1 (in the evening), placebo to salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler®
- QMF149 150/320 µg o.d. delivered via Concept1 (in the evening), placebo to salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler®
- Salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler®, placebo to QVM149 delivered via Concept1 (in the evening).

5.2 Treatment assignment, randomization

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

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by region.

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

[redacted]

5.3 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study.
- The identity of the treatment will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

The bioanalyst will be unblinded to enable identification of samples from the QVM149 and QMF149 arms of the study to facilitate indacaterol, glycopyrronium bromide (QVM149 treated patients only) and mometasone furoate bioanalysis. [redacted]

Unblinding for primary analysis

At the time of primary analysis once all patients have completed the assessments after 26 weeks of treatment (Visit 207), limited pre-specified members will be unblinded. The study will continue under the management of ***a separate blinded*** team who will be responsible for study conduct after the primary analysis (at 26 week) until the end of study. In order to maintain the integrity of the study data, separate blinded team members will not have access to any of the unblinded data. The detailed procedures will be described in a separate charter. The remainder of members including clinical study team, investigators, and patients will be kept blinded until final database lock.

During the study, the individual patient unblinding can occur in the case of patient emergencies, request from the Data Monitoring Committee if needed for the safety interim analysis (Section 8.4) or as an outcome of their evaluation and at the conclusion of the study (see Section 5.4.12). Health authorities will be granted access to unblinded data if needed. Any patient whose treatment code has been broken inadvertently or for any non-emergency reason will be discontinued from the trial.

5.4 Treating the patient

5.4.1 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 should select the CRF book with a matching Subject Number from the EDC system to enter data.

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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 CRF.

5.4.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance.

The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the investigational drugs. Investigator staff will identify the investigational treatment 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.

5.4.3 Handling of study treatment

5.4.3.1 Handling of investigational treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should 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 investigational 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 investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused investigational treatment and packaging at the end of the study or at the time of discontinuation of investigational treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational 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.

5.4.3.2 Handling of other study treatment

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

The non-investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the

[redacted]

investigator and designees have access. Clinical supplies are to be dispensed only in accordance with the protocol.

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

These medications are:

- Salbutamol (100 µg) or albuterol (90 µg) used as rescue medication from Visit 1 to Visit 214
- Salmeterol xinafoate/fluticasone propionate 50/250 µg b.i.d. via Accuhaler® used as run-in medication from Visit 101 to Visit 102

Details are described in the CRF completion guidelines.

5.4.4 Instructions for prescribing and taking study treatment

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

Patients will be provided with medication as described in Section 5.1.

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

At Visit 1 all patients will be instructed how to use a MDI to administer rescue salbutamol/albuterol correctly. At Visit 102 (before randomization), all patients will be fully trained in the correct use of the Concept1 and Accuhaler® inhaler devices used to administer study medication. Patients who are unable to use either device correctly at Visit 102 will not be eligible to enter the treatment epoch. Additional training devices will be supplied for demonstration purposes. At clinic visits the investigator should check the patient's use of the two inhalational devices to ensure that they are using each device correctly. Additional device training should be provided if required.

Patients will be instructed to take both morning and evening doses of study medication at approximately the same time of day (both in the morning and evening). Patients will be instructed to rinse their mouth after inhalation of study drug (2 times with approximately 30 mL water). Water used for mouth rinsing should be spat out and should NOT be swallowed. In the evening when sequential inhalations of study drugs from two devices are required, mouth rinsing should be done after the last inhalation.

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

The evening dose (to be taken between 05:00 and 08:00 pm) will consist of **sequential single inhalations from each of the following two devices:**

[redacted]

- One inhalation from the Concept1 device containing either QVM149, QMF149 or placebo
- One inhalation from the Accuhaler® device containing either salmeterol/fluticasone or placebo

Inhalations from the two devices should be taken as close together as possible. Instructions for use of the Concept1 and Accuhaler® devices are given in Appendix 1 and Appendix 2, respectively.

Table 5-1 Study Treatments

Treatment arm	Morning		Evening	
QVM149 150/50/80 µg	Placebo to Salmeterol/ fluticasone 50/500 µg	Accuhaler®	**QVM149 150/50/80 µg** Placebo to Salmeterol/fluticasone 50/500 µg	Concept 1 Accuhaler®
QVM149 150/50/160 µg	Placebo to Salmeterol/ fluticasone 50/500 µg	Accuhaler®	**QVM149 150/50/160 µg** Placebo to Salmeterol/fluticasone 50/500 µg	Concept 1 Accuhaler®
QMF149 150/160 µg	Placebo to Salmeterol/ fluticasone 50/500 µg	Accuhaler®	**QMF149 150/160** µg Placebo to salmeterol/fluticasone 50/500 µg	Concept 1 Accuhaler®
QMF149 150/320 µg	Placebo to Salmeterol/ fluticasone 50/500 µg	Accuhaler®	**QMF149 150/320** µg Placebo to Salmeterol/fluticasone 50/500 µg	Concept 1 Accuhaler®
Salmeterol/ fluticasone 50/500 µg b.i.d.	Salmeterol/ fluticasone 50/500 µg	Accuhaler®	**Salmeterol/ fluticasone 50/500 µg b.i.d.** Placebo to QVM/QMF	Accuhaler® Concept 1

The study treatment can be taken without regard to sleep, meals, and other activities. On days of scheduled clinic visits, patients should take their evening dose of study treatment at the study center. Therefore patients will be instructed not to take their evening dose of study medication when he/she returns home.

The duration of active treatment is 52 weeks, with the last dose of study treatment occurring in the morning of Day 365 (Visit 214).

All kits of investigational treatment 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.

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

[redacted]

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.

5.4.5 Permitted dose adjustments and interruptions of study treatment

Investigational treatment dose adjustments and/or interruptions are not permitted unless the investigator considers an interruption is necessary for the treatment of an adverse event. Any interruption of study medication should be for the shortest time period possible and recorded in the Dosage Administration Record CRF (e-CRF).

In case of blind broken, the study medication is to be permanently discontinued.

5.4.6 Rescue medication

At Visit 1, all patients will be provided with a short acting β_2-agonist (100 µg salbutamol/90 µg albuterol via MDI) which they will be instructed to use throughout the study as rescue medication. Nebulized salbutamol is not allowed as rescue medication throughout the entire trial. No other rescue treatment is permitted 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 medication (salbutamol) within 6 hours of the start of each visit where spirometry is being performed unless absolutely necessary. If rescue medication is taken within 6 h 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 e-CRF, with the stop date for these bronchodilators recorded as the date of Visit 1. The rescue salbutamol/albuterol provided at Visit 1 for use during the study should NOT be recorded on the asthma-related prior/concurrent medication page of the e-CRF. From Visit 1, daily use of rescue medication (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 in their electronic diary.

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

5.4.7 Concomitant treatment

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

5.4.8 Prohibited Treatment

Prohibited medications, as listed in Table 5-2, must not be taken during the study (unless for the treatment of asthma exacerbations). The specified minimum washout periods prior to the Run-In epoch (Visit 101) and/or randomization (Visit 201) are described in Table 5-2. The classes of medication listed in Table 5-3 are not permitted to be taken during the study. The

[redacted]

medications in Table 5-4 are only permitted under the circumstances given. Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it is allowed. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

Table 5-2 Prohibited asthma-related medications

Class of medication	Minimum washout period prior to Screening (Visit 1), Run-in (Visit 101) and Randomization (Visit 201) [1,2,3]
Long-acting anticholinergics (LAMA)	Must not be used within 3 months prior to Visit 1.
Short acting anticholinergics (SAMA)	Must not be used within 8 hours prior to Visit 101.
Fixed combinations of β_2-agonists and inhaled corticosteroids	Must not be used within 12 hours (24 hours for once daily combination) prior to Visit 101.
Fixed combinations of short-acting β2-agonist and short-acting anticholinergic	Must not be used within 12 hours prior to Visit 101.
Salbutamol/albuterol (SABA) provided at Visit 1 and throughout study as required for rescue medication as needed[4]	Must not be used within 6 hours prior to Visit 101 and Randomization (Visit 102)
Short acting β2-agonists (SABAs) (other than Salbutamol/albuterol provided at Visit 1 for rescue medication)	Must not be used at Visit 1 and are not permitted during the study
Parenteral corticosteroids (systemic corticosteroids are permitted for the treatment of asthma exacerbations)	Must not be used within 4 weeks prior to Run-In (Visit 101)
Intra-muscular depot corticosteroids	Must not be used within 3 months prior to Run-In (Visit 101)

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

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

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

[4] SABA (salbutamol/albuterol rescue medication) should be withheld for at least 6 hours prior to spirometry measurements at clinic visits if possible. Clinic visits may be rescheduled if rescue medication were taken less than 6 hours prior to the spirometry assessments

Table 5-3 Prohibited Medications

Class of medication[1]	Minimum cessation period prior to Run-in (Visit 101)
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug	7 days
Non-selective systemic β –blocking agents	7 days
Cardiac anti-arrhythmics Class Ia	7 days
Cardiac anti-arrhythmics Class III	7 days, amiodarone 3 months
Other drugs with potential to significantly prolong the QT interval	14 days or 5 half-lives, whichever is longer
All antipsychotic agents (first, second and third generation, inclusive of atypical	14 days

[redacted]

Class of medication[1]	Minimum cessation period prior to Run-in (Visit 101)
antipsychotics). Combinations of antipsychotic agents with antidepressants are prohibited	
Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)	14 days
Monoamine-oxidase inhibitors	14 days
Systemic anticholinergics	7 days
Mizolastin or terfenadine (H_1 antagonists)	5 days
Strong inhibitors of cytochrome P4503A e.g. ketoconazole	7 days
Tricyclic antidepressants (Please note that tetracyclics which are similar in class with regards to drug interaction are also to be excluded)	14 days
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Noradrenaline reuptake inhibitors	7 days
Live attenuated vaccine	30 days

[1] This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria. The wash-out of these prohibited medications is not to be encouraged.

Table 5-4 Medications allowed under certain conditions

Class of medication	Condition
Monoclonal antibody: IgE inhibitors (e.g. omalizumab), IL-5 inhibitors (e.g. mepolizumab)	Allowed if at stable dose for at least 3 months prior to Visit 1
Oral corticosteroids*	Allowed if at stable dose for at least 1 month prior to Visit 1 and throughout the study at prednisone equivalent dose of 5 mg daily to 10 mg every other day
Leukotriene Antagonist and leukotriene synthesis inhibitors	Allowed if at stable dose for at least 1 month prior to Visit 1 and throughout the study.
Long-acting theophylline (methylxanthine) preparations	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial. Not administered within 24h prior to study visit.
Short- acting theophylline (methylxanthine)	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial. Not administered within 12h prior to study visit.
Mucolytic agents not containing bronchodilators	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial.
Systemic mast cell stabilizers e.g cromoglycate, nedocromil, ketotifen	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial.
Pure Selective Serotonin Reuptake Inhibitors (they must have no documented effect on any other neurotransmitters or other biological pathways. E.g. muscarinic pathway)	Treatment regimen is stable for at least one month at Visit 1.
Inactivated influenza vaccination,	Not administered within 48 hours prior to a study

[redacted]

Class of medication	Condition
pneumococcal vaccination or any other inactivated vaccine	visit.
Intra-nasal corticosteroids	Stable dose for at least 4 weeks prior to Visit 101 In the case of as needed, provided an established pattern of use has been documented.
Antihistamines (e.g. loratadine, cetirizine)	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial. In the case of as needed, provided an established pattern of use has been documented
Topical corticosteroids for the treatment of eczema	In recommended doses and dosage regimens
Maintenance immunotherapy for allergies	Stable dose for at least 3 months prior to Visit 101 and unchanged throughout study treatment.

* The treatment of asthma exacerbations including the initiation of systemic corticosteroids or increase in the maintenance dose of OCS should be done according to investigator's or treating physician's medical judgement and should be in line with national and international recommendations. If systemic corticosteroids are required, a patient may return to the study after successfully completing a taper of approximately 7-10 days. If longer 7 -10 days is expected, Novartis Medical Monitor should be contacted and the discontinuation of study treatment should be considered.

If patients cannot be safely tapered, oral corticosteroids may be taken chronically after an exacerbation if clinically indicated as per Principal Investigator clinical judgement and in accordance with national/local guidelines (and in doses not to exceed equivalent of prednisone 5mg daily). Dose should be maintained for at least 3 months before tapering.

If indicated for the treatment of an adverse event, including asthma exacerbation, any treatment deemed necessary by treating physician for the safety of the patient is allowed from the start of the event (asthma exacerbations are defined in Section 6.4.5) until the event is resolved. If it is transitioning to chronic treatment, the investigator should discuss with Novartis Medical Monitor. Patients may NOT self-medicate (other than administration of rescue medication) or adjust therapy without permission/guidance from treating physician.

Dosing of biologic therapy (e.g, omalizumab, mepolizumab) should be guided by local labelling.

5.4.9 Discontinuation of study treatment

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 until the scheduled final visit in order to ensure the scientific integrity of the trial.

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.

In addition study treatment *must* be discontinued under the following circumstances:

- 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 during the run-in (e.g. Visit 101) or treatment epochs (e.g. Visit 201).

[redacted]

- If a patient develops a medical condition/AE that requires prolonged use of prohibited treatment as per Section 5.4.8, or if patient exhibits a behavior of non-compliance regarding prohibited medications.

Any other protocol deviation that results in a significant risk to the patient's safety

Discontinuation of study treatment (but continued study participation)

- For this study it is very important to continue collecting data, especially vital status, on all patients whether or not they complete treatment to continue collecting safety information. The patient should NOT be considered withdrawn from the study due to study treatment interruption or discontinuation.
- If premature discontinuation of study treatment occurs, the patient should return to the clinic as soon as possible for a study treatment discontinuation visit. At this study treatment discontinuation visit the assessments listed in Table 5-5 should be completed and recorded in the e-CRF if the discontinuation takes place at a scheduled or unscheduled visit time. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the End of Study Treatment e-CRF page. 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. This telephone contact should preferably be done according to the study visit schedule.
- The data which must continue to be collected for all patients (including those discontinuing the study treatment) are adverse events and serious adverse events for up to 30 days after drug discontinuation and survival status until the end of study follow-up visit (Visit 301).
- Any patient whose treatment code has been broken inadvertently or for any non-emergency reason will be discontinued from the trial.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Table 5-5. If they fail to return for these assessments for unknown reasons, every effort (*e.g.* telephone, e-mail, letter) should be made to contact them as specified in Section 5.4.11.

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

Table 5-5 Table of Assessment for Patients who Discontinue Study Treatment prematurely

Assessment	**Early Study Treatment** Discontinuation Visit	Unscheduled Safety Follow-Up Visit	At time of original Scheduled Clinic Visit	Early Study discontinuation	**Follow-up Visit 301**
Clinic/**T**elephone	C	T	T	T	T
Week	Disc. Date	Disc.date+4 weeks			56
Day	Disc. Date	Disc.date+30 days			395

[redacted]

Assessment	**Early Study Treatment** Discontinuation Visit	Unscheduled Safety Follow-Up Visit	At time of original Scheduled Clinic Visit	Early Study discontinuation	**Follow-up Visit 301**
IRT treatment discontinuation call	X				
Vital Signs	X				
Physical exam	X				
Oropharyngeal examination	S				
Pregnancy test (serum)	X				
Collect study medication	X				
Concomitant medication	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	X	X	X
Safety Lab assessments (haematology, clinical chemistry, urinalysis)	X				
Spirometry[1]	X				
ECG	X				
[redacted]					
ACQ-7 [2]	X				
[redacted]					
Evening Plasma cortisol	X				
Survival Status		X	X	X	X
Record Healthcare visit for asthma worsening	X				
Record end of treatment epoch disposition page				X	

[1] Details of timed assessments are provided in Table 6-2

[2] All PROs assessed at Clinic should be completed before any other assessment. When a scheduled visit is planned on 2 consecutive days the PROs are to be completed on the first day for the discontinuation.

[redacted]

5.4.10 Withdrawal of consent

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

[redacted]

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material.

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

Patients who discontinued from study treatment and from the study simultaneously

- For patients who decide to discontinue study treatment and immediately withdraw completely from the study (refuse any further study participation or contact) the Investigator should make every effort to perform the assessments detailed for the early study treatment discontinuation visit (see section relating to Discontinuation of Study Treatment above), and enter on the e-CRF as Early Study Discontinuation Visit provided the patient gives consent for these assessments. The investigator should document an explanation of why the patient is withdrawing from the study. Following these assessments all study participation for that patient will cease and data to be collected at subsequent visits will be considered missing. Publically available survival information should be obtained until the safety follow-up visit (Visit 301) unless the patient requests this should not be used.
- The investigator must also notify the IRT (IVRS/IWRS) of the premature discontinuation of study treatment.
- Patients who prematurely discontinue study treatment and withdraw from the study will not be replaced.

5.4.11 Lost to follow-up

For patients who are lost to follow-up (i.e. those patients whose status is unclear because he/she fails to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by making appropriate efforts to re-establish contact with patient and attempts to contact the patient should be documented in the source documents, e.g. dates of telephone calls / emails, registered letters, etc. If contact has not been re-established, all efforts should still be made to locate the patient and obtain information regarding concomitant medications, serious adverse events, and survival status at the end of the 52 weeks intended treatment epoch (Visit 214). This information should also be obtained at the safety follow-up visit (Visit 301).

5.4.12 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the

treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Global Trial Lead (GTL) that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT code break in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study treatment name (if available, patient number, and instructions for contacting the local Novartis Country Pharma Organization CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

Study drug must be discontinued after emergency unblinding. Study drug must also be discontinued for any patient whose treatment code has been inadvertently broken.

5.4.13 Study completion and post-study treatment

Completion of the study for an individual patient will be when he/she has completed Visit 214 and as close as possible to SAE follow-up at day 395. Completion of the study will be when the last patient completed the study treatment epoch phase.

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

5.4.14 Early study termination

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

6 Visit schedule and assessments

Table 6-1 lists all the assessments to be performed for the study and indicates with an "X" the visits at which they will be performed. Patients should be seen for all visits on the designated day or as close as possible to that date. A visit window of 4 days is allowed for Visit 214 as described in Section 3.1. All data obtained for these assessments must be supported in the patients' source documentation.

The following assessments are scheduled to be performed in order as follows: Patient reported outcome (PRO) questionnaires (i.e. AQLQ, [redacted], ACQ), ECG, pulse rate, blood pressure, blood sample/urine samples, followed by spirometry in a manner that the spirometry measurements occur at the scheduled time point (See Table 6-2 for Timed Assessments). ECG assessments to the start of spirometry manoeuvres must be observed at all times. Whenever ECG is to be taken after a succession of spirometry measurements as described in Table 6-2, a

[redacted]

minimum 10 min rest period from the end of spirometry maneuvers and the beginning of ECG assessments must be observed.

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

[redacted]

Table 6-1 Table of Assessment

Visit Number	**1**	**101**	**102**	**201**	**202**	**203[5]**	**204**	**205[5]**	**206[5]**	**207**	**208[5]**	**209[5]**	**210**	**211[5]**	**212[5]**	**213[5]**	**214**	**EOT Early treat-ment dis-continuation**	**Early Study Discontinuation**	**301[9]**
Epoch	**Screen**	**Run-In**		**Treatment**															**PSW**	**Follow up**
Clinic(C) /Telephone(T)	C	C	C	C	C	T	C	T	T	C	T	T	C	T	T	T	C	C	T	T
Week – Start of Week	-4 to -2*	-2	0	0	4	8	12	16	20	26	28	32	36	40	44	48	52			56
Day Number	-28 to -14*	-14	1	½	30	57	86	113	141	183/ 184	197	225	254	281	309	337	364/ 365[6]			395
Obtain Informed Consent (including for sub-group)	X																			
Current medication review/adjustment	X																			
Inclusion/exclusion criteria	X	X	X																	
Randomization via IRT				S																
Medical History, Demography	X																			
History of Asthma exacerbation	X																			
Smoking history and status	X																			
Run-in medication		X																		
Pregnancy test (serum)[1]		X															X	X		
Pregnancy test (urine) [1]	X		X							X										

[redacted]

Visit Number	**1**	**101**	**102**	**201**	**202**	**203[5]**	**204**	**205[5]**	**206[5]**	**207**	**208[5]**	**209[5]**	**210**	**211[5]**	**212[5]**	**213[5]**	**214**	**EOT Early treat-ment dis-continuation**	**Early Study Discontinuation**	**301[9]**
Epoch	**Screen**	**Run-In**		**Treatment**															**PSW**	**Follow up**
Clinic(C) /Telephone(T)	C	C	C	C	C	T	C	T	T	C	T	T	C	T	T	T	C	C	T	T
Week – Start of Week	-4 to -2*	-2	0	0	4	8	12	16	20	26	28	32	36	40	44	48	52			56
Day Number	-28 to -14*	-14	1	½	30	57	86	113	141	183/ 184	197	225	254	281	309	337	364/ 365[6]			395
Urine analysis (dipstick)		S		S			S			S							S	S		
Device training[4]	S		S																	
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Physical examination		S								S							S	S		
Oropharyngeal examination		S	S	S	S		S			S			S				S	S		
Record height (Visit 101 only), weight, abdominal circumference (hip and waist)		X								X							X	X		
ECG[2]		X		X			X			X			X				X	X		
Vital signs[2]		X	X	X	X		X			X			X				X	X		
Issue rescue medication as necessary	S	S		S	S		S			S			S							
Review rescue medication use		X	X	X	X		X			X			X				X	X		

[redacted]

Visit Number	**1**	**101**	**102**	**201**	**202**	**203[5]**	**204**	**205[5]**	**206[5]**	**207**	**208[5]**	**209[5]**	**210**	**211[5]**	**212[5]**	**213[5]**	**214**	**EOT Early treat-ment dis-continuation**	**Early Study Discontinuation**	**301[9]**
Epoch	**Screen**	**Run-In**		**Treatment**															**PSW**	**Follow up**
Clinic(C) /Telephone(T)	C	C	C	C	C	T	C	T	T	C	T	T	C	T	T	T	C	C	T	T
Week – Start of Week	-4 to -2*	-2	0	0	4	8	12	16	20	26	28	32	36	40	44	48	52			56
Day Number	-28 to -14*	-14	1	½	30	57	86	113	141	183/ 184	197	225	254	281	309	337	364/ 365[6]			395
Spirometry Practice (optional)	X																			
Screening spirometry and FEV_1 reversibility test (SABA)[10]		X																		
Spirometry[2]			X	X	X		X			X							X	X		
Issue e-Diary [5]	X																			
Issue of Peak Flow meter	X																			
Review and upload e-Diary recordings[5]			S		S		S			S			S				S	S		
Administer study drug at visit				X	X		X			X			X				X			
Dispense study medication via IRT				X	X		X			X			X							
Call IRT for visit confirmation	S	S		S	S		S	S	S	S	S	S	S	S	S	S	S	S	S	S
Collect unused study medication					S		S			S			S				S	S		

[redacted]

Visit Number	**1**	**101**	**102**	**201**	**202**	**203[5]**	**204**	**205[5]**	**206[5]**	**207**	**208[5]**	**209[5]**	**210**	**211[5]**	**212[5]**	**213[5]**	**214**	**EOT Early treat-ment dis-continuation**	**Early Study Discontinuation**	**301[9]**
Epoch	**Screen**	**Run-In**		**Treatment**															**PSW**	**Follow up**
Clinic(C) /Telephone(T)	C	C	C	C	C	T	C	T	T	C	T	T	C	T	T	T	C	C	T	T
Week – Start of Week	-4 to -2*	-2	0	0	4	8	12	16	20	26	28	32	36	40	44	48	52			56
Day Number	-28 to -14*	-14	1	½	30	57	86	113	141	183/ 184	197	225	254	281	309	337	364/ 365[6]			395
Record interruption/ changes in Drug Administration to assess compliance					X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AE recordings		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SAE recording	X	X	X	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	X	X
Study Disposition (Screening)	X																			
Study disposition (Run-In)		X	X																	
Study disposition End of Treatment epoch (end of study)																	X		X	
Study disposition (Follow-Up)																				X
Survival Status																			X	X
Review asthma exacerbations	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Visit Number	**1**	**101**	**102**	**201**	**202**	**203[5]**	**204**	**205[5]**	**206[5]**	**207**	**208[5]**	**209[5]**	**210**	**211[5]**	**212[5]**	**213[5]**	**214**	**EOT Early treat-ment dis-continuation**	**Early Study Discontinuation**	**301[9]**
Epoch	**Screen**	**Run-In**		**Treatment**															**PSW**	**Follow up**
Clinic(C) /Telephone(T)	C	C	C	C	C	T	C	T	T	C	T	T	C	T	T	T	C	C	T	T
Week – Start of Week	-4 to -2*	-2	0	0	4	8	12	16	20	26	28	32	36	40	44	48	52			56
Day Number	-28 to -14*	-14	1	½	30	57	86	113	141	183/ 184	197	225	254	281	309	337	364/ 365[6]			395
Safety Lab assessments (haematology, clinical chemistry, urinalysis, [redacted])		X		X			X			X							X	X		
Evening plasma cortisol [2]				X						X							X	X		
[redacted]																				
ACQ-7[3]		X	X		X		X			X							X	X		
AQLQ-S[3]			X		X		X			X			X				X			
[redacted]																				
Telephone patient 1 day in advance of visit				S	S		S			S			S				S			
Record healthcare visits for asthma worsening					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[redacted]

Visit Number	**1**	**101**	**102**	**201**	**202**	**203[5]**	**204**	**205[5]**	**206[5]**	**207**	**208[5]**	**209[5]**	**210**	**211[5]**	**212[5]**	**213[5]**	**214**	**EOT Early treat-ment dis-continuation**	**Early Study Discontinuation**	**301[9]**
Epoch	**Screen**	**Run-In**		**Treatment**															**PSW**	**Follow up**
Clinic(C) /Telephone(T)	C	C	C	C	C	T	C	T	T	C	T	T	C	T	T	T	C	C	T	T
Week – Start of Week	-4 to -2*	-2	0	0	4	8	12	16	20	26	28	32	36	40	44	48	52			56
Day Number	-28 to -14*	-14	1	½	30	57	86	113	141	183/ 184	197	225	254	281	309	337	364/ 365[6]			395

Early Study Discontinuation Visit should be used for Premature study withdrawal (please refer to Section 5.4.9)

*: Time between Visit 1 and 101 can be adapted according to the required wash-out from previous medication listed in Table 5-2.

S: These assessments are source documentation only and will not be entered into the e-CRF

X: Assessment to be reported in the clinical database

[1] For females of child-bearing potential only unless surgically sterile. Additional pregnancy testing might be performed if requested by local requirements

[2] Details of timed assessments are provided in Table 6-2

[3] All PROs assessed at Clinic should be completed before any other assessment. When a scheduled visit is planned on 2 consecutive days the PROs are to be completed on the first day. For the ACQ7, question 7 regarding FEV1% predicted should be answered by the investigator based on the spirometry measurement at the site using the equipment provided by spirometry vendor.

[4] Device training at Visit 1 is for e-diary/peak flow meter. Device training at Visit 102 is for Concept1 and Accuhaler®. The diary is an electronic device. The questionnaires and other assessments are based on asthma symptoms

[5] Site to call patient at specified timepoints in between clinic visits to check if patient asthma symptoms have worsened, any treatment required and e-diary completed accordingly. In case of an asthma exacerbation, the patient should be encouraged by the site to contact it for advice. If necessary, an unscheduled visit to the site may be organized and should capture AEs/SAEs, concomitant medication and safety laboratory exams as appropriate.

[6] The last dose of study medication will be taken on day 365 in the morning (Visit 214)

[redacted]

[9] 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

[10] If reversibility fails on the first attempt as well as on the repeat, historical reversibility or bronchoprovocation would be acceptable as specified in Section 4.1

[redacted]

Table 6-2 Timed Assessment**

Visit (Day)	Timepoint[1]	Spirometry (FEV_1, FVC)[4]	[redacted]	Hematology Chemistry Urinalysis	Plasma cortisol	ECG[3]	Vital sign[2]
Visit 201 (Day 1)	-45 min	X					
	- 35 min					X	
	-25 min						X
	-20 min			X[5]	X[6]		
	-15 min	X					
	0 min			Evening dosage			
	5 min	X					
	15 min	X					
	20 min						X
	30 min	X		X			
	1 h	X				X	X
Visit 201 (Day 2)	23h15 min	X					
	23h45 min	X					
	0 min			Evening dosage			
Visit 202 (Day 30)	-45 min	X					
	-25 min						
	-15 min	X					X
	0 min			Evening dosage			
	2 min						
	5 min	X					
	15 min						
	30 min	X					
	1 h	X					
Visit 204 (Day 86)	-45 min	X					
	- 35 min					X	
	-25 min						
	-15 min	X		X[5]			X
	0 min			Evening dosage			
	2 min						
	5 min	X					
	15 min						
	30 min	X					
	1 h	X					
Visit 207 (Day 183)	-45 min	X					
	- 35 min					X	
	-25 min						X
	- 20 min			X[5]	X		
	-15 min	X					
	0 min	Evening dosage					

[redacted]

Visit (Day)	Timepoint[1]	Spirometry (FEV_1, FVC)[4]	[redacted]	Hematology Chemistry Urinalysis	Plasma cortisol	ECG[3]	Vital sign[2]
	5 min	X					
	30 min	X		X			
	1h	X				X	
Visit 207 (Day 184)	23hr15 min	X					
	23h45 min	X					
Visit 214 (Day 364)	-45 min	X					
	- 35 min					X	
	-25 min						X
	- 20 min			X[5]	X		
	-15 min	X					
	0 min			Evening dosage			
	5 min	X					
	20 min						X
	30 min	X		X			
	1h	X				X	X
Visit 214 (Day 365)	23h15 min	X					
	23h45 min	X		X	X		

[1] Study drug timed doses. All study medication doses to be administered in the clinic. Time relates to the dose given from first device at visit unless otherwise specified

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

[3] A minimum 3 min rest period from the beginning of ECG assessments to the start of spirometry manoeuvres must be observed at all times.

[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. At all timepoints ECG should always be done first.

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

[6] It is baseline for the evening plasma cortisol

[redacted]

**Assessments are to be completed within a 5 min window from Table 6-2 schedule, except for the 2 min sample which will be collected as a post-dose sample within a 2 min window.

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the run-in epoch will have the study completion page for the screening and/or run-in epoch, demographics, baseline characteristics, 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 (calculated)
- Sex

[redacted]

- Race and ethnicity
- Patients initials (where allowed by local legislation)
- 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
- Health status
- Prior concomitant medication (Both asthma related and non-asthma related)
- Pre and post-bronchodilator spirometry (screening spirometry and reversibility testing).

6.3 Treatment exposure and compliance

The time of study treatment administration at each in-office dosing visit will be collected on the e-CRF 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. 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 202, 204, 207, 210 and 214 (or at Early Treatment Discontinuation/end of treatment Visit (EOT) or Study Withdrawal visit if applicable). Study treatment compliance will be assessed from the capsule count from previously dispensed blister strips for the Concept1® and Accuhaler® dose counter.

6.4 Efficacy

The following assessments of efficacy will be performed:

- Spirometry
- Health Status (PROs)
- e-Diary
- Peak Expiratory Flow
- Rescue Medication Use
- Asthma Exacerbations

6.4.1 Spirometry

The following spirometric assessments will be made:

[redacted]

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

Spirometric assessments will be measured at Visit 201, 202, 204, 207, 214 and EOT if applicable as indicated in Table 6-2.

Trough FEV_1 for QMF149 150/160 µg, QMF149 150/320 µg o.d., QVM149 150/50/80 µg and QVM149 150/50/160 µg o.d. delivered via Concept1 is the 24 hr post-dose FEV_1 is calculated as the mean of the two FEV_1, values measured at 23 hr 15 min and 23 hr 45 min after the evening dose taken at the site. Pre-dose FEV_1 is defined as the mean of the two FEV_1 values measures at -45 min and -15 min prior to evening dose.

Please refer to the Spirometry Guidance in Appendix 3 and Table 6-2 for full details on scheduling and performing spirometry

6.4.2 Health Status (Patient Reported Outcomes)

6.4.2.1 Asthma Control Questionnaire (ACQ-7)

In this study, the ACQ-7 (Appendix 4) will be used to assess improvements in asthma symptom control. The ACQ-7 (Juniper 1999; Juniper 2005; Juniper 2006) is a seven-item disease-specific instrument developed and validated to assess asthma control in patients in clinical trials as well as in individuals in clinical practice. The ACQ-7 questionnaire will be provided to the site. The ACQ-7 questionnaire consists of five items to assess symptoms and activity limitations, one question to assess rescue medication use, and one question to assess airway caliber (FEV1% 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 equipment provided by spirometry vendor. The ACQ-7 should be completed at the investigators site at Visits 101, 102, 202, 204, 207, 214 and EOT if applicable (see footnote 3 of Table 6-1).

6.4.2.2 Asthma Quality of Life Questionnaire (AQLQ-S)

The AQLQ is a 32-item disease specific questionnaire designed to measure functional impairments that are most important to patients with asthma (Appendix 5). It consists of 4 domains: symptoms, emotions, exposure to environmental stimuli and activity limitation. Patients are asked to recall their experiences during the previous 2 weeks and to score each item on a 7-point scale (Juniper 1992, Juniper 1993). The overall AQLQ score is the mean response to all 32 questions. Clinically important differences in scores between any two assessments have been determined by the authors of the AQLQ. Changes in scores of 0.5 are considered clinically meaningful; changes of 1.0 are considered as moderate and > 1.5 as large changes for any individual domain or for the overall summary score (Juniper 1994).

[redacted]

AQLQ should be completed at Visits 102, 202, 204, 207, 210 and 214.

[redacted]

6.4.3 Electronic Diary

At Visit 1, all patients will be provided with an electronic diary (referred to as an e-Diary) to record rescue medication (salbutamol/albuterol) use. From Visit 101 they will also record clinical symptoms and PEF in the e-diary and from Visit 201 they will record the study medication compliance weekly. Daily inhalation of study treatments will also be checked. The patients will be instructed to routinely complete the e-Diary twice daily – at the same time each morning and again approximately 12 hours later in the evening. 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. A list of the Patient asthma control e-Diary questions is provided in Appendix 7.

[redacted]

6.4.3.1 Peak Expiratory Flow (PEF)

An electronic Peak Flow Meter will be given to each patient at Visit 1 for the measurement of morning and evening PEF from Visit 101 until the end of the treatment period.

PEF will be measured at consistent times for a patient, in the morning and evening each day during the study from Visit 101 to Early Study Discontinuation Visit. The measurements will be performed using an ePeak Flow Meter 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 timepoint, the patient should be instructed to perform 3 consecutive maneuvers within 10 minutes. These PEF values are captured in the ePEF/diary. The best of 3 values will be used.

6.4.3.2 Rescue Medication Usage

The use of rescue salbutamol/albuterol should be recorded by patients in their e-Diary twice each day in the morning and evening prior to taking study medication. In the morning patients should record the number of puffs of rescue medication they have taken during the night and since the last diary entry, and in the evening patients should record the number of puffs of rescue medication they have taken during the day since the morning diary entry.

6.4.3.3 Investigational Medication Usage

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 morning or in the evening, and from which inhalation device from Visit 201 to 214.

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 run-in onwards one or more of the following criteria of worsening asthma develops:

Asthma Worsening Criteria

1. > 20% decrease in FEV_1 from baseline value (this criterion applies to Investigator review at the time of a study visit or possibly an alert setting if device structured to capture)
2. > 50% increase in SABA use and >8 puffs per day on 2 out of any 3 consecutive days compared to baseline
3. ≥ 20% decrease in 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

[redacted]

Note: The reference for the worsening of asthma during the run-in epoch would be the FEV_1 and PEF taken at Visit 101. The baseline FEV_1 for the treatment epoch is taken at treatment Day 1 (Visit 201). The baseline PEF (morning and evening) for the treatment epoch is calculated at Visit 102 and is the average of the best of the 3 PEF measurements over the past 14 days.

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

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.
- Reporting all type of events in the Asthma Exacerbation Episode CRF.

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.

Should there be any compliance issue on study drug or e-diary completion potentially putting the patient's safety at risk, please consider temporary or permanent discontinuation of study drug.

Patients may 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.

6.4.5 Asthma Exacerbation

All type of asthma exacerbations meeting below criteria must be recorded in the Asthma Exacerbation Episode CRF (Asthma worsening as defined above should also be reported).

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

- Start date and end date:

[redacted]

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

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

1. Progressive increase of at least one of the asthma symptoms like shortness of breath, cough, wheezing, or chest tightness. The symptoms should be outside the patient's usual range of day-to-day asthma and should last at least two consecutive days.
2. Increased use of "rescue" inhaled bronchodilators defined by:
   - > 50% increase in SABA use and >8 puffs on 2 out of any 3 consecutive days compared to baseline captured
     Or
   - Night time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights
3. Deterioration in lung function, which last for two days or more but usually not severe enough to warrant SCSs for more than 2 days or hospitalization. This deterioration would be defined by:
   - > 20% decrease in FEV_1 from baseline value
     Or
   - ≥ 20% decrease in am or pm PEF from baseline on 2 out of any 3 consecutive days compared to baseline.
     Or
   - < 60% of PEF compared to baseline

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

1. Deterioration of at least one asthma symptoms like shortness of breath, cough, wheezing or chest tightness.
2. Increased use of "rescue" inhaled bronchodilators
3. Deterioration in lung function, which last for two days or more but usually not severe enough to warrant SCSs or hospitalization.
   This deterioration would be defined by:
   - > 20% decrease in FEV_1 from baseline value
     Or
   - ≥ 20% decrease in am or pm PEF from baseline on 2 out of any 3 consecutive days compared to baseline
     Or
   - < 60% of PEF compared to baseline

"Start and end dates" of each reported event in the CRF will be used to determine whether two consecutively reported events should be considered as separate events or as a prolonged one. If a second exacerbation is reported less than 7 days after the end date of a previous episode, then this will be assumed to be one continuous exacerbation with the start date taken

[redacted]

from the first episode and the end date from the second or last episode. If two events are merged based on this "7 day rule", the highest reported severity will be used to describe the overall severity of the prolonged event.

The treatment of asthma exacerbations including the initiation of systemic corticosteroids or increase in the maintenance dose of OCS should be done according to investigator's or treating physician's medical judgement and should be in line with national and international recommendations. If systemic corticosteroids are required, a patient may return to the study after successfully completing a taper of approximately 7-10 days. If longer than 7-10 days is expected, Novartis Medical Monitor should be contacted and the discontinuation of study treatment should be considered.

If patients cannot be safely tapered, oral corticosteroids may be taken chronically after an exacerbation if clinically indicated as per Principal Investigator clinical judgement and in accordance with national/local guidelines (and in doses not to exceed equivalent of prednisone 5mg daily). Dose should be maintained for at least 3 months before tapering.

At no time may patients self-medicate (other than rescue medication use) for treatment of asthma exacerbation or worsening of symptoms.

6.4.6 Appropriateness of efficacy assessments

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

6.5 Safety

The following safety assessments will be performed:

- Medical history and physical examination including oropharyngeal examination
- Vital signs
- Hematology, Blood 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 101, 207, 214 and in case of early study treatment discontinuation visit as described in Table 5-5. An oropharyngeal examination will be performed at each clinic visit.

[redacted]

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to informed consent being signed must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after informed consent (Visit 1) is given which meet the definition of an Adverse Event must be recorded on the Adverse Event 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 6-2. At Visits 101, 102, 201, 202, 204, 207, 210, 214, or EOT if applicable, vital signs should be measured directly after the ECG assessments.

6.5.3 Height, weight and abdominal circumference

Height in centimeters (cm) will be measured at Visit 101. Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) and abdominal circumference (hip and waist) will be measured at Visits 101, 207, 214 or EOT (if applicable). 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, [redacted]) will be performed at Visits 101, 201, 204, 207, 214 and EOT if applicable.

6.5.4.1 Hematology

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

6.5.4.2 Clinical chemistry

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

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

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

[redacted]

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 101, 201, 204, 207, 214 and EOT if applicable.

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

6.5.4.4 Hepatotoxicity

Any liver event which meets the criteria for "**medically significant**" event as outlined in Table 13-1 of Appendix 8 should follow the **standard procedures for SAE reporting** as described in Section 7.2.

6.5.4.5 Plasma Cortisol

Plasma cortisol will be measured at Visits 201, 207, 214 and EOT (if applicable). The sampling point is as shown in Table 6-2.

6.5.5 Electrocardiogram (ECG)

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 101, 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 Visits 102/201, 207, 214 or EOT (if applicable), ECGs will be measured at -35min pre-dose (evening dose) and post dose 30 min/ 1 hours, at Visit 204 ECG will be measured pre-dose only as indicated in Table 6-2. At Visit 210, the ECG will be done pre-dose. 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 trace should be printed. Each ECG will be sent electronically for central review directly from the ECG machine. One print-out will be generated and kept at the investigator site as source documentation and will be dated and signed. The subject's number, the date, actual time of the tracing, and Study Code must appear on each page of the tracing.

Full details of all procedures relating to the ECG collection and reporting will be contained in an investigator manual to be provided by the central laboratory to each investigator site. In the event that the central cardiologist reports that an ECG is abnormal, the investigator must

[redacted]

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/Current medical conditions/AE CRF/e-CRF page as appropriate.

New cases (not present during screening / run-in epochs) 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

A urine or serum pregnancy test will be performed in pre-menopausal women who are not surgically sterile (tests provided by the Central Laboratory) per Assessment Schedule Table 6-1. If the urine pregnancy test at Visit 1, Visit 102 and Visit 207 is positive, a plasma testing is to be done to confirm the pregnancy. A positive pregnancy test at Visits 1, 101, 102, 207 (Week 26), and 214, EOT Visit (if applicable) or at any time during the study requires the patient to be discontinued from the study treatment. Refer to Section 5.4.9 and Section 7.4 for more details. Additional pregnancy testing might be performed if requested by local requirements.

6.5.8 Appropriateness of safety measurements

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

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,

- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events.

Adverse events should 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 drug (s) (suspected/not suspected)
- study treatment (no/yes), or
- investigational treatment (no/yes), or
- the other study treatment (non-investigational) (no/yes) or both or indistinguishable,
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE)
- action taken regarding the study treatment

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

- no action taken (i.e. further observation only)
- Study treatment dosage adjusted/temporarily interrupted
- Study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

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

[redacted]

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

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, i.e. 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 more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

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

[redacted]

All AEs (serious and non-serious) are captured on the e-CRF, SAEs also require individual reporting to DS&E as per Section 7.2.2.

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 alter) must be reported to Novartis 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 (either initial or follow up information) 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 reoccurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational 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 investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.2.3 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

[redacted]

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.

7.3 Liver safety monitoring

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

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

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

Please refer to Table 13-1 in Appendix 8 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 8 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 8.

For the liver laboratory trigger:

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

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

- 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 should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

[redacted]

7.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment 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 should 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 CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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

[redacted]

8.2 Data collection

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.

Prior to the final database lock, CSR I (Section 3.5) will be prepared. The database for this CSR will consist of:

- All data in all patients up to 26 weeks (Visit 207)
- Data for the subset of patients who have completed 52 weeks treatment plus follow up (Visit 214 and 301) or prematurely withdrawn from the study.
- Data up to last available visit for patients who have already completed 26 weeks (Visit 207) but have not yet completed 52 week treatment plus follow up (Visit 214/301)

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.

[redacted]

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

8.4 Data Monitoring Committee

An independent, external data safety monitoring committee (DMC), comprising of experts (as defined in the Charter) will be set up to review all serious adverse events (including deaths and all hospitalizations) and pneumonia. DMC members will review this data generated externally and independently of Novartis, at predetermined intervals. If significant safety issues arise in between scheduled meetings, ad-hoc meetings will be scheduled to review the data. Based on the safety implications of the data, the DMC may recommend modification or termination of the study.

A charter for the DMC will be developed in a separate document. The DMC is the autonomous data and safety advisory group for Novartis. The purpose of the charter is to define:

1. The membership of the DMC
2. Responsibilities of the DMC and Novartis
3. Responsibilities of independent biostatistician and programmer
4. The relationship of the DMC with other trial components and data flow
5. The purpose and timing of DMC meetings
6. Procedures for ensuring proper confidentiality, addressing conflict of interest, and ensuring proper communication

The charter complies with Novartis SOPs and is in accordance with the FDA guidance [FDA, 2006] and CHMP guidelines [CHMP, 2006] on DMC's.

8.5 Adjudication Committee

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

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

Further details will be provided in the Adjudication Committee Charter.

8.6 Advisory Board

An Advisory Board will be established to provide guidance regarding the conduct of this study. This board will consist of a group of independent non-sponsor clinical experts and clinical/medical/statistical sponsor representatives.

In general, the functions of the advisory board will include:

[redacted]

- Data interpretation
- Publications
- Presentations

9 Data analysis

There will be two separate CSRs prepared for this study.

- CSR I: To support analyses once all patients have completed the assessments after 26 weeks of treatment (Visit 207) or prematurely withdrawn from the study. This will consist of :
  - Primary and key secondary objectives as well as other secondary objectives up to and including Week 26.
  - [redacted]
- CSR II: To support analysis once all patients have completed 52 weeks of treatment (Visit 214) plus follow up (Visit 301) or prematurely withdrawn from the study. CSR II will consist of:
  - Primary and secondary objectives analyzed in CSR I
  - All other objectives evaluated after 26 weeks up to 52 weeks (plus follow up), which will be updated from CSR I.

9.1 Analysis sets

The following analysis sets are defined for data analysis.

The randomized (RAN) set will consist of all patients who were assigned a randomization number, regardless of whether or not they actually received study medication.

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

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

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

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

[redacted]

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

9.2 Patient demographics and other baseline characteristics

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

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

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

No statistical analyses will be provided for baseline comparability among the treatment groups.

9.3 Treatments

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

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

Medications started and stopped prior to study drug, and taken concomitantly will be summarized by treatment group in separate tables in the Safety Set.

Concomitant therapies will be recorded, listed and summarized separately for asthma related medications / non-drug therapies and other medications. Concomitant asthma related medications will be summarized by route of administration, the recorded pre-specified drug subcategories (including types of combination) and preferred term. Concomitant medications not related to asthma will be summarized by route of administration and preferred term.

SABA usage (number of puffs) during the screening epoch will be summarized.

Patients taking prohibited concomitant medications will be noted in the summary of protocol deviations.

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

[redacted]

9.4 Analysis of the primary variable(s) and key secondary variables

9.4.1 Variable(s)

The primary objective of this study is to demonstrate superiority of either QVM149 150/50/80 µg o.d. to QMF149 150/160 µg o.d. or QVM149 150/50/160 µg o.d. to QMF149 150/320 µg o.d, all delivered via Concept1, in terms of trough FEV_1 after 26 weeks of treatment in patients with asthma.

The key secondary objective of this study is to demonstrate superiority of either QVM149 150/50/80 µg o.d. to QMF149 150/160 µg o.d.or QVM149 150/50/160 µg o.d. to QMF149 150/320 µg o.d., all delivered via Concept1, in terms of ACQ-7 after 26 weeks treatment in patients with asthma.

9.4.2 Statistical model, hypothesis, and method of analysis

The comparisons of QVM149 150/50/80 µg o.d. versus QMF149 150/160 µg o.d. and QVM149 150/50/160 µg o.d. versus QMF149 150/320 µg o.d., all delivered via Concept1, will be evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a):

H_0: QVM149 treatment group is equal to QMF149 treatment group in trough FEV_1 at Week 26

H_a: QVM149 treatment group is not equal to QMF149 treatment group in trough FEV_1 at Week 26

The primary variable will be analyzed using a mixed model for repeated measure (MMRM) on the FAS. The model will contain treatment, region, visit (Days 2, 184 and 365), and treatment-by-visit interaction as fixed effects with baseline FEV_1 measurement, baseline-by-visit interaction, FEV_1 prior to inhalation and FEV_1 within 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates, and center nested within region as a random effect. The within-patient correlation will be modeled using the unstructured covariance matrix in the mixed model. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger, 1997).

For the primary analysis, if the model does not converge, data only up to week 26 (i.e. Days 2 and 184) will be used (with unstructured covariance matrix). If still the model fails to converge, compound symmetry covariance matrix will be used. For the final analysis, if the model does not converge with unstructured covariance matrix, the compound symmetry covariance matrix will be used in the mixed model.

Restricted maximum likelihood method will be used. Each between-treatment comparison will be carried out using the adjusted mean (least-square mean) difference based on the treatment main effect and the coefficient for the treatment-by-visit interaction factor corresponding to Day 184. The estimated adjusted treatment difference (QVM149-QMF149) will be displayed along with the associated standard error, 2-sided 95% confidence interval (CI), and p-value (2-sided).

[redacted]

9.4.3 Handling of missing values/censoring/discontinuations

If any of the 23 hr 15 min and 23 hr 45 min values contributing to the trough FEV_1 are collected within 7 days of systemic corticosteroid use, 6 h of rescue medication, or actual measurement times are outside the 22 - 25 hour post-evening dose time window (or 10 – 13 hours post-morning dose time window) then the individual FEV_1 value will be set to missing.

If one of the two values is missing (or set to missing) then the remaining non-missing value will be taken as trough FEV_1. If both values are missing, or if the patient withdrew from the study, regardless of the reason for discontinuation, then trough FEV_1 will be regarded as missing in which case the missing value(s) of the patient at the particular visit(s) would not directly contribute to the primary analysis.

The MMRM model which is used for the primary variable is based on missing at random mechanism for the missing values and assesses the treatment effects of trough FEV_1 without imputation.

9.4.4 Multiplicity Adjustment

To control the family-wise type-I error rate at the two-sided 5% significance level, a graphic testing procedure based on the generalized Simes test in Maurer et al (2011) is used. The family for the overall type-I error rate control contains total 4 hypotheses including: two hypotheses for the primary endpoint trough FEV_1 and two hypotheses for the key secondary endpoint ACQ-7. Denote the two hypotheses for the primary endpoint as H1 and H2 for comparing QVM149 150/50/80 µg o.d. versus QMF149 150/160 µg o.d. and QVM149 150/50/160 µg o.d. versus QMF149 150/320 µg o.d. respectively. Similarly, denote the two hypotheses for the key secondary endpoint ACQ-7 as H3 and H4 for comparing QVM149 150/50/80 µg o.d. versus QMF149 150/160 µg o.d. and QVM149 150/50/160 µg o.d. versus QMF149 150/320 µg o.d. respectively.

Below is a brief description of the testing procedure based on the generalized Simes test in Maurer et al (2011).

Let p_1, p_2, p_3, p_4 be the corresponding p-values (2-sided) of the four hypotheses of H1, H2, H3, and H4.

Step 1: Retain all four hypotheses if $p_i <= 0.05$ **AND** the observed treatment difference for the corresponding p_i is in the wrong direction (i.e. QMF149 is performing better than QVM) for **ANY** i=1, 2, 3, 4, stop here; otherwise go to step 2;

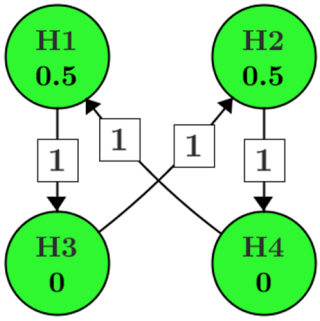
Step 2: Reject all four hypotheses if $p_i < 0.05$ for **ALL** i=1, 2, 3, 4 and stop here; otherwise go to step 3;

Step 3: If neither step 1 or 2 applies, perform a closed successive weighted Bonferroni test as given in Figure 9-1. The initial weights of 0.5 to H1 (corresponding to 0.025 alpha level, 2-sided) and 0.5 to H2 (corresponding to 0.025 alpha level, 2-sided) were assigned. Here is a brief summarization of the successive weighted Bonferroni test based on Bretz et al (2011): If null H1 is rejected at the initial significance level of 0.025, then H3 can be tested at the significance level of 0.025. Similarly, if null H2 is rejected at the initial significance level of 0.025, then H4 can be tested at the significance level of 0.025. If neither primary null

[redacted]

hypothesis can be rejected at the initial significance levels, then the testing stops and efficacy cannot be claimed for neither of the doses and endpoints. Otherwise the graph is sequentially updated with reallocated weights after each hypothesis is rejected. In addition, if efficacy can be shown for one of the doses on both the primary and key secondary endpoints at the initial significance level, the associated weight is passed on to the other dose for further testing.

Figure 9-1 Testing Procedure



Note: Full details of the testing procedure will be described in a reporting analysis plan before unblinding of the treatment code and database lock.

For each of the four hypotheses, the corresponding testing statistics (estimated least square mean difference) follows normal distribution. Hence for any two out of the four hypotheses, their corresponding testing statistics follow jointly bivariate normal distribution. Therefore this testing procedure controls the overall type –I error rate at the 2-sided 0.05 level in the strong sense regardless if the bivariate normal distributions have positive or negative correlations as shown in Mauer et al (2011).

Other than the 4 analyses mentioned above for the primary and the key secondary endpoint, all other analyses will be performed at the nominal 2-sided 0.05 level (2-sided) without multiplicity adjustment.

9.4.5 Key secondary variable

The key secondary variable is ACQ-7 after 26 weeks of treatment.

It will be analyzed using the same MMRM model (including all available visits) on the FAS as used for the primary analysis but will include baseline ACQ-7 score instead of baseline FEV_1.

9.4.6 Supportive analyses

As supportive analyses, the same MMRM model used in the primary analysis will be also performed on the PPS to assess the treatment effect in protocol adherers. The same primary MMRM model on the FAS will be performed including all spirometric measures irrespective of systemic corticosteroid or rescue medication use but those measures taken outside of the 22 - 25 hour post-evening dose window (or 10-13 hour post-morning dose window) will not be included.

[redacted]

For ACQ-7, the same MMRM model used for key secondary endpoint will also be performed on the FAS excluding measurements in patients requiring chronic corticosteroid use after an exacerbation (beyond permitted steroid taper for exacerbation of approximately 7-10 days).

The following exploratory subgroup analyses for trough FEV_1 using MMRM will be performed (using the appropriate interaction term in the model and additional covariate as a fixed effect if necessary) for the FAS population to explore the treatment effect in:

- Race (Caucasian, Black, Asian, Other)
- Sex (male, female)
- History of asthma exacerbation in the 12 months prior to screening (1, 2, 3, ≥4)
- Patients' prior therapies before Run-in period (e.g. mid and high dose ICS/LABA)
- FEV1 response according to % predicted FEV1 range at baseline (<40%, 40% -<60% and 60%-80%)
- ACQ-7 Baseline (1.5 - <2; 2 - <2.5; >2.5)

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The comparison of each dose of QVM149 o.d vs. salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. will be performed using the same model for the comparison of QVM149 versus QMF149 at the corresponding doses as specified below for the corresponding endpoint unless otherwise specified.

9.5.1.1 Spirometry

All spirometric efficacy variables will be analyzed for the FAS, unless otherwise specified.

Spirometry measurements contributing to the trough FEV_1, if collected within 7 days of systemic corticosteroid use (except for patients who were on stable corticosteroids), 6 hours of rescue use and/or 3 months of single depot corticosteroid injection, will be set to missing and not be imputed, unless specified otherwise.

Spirometry data by visit

Trough FEV_1 at Day 2 and at post-baseline visits will be analyzed using the same MMRM model as specified for the primary analysis, i.e., the visit factor will include all available visits as a factor and between-treatment comparison will be carried out using the adjusted mean (least-square mean) difference based on the treatment main effect and the coefficient for the treatment-by-visit interaction corresponding to the respective visit. Adjusted mean (LS mean) will be displayed for each treatment group along with the estimated treatment differences and the 95% confidence intervals and the two-sided p-values by visit.

Similar analyses will be performed for pre-dose FEV_1, post-dose FEV_1 (5 mins, 30 mins, 1 hr), FVC and FEF_{25-75}.

Change from baseline in the spirometry values will be also analyzed using the same MMRM model.

[redacted]

To estimate the add-on effect of glycopyrronium over QMF149, the average of following treatment contrasts will be computed:

QVM149 (150/50/80 µg) vs. QMF149 (150/160 µg)

QVM149 (150/50/160 µg) vs.QMF149 (150/320 µg)

QVM149 and QMF149 doses will be pooled using appropriate contrasts within the MMRM model, as specified for the primary analysis. The details of this analysis will be provided in the SAP.

9.5.1.2 ACQ at Weeks 4, 12, and 52

The ACQ measures asthma symptom control and consists of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway caliber (FEV_1 % predicted). Patient recall is 1 week. All 7 questions of the ACQ are equally weighted. Items 1-5 are scored along a 7-point response scale, where 0 = totally controlled and 6 = severely uncontrolled.

The 7^{th} item will be scored by the investigator based on the FEV_1 % predicted from the equipment provided by spirometry vendor at the site. The total score is calculated as the mean of the scores on all questions.

ACQ-7 at post-baseline visits will be analyzed using the same MMRM model as specified for the primary analysis (including all available visits) except that baseline FEV_1 will be replaced with baseline ACQ-7.

Change from baseline in the ACQ-7 will be also analyzed using the same MMRM model.

The proportion of patients who achieve an improvement of at least 0.5 in ACQ-7 (i.e. decrease of ACQ-7 score of at least 0.5 from baseline) at post-baseline visits will be analyzed using the logistic regression model via the generalized estimating equations (GEE). The model will include terms for treatment, region, visit, and treatment-by-visit interaction as fixed effects with baseline ACQ-7 measurement, baseline-by-visit interaction, FEV_1 prior to inhalation and FEV_1 within 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates.

The estimated adjusted odds ratios will be displayed along with the associated 95% (two-sided) confidence intervals and p-values.

To estimate the add-on effect of glycopyrronium over QMF149, the average of following treatment contrasts will be computed:

QVM149 (150/50/80 µg) vs. QMF149 (150/160 µg)

QVM149 (150/50/160 µg) vs.QMF149 (150/320 µg) The details of this analysis will be provided in the SAP.

All the analyses described above will be repeated for ACQ-5.

[redacted]

9.5.1.3 Rescue medication

The number of puffs of the rescue medication use in the previous 12-hour is recorded twice (morning/evening) by the patient in the e-Diary. The mean daily number of puffs of rescue medication use over the first 26 weeks and over the whole 52 weeks of treatment will be summarized by treatment. The mean change from baseline in the daily number of puffs of rescue medication use will be analyzed using an ANCOVA model. The model will contain treatment, region as fixed effect factors with center nested within region as a random effect, and baseline rescue medication use, FEV_1 prior to inhalation and FEV_1 within 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates. No imputation will be done for missing data.

The adjusted mean (LS mean) treatment differences along with the corresponding two-sided 95% confidence intervals and corresponding p-values will be presented. This analysis will be performed for morning (nighttime) and evening (daytime) rescue medication use.

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 by treatment and analyzed the same way as described for the number of puffs of the rescue medication use with appropriate baseline as a covariate. In addition, the mean number of puffs of rescue medication per day, in the morning and in the evening and the percentage of 'rescue medication free days' will be summarized by approximate 4 weekly intervals and analyzed using a similar MMRM model as specified for the primary analysis with the baseline FEV_1 value replaced with the appropriate rescue medication use.

9.5.1.4 Peak Expiratory Flow Rate (PEF)

All the patients are instructed to record PEF twice daily using a mini Peak Flow Meter device, once in the morning (before taking the morning dose) and once approximately 12 h later in the evening (before taking the evening dose), from screening and throughout the study.

The morning/evening PEF (liters/min) will be averaged over the first 26 weeks and over the whole 52 weeks. E-diary data recorded during the screening period will be used to calculate the baseline value.

Mean morning/evening PEF will be summarized by treatment. Between-treatment differences of the change from baseline in mean morning/evening PEF will be performed using the same models as specified for rescue medication data except that baseline rescue medication use will be replaced with baseline morning/evening PEF as the covariate. LS mean and associated 95% confidence intervals will be presented for treatments and treatment differences.

In addition, the mean morning/evening PEF will be summarized by approximate 4 weekly intervals and analysed using a similar MMRM model as specified for the primary analysis with baseline FEV_1 value replaced with the appropriate baseline PEF.

9.5.1.5 Asthma symptom based on e-Diary

The percentage of days with no day-time symptoms will be calculated for each patient over the 52 weeks of treatment period and will be analyzed by the same ANCOVA model used for the analysis of % of rescue medication free days with the appropriate baseline as a covariate.

[redacted]

The same ANCOVA model as specified above except using the appropriate baseline as a covariate will be used to analyze the percentage of days with no night-time awakenings over 52 weeks of treatment, the mean total daily symptom scores averaged over 26 and 52 weeks of treatment and the percentage of mornings with no symptoms on rising over 52 weeks of treatment.

In addition, the percentage of days with no night-time awakenings, the mean total daily symptom scores and the percentage of mornings with no symptoms on rising will be summarized by approximate 4 weekly intervals and analyzed using a similar MMRM as specified for the primary analysis but including the appropriate visits and baseline as a covariate.

9.5.1.6 Asthma Exacerbations

The following asthma exacerbation-related parameters over the 52 weeks will be summarized by treatment (asthma exacerbation is defined in Section 6.4.5): The analysis will be performed by exacerbation category wherever specified. The exacerbation categories are: ALL (mild, moderate, severe), and the combination of moderate or severe, and severe.

- Time to first asthma exacerbation by exacerbation category
- Time to first hospitalization for asthma exacerbation
- The annual rate of asthma exacerbations by exacerbation category
- The annual rate of asthma exacerbation excluding measurements in patients requiring corticosteroid use after an exacerbation (beyond permitted steroid taper for exacerbation) by exacerbation category.
- Duration of asthma exacerbations in days by exacerbation category
- The percentage of patients with at least one asthma exacerbation by exacerbation category
- Time to permanent study drug discontinuation due to asthma exacerbation
- The percentage of patients who permanently discontinued study drug due to asthma exacerbation
- Total amounts (in doses) of systemic corticosteroids used to treat asthma exacerbations

Time-to-event variables will be analyzed using a Cox regression model stratified by region. The model will include treatment and history of asthma exacerbation in the 12 months prior to screening (the number of asthma exacerbations in the 12 months prior to screening) as fixed-effect factors, and FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates. The estimated adjusted hazard ratio for QVM149 over QMF149 will be displayed along with the associated two-sided 95% confidence interval and corresponding p-value.

Kaplan-Meier analysis stratified by treatment group will be also presented and displayed graphically.

Number of the asthma exacerbation will be analyzed using the generalized linear model assuming the negative binomial distribution including treatment, region and history of asthma exacerbation in the 12 months prior to screening (the number of asthma exacerbations in the

[redacted]

12 months prior to screening) as fixed-effect factors, and FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates. The log exposure in years will be included as an offset variable in the model. The estimated rate ratio along with two-sided 95% interval and corresponding p-value will be provided.

The duration of asthma exacerbation is defined as the sum of the duration of days recorded as an exacerbation for all exacerbations recorded per patient. This will be analyzed for treatment group differences using the Van Elteren test stratified for region and history of asthma exacerbation in the 12 months prior to screening (1, 2, ≥3).Total amount (in prednisone-equivalent doses) of systemic corticosteroid used to treat asthma exacerbation during the 52 week treatment period will be summarized descriptively (i.e., n, mean, standard deviation, median, first and third quartile, minimum and maximum) by treatment group.

To estimate the add-on effect of glycopyrronium over QMF149 in terms of exacerbations, the average of following treatment contrasts will be computed:

QVM149 (150/50/80 µg) vs. QMF149 (150/160 µg)

QVM149 (150/50/160 µg) vs.QMF149 (150/320 µg)

All inferential analyses mentioned above for exacerbation will be repeated to explore the overall efficacy of QVM149 compared with QMF149, QVM149 and QMF149 doses will be pooled using appropriate contrasts within the analyses models. The details of these analyses will be provided in the SAP.

9.5.2 Safety variables

All safety endpoints will be summarized for the safety set.

Adverse events

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 will be classified as a treatment emergent adverse event. Any adverse events that started during the study before the time of the first inhalation of study drug will be classified as a prior adverse event.

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

The number and exposure-adjusted event rate of patients with the most frequent AEs will be summarized by treatment.

Electrocardiogram (ECG) and vital signs

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

[redacted]

Vital signs (blood pressure and radial pulse rate) data will be summarized by treatment and visit.

The maximum (QTc, systolic blood pressure, pulse rate and heart rate) or minimum (diastolic blood pressure) post first dosing (i.e. post baseline) value will also be summarized. Changes from baseline will also be summarized by treatment.

Weight will be summarized by visit and treatment group. Changes from baseline will also be summarized by treatment. The baseline measurement will be the measurement at Visit 101.

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

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

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

Systolic blood pressure

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

"High" criterion: *>200 mmHg, or ≥180 mmHg and increase from baseline ≥20 mmHg*

Diastolic blood pressure

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

"High" criterion: *>115 mmHg, or ≥105 mmHg and increase from baseline ≥15 mmHg*

Pulse rate

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

"High" criterion: *>130 bpm, or ≥120 bpm and increase from baseline ≥15 bpm*

Notable QTc values and changes from baseline will be summarized. A notable value is defined as a QTc interval of greater than *450 ms (male), 460 ms (female) and 500 ms (both)* at baseline and the number of newly occurring or worsening notable QTc values for post baseline time points.. The categories used for the change from baseline in QTc are less than *30 ms, 30 to 60 ms and greater than 60 ms*.

QTc will be calculated from the QT interval and RR (in seconds) using Fridericia's formula: $QTc = QT / 3\sqrt{RR}$, where $3\sqrt{}$ denotes the cube root

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

Laboratory data

All 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.

[redacted]

Shift tables relative to the normal reference ranges will be used to summarize the change from baseline to post-baseline by visit for each laboratory parameter.

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

Unscheduled primary and secondary care visits due to asthma worsening

The number of unscheduled primary and secondary care visits per patient per year will be analyzed for the FAS using the same generalized linear model assuming negative binomial distribution as specified for the number of asthma exacerbations except excluding history of asthma exacerbation in the 12 months prior to screening (the number of asthma exacerbations in the 12 months prior to screening) from the model.

Absenteeism from work due to asthma worsening

The number of days off (absenteeism) from work due to asthma worsening will be described descriptively by treatment on the FAS. The number and percentage of patients absent from work due to asthma worsening will be summarized by treatment on the FAS.

[redacted]

9.5.2.2 Asthma Quality of Life Questionnaire (AQLQ) at Post-baseline Visits

AQLQ (Asthma Quality of Life Questionnaire) is a 32-item disease specific questionnaire designed to measure functional impairments that are most important to patients with asthma, with 7-point scale (1-totally limited/problems all the time, 7-not at all limited/no problems). It consists of 4 domains: symptoms, emotions, exposure to environmental stimuli and activity limitation. Mean score will be calculated for the four domains, as well as the overall quality-of-life score defined as the mean score of all 32 items.

For the overall score and each respective domain score, treatment group comparisons will be performed using the same MMRM model as specified for the primary analysis with baseline AQLQ as covariate.

The proportion of patients who achieve an improvement of at least 0.5 in the change from baseline in AQLQ (i.e. increase of AQLQ score of at least 0.5 from baseline) at post-baseline visits will be analyzed using the same logistic regression model via GEE specified for the ACQ-7 analysis except that baseline AQLQ will be used instead of the baseline ACQ-7.

[redacted]

The analyses on AQLQ will be based on the FAS for all post-baseline visits.

9.5.6 PK/PD

Not applicable

9.6 Interim Analysis

The primary and key secondary endpoints of CQVM149B2302 study are trough FEV_1 and ACQ-7 after 26 weeks of treatment, respectively while the entire study treatment period is 52 weeks. Novartis has decided to perform primary analysis once all patients have completed 26 weeks of treatment (Visit 207) or prematurely withdrawn from the study which will be used for internal decision making prior to study completion. The study will continue as planned in a blinded manner for full 52 weeks period (plus 30 days of safety follow-up).

9.7 Safety Monitoring Analysis

It is planned that the independent DMC will review semi-blinded (i.e., treatment group named as A, B, C, D or E) safety data. The details of the information flow, confidentiality and specific analyses required for the safety monitoring analysis will be documented in the DMC Charter. The Charter will be finalized prior to semi-blinding the data for the safety monitoring

analysis. Since the purpose of the DMC is not based on efficacy for stopping rule, there will be no alpha spent for the safety monitoring analysis. All analyses will be considered exploratory.

9.8 Sample size calculation

The sample size calculation takes into account the following consideration:

1. To achieve at least 90% power (with multiplicity adjustment) for primary endpoint trough FEV_1 with a treatment difference of 90mL between QVM149 vs. QMF149 at the corresponding doses, assuming standard deviation of 380mL based on studies QMF149A2210, QMF149E2201 and QMF149E2203, and Kerstjens (2012);
2. To achieve at least 80% power (with multiplicity adjustment) for key secondary endpoint ACQ-7 with a treatment difference of 0.15 between QVM149 vs. QMF149 at the corresponding doses, assuming standard deviation of 0.80 based on studies QMF149A2210, QMF149E2201 and QMF149E2203 and Kerstjens (2012);

If 10% dropout rate is assumed, then calculation shows that the sample size of 2980 patients (i.e 596/arm) will provide 97% power for item 1 and 82% power for item 2, with multiplicity adjustment as given in Figure 9-1.

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

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US 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 may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, 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 should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should 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 (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should 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

[redacted]

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 should 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 should not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

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

Investigators 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. All significant protocol deviations will be recorded and reported in the CSR.

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

[redacted]

implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 for safety monitoring should be followed.

12 References

References are available upon request:

Barnes PJ et al (2014) The Asthma Control Questionnaire as a clinical trial endpoint: past experience and recommendations for future use.

Bateman ED et al (2004) Can guideline-defined asthma control be achieved? The Gaining optimal Asthma ControL Study. Am J Respir Crit Care Med;170:836-844.

Bateman ED et al (2011) Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. J Allergy Clin Immunol 2011; 128:315-22.

Beakes DE (1997) The use of anticholinergics in asthma. J Asthma 34 (5): 357-368).

Beasley R, Lanier B, Varkonyi I et al (2012). Safety of once-daily QMF149 in patients with persistent asthma. Eur Respir J; 40 (Suppl 56): P371.

Beasley R, Lanier B, Mark Z et al (2012a). Long-term efficacy of QMF149 in persistent asthma. Eur Respir J; 40 (Suppl 56): P31

Beasley R et al (2015). Effect of once-daily indacaterol maleate/mometasone furoate on exacerbation risk in adolescent and adult asthma: a double-blind randomised controlled trial; BMJ Open 5(2):e006131. doi: 10.1136/bmjopen-2014-006131

Befekadu E, Onofrei C, Colice GL (2014) . Tiotropium in asthma, a systemic review. JAA ; 7: 11-21.

Bretz F, Maurer W, Brannath W, and Posch M (2009). A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine; 28: 586-604.

Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, and Rohmeyer K (2011). Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. Biometrical Journal; 53: 894-913.

European Medicines Agency (2013). Note for guidance on clinical investigation of medicinal products for treatment of asthma. CHMP/EWP/2922/01-rev.1. 27 June 2013.

Fardon T et al (2007) A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma. Respiratory Medicine; 101: 1218-1228.

Global Initiative for Asthma (GINA) 2015 Global Strategy for Asthma Management and Prevention (available on GINA website) Updated 2017 (available upon request)

[redacted]

Guyer AC, Long AA (2013) Long-acting anticholinergics in the treatment of asthma. Allergy Clin Immunol; 13:392-398

Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE (1993) Measuring quality of life in asthma. Am Rev Respir Dis. Apr; 147(4):832-8

Juniper EF et al (1994) Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol; 47: 81-87.

Juniper EF et al (1999) Development and validation of the questionnaire to measure asthma control. Eur Resp J; 14: 902-907.

Juniper EF, Svensson K, Mork AC et al. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005; 99:553-8.

Juniper EF et al (2006) Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med; 100: 616-62.

Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53(3):983-97.

Kerstjens HAM et al (2011) Tiotropium improves lung function in patients with severe uncontrolled asthma: A randomized controlled trial. J Allergy Clin Immunol; 128:308-314.

Kerstjens HAM et al (2012). Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy. N Engl J Med; 367: 1198-1207

Kerstjens HAM et al (2015) Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. Lancet Respir Med.3(5):367-76

Masoli M et al (2004). The Global Burden of Asthma Report, Global Initiative for Asthma (GINA). Available from www.ginasthma.org

Maurer W, Glimm, and Bretz F (2011). Multiple and repeated testing of primary, coprimary, and secondary hypotheses. Statistics in Biopharmaceutical Research; 3; 336-352.

Peters SP et al (2010) Tiotropium bromide as step-up therapy for adults with uncontrolled asthma. N Engl J Med; 363(18): 1715-1726.

Quanjer PH., et al. (1993), Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J; 6 suppl. 16: 5-40.

Rohmeyer K, Klinglmueller F, and Bornkamp B (2012). Package 'gMCP' graph based multiple comparison procedures: http://cran.r-project.org/web/packages/gMCP/gMCP.pdf.

Testi 2014, White Paper, Long Acting Muscarinic Agent (LAMA). A new Frontier for COPD and Asthma Treatment. Available on www.cromsource.com

Vaidya S, Khindri S, Robertson J et al (2012) Pharmacokinetics (PK) of single doses of mometasone furoate (MF) delivered via the Breezhaler® (BH) and Twisthaler® devices in healthy subjects. Eur Respir J; 40 (Suppl 56): P382.

[redacted]

13 Appendices

Appendix 1: Instruction for Use of Concept1

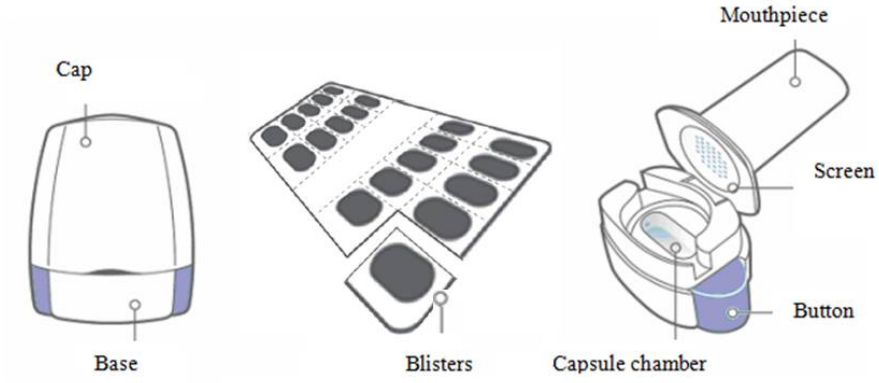
Instructions for using inhaler and capsules.

Do not swallow capsules.

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

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

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



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

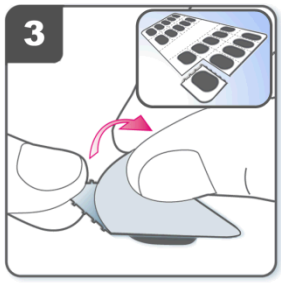
Do not use the study medication capsules with any other capsule inhaler, and do not use the inhaler to take any other capsule medicine.

[redacted]

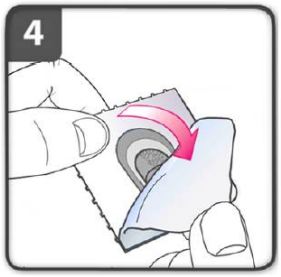
How to use your inhaler

Pull off cap.

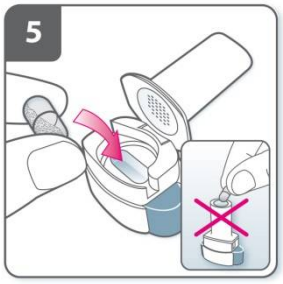
Open inhaler:
Hold the base of the inhaler firmly and tilt back the mouthpiece. This opens the inhaler.



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.



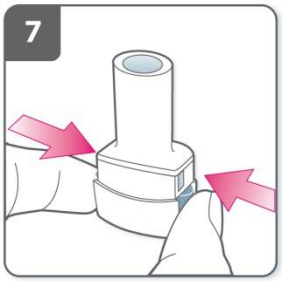
Remove a capsule:
Peel away the foil and remove the capsule from the blister.



Insert capsule:
Place the capsule into the capsule chamber.
Never place a capsule directly into the mouthpiece.

[redacted]

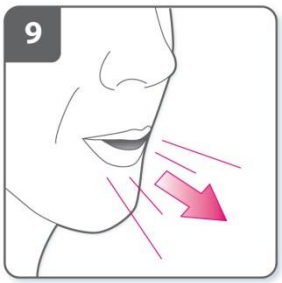
Close the inhaler:
You should hear a “click” as the mouthpiece closes onto the inhaler base.



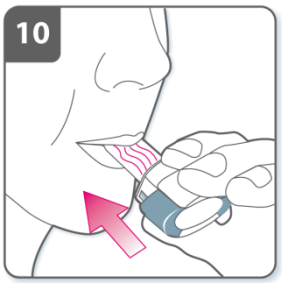
Pierce the capsule:

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

Release the side buttons fully.



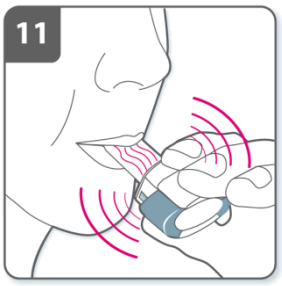
Breathe out:
Before placing the mouthpiece in your mouth, breathe out fully.
Do not blow into the mouthpiece.



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.

[redacted]

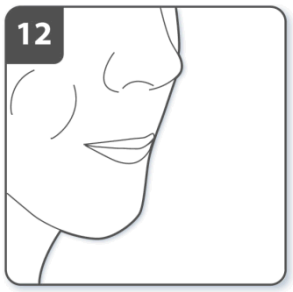


Note:
As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. You will experience a sweet flavor as the medicine goes into your lungs.

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.

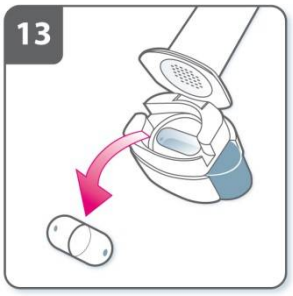
If there is powder left in the capsule:

- 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.

[redacted]



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.

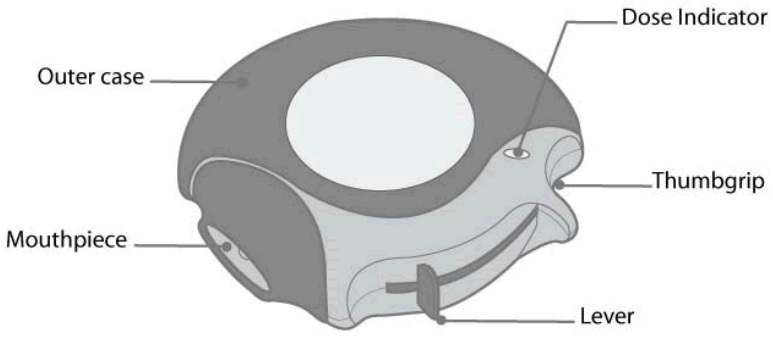
[redacted]

Appendix 2: Instruction for use of Accuhaler®/Diskus®

Instructions for use

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

Figure 1 Parts of the Diskus



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

Figure 2 Dose Indicator for the Diskus

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

1. OPEN

[redacted]

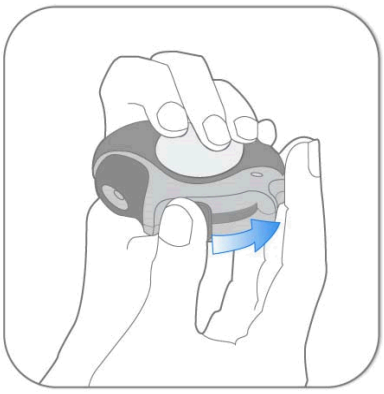
Hold the Diskus in one hand and put the thumb of your other hand on the **thumbgrip.** Push your thumb away from you as far as it will go until the mouthpiece appears and snaps into position (see Figure 3*)*.

Figure 3 Opening the Mouthpiece Cover

2. CLICK

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

Figure 4 Sliding the Lever Until It Clicks



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

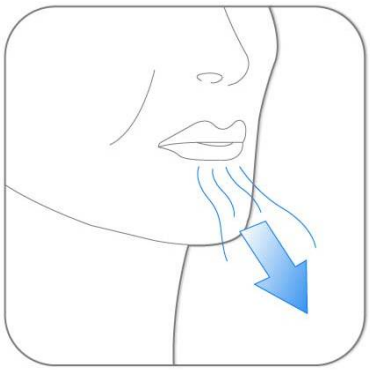
- Do not close the Diskus.
- Do not tilt the Diskus.
- Do not play with the lever.
- Do not move the lever more than once.

3. INHALE

[redacted]

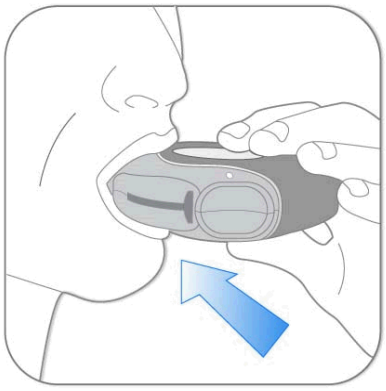
Before inhaling your dose from the Diskus, breathe out (exhale) fully while holding the Diskus level and away from your mouth (see Figure 5). **Remember, never breathe out into the Diskus mouthpiece.**

Figure 5 Exhaling



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

Figure 6 Inhaling



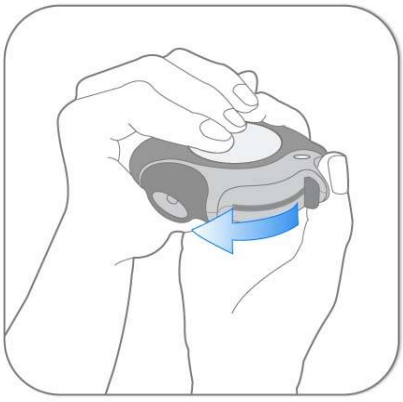
Remove the Diskus from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly. The Diskus delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the Diskus if you do not feel or taste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

4. CLOSE

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

[redacted]

Figure 7 Closing the Mouthpiece Cover



Remember:

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

[redacted]

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.

[redacted]

Acceptability

An acceptable maneuver has the following characteristics:

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

Repeatability

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

Recording of data

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

Predicted normal

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

Reversibility

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

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

Reversibility is calculated as:

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

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

References

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

[2] Quanjer PH et al. ERS Global Lung Function Initiative. Multi ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. Report of the

[redacted]

Global Lung Function Initiative (GLI). ERS Task Force to establish improved Lung Function Reference Values.

[3]Kubota, Kobayashi, Quanjer PH, et al. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. Clinical Pulmonary Functions Committee of the Japanese Respiratory Society. Respiratory Investigations 2014, 242-250.

[redacted]

Appendix 4: ACQ-7

ASTHMA CONTROL QUESTIONNAIRE© PATIENT ID:_____

DATE:_____

Page 1 of 2

Please answer questions 1 - 6.

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

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

[redacted]

ASTHMA CONTROL QUESTIONNAIRE© PATIENT ID:_____

DATE:_____

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

To be completed by a member of the clinic staff

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

[redacted]

Appendix 5: AQLQ-S

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE _____

Page 1 of 5

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

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

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

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

5. SLEEPING	1	2	3	4	5	6	7

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

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

[redacted]

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE _____

Page 2 of 5

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

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

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

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

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

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

[redacted]

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE _____

Page 3 of 5

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

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

[redacted]

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE _____

Page 4 of 5

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

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

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

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

[redacted]

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID _____

SELF-ADMINISTERED DATE _____

Page 5 of 5

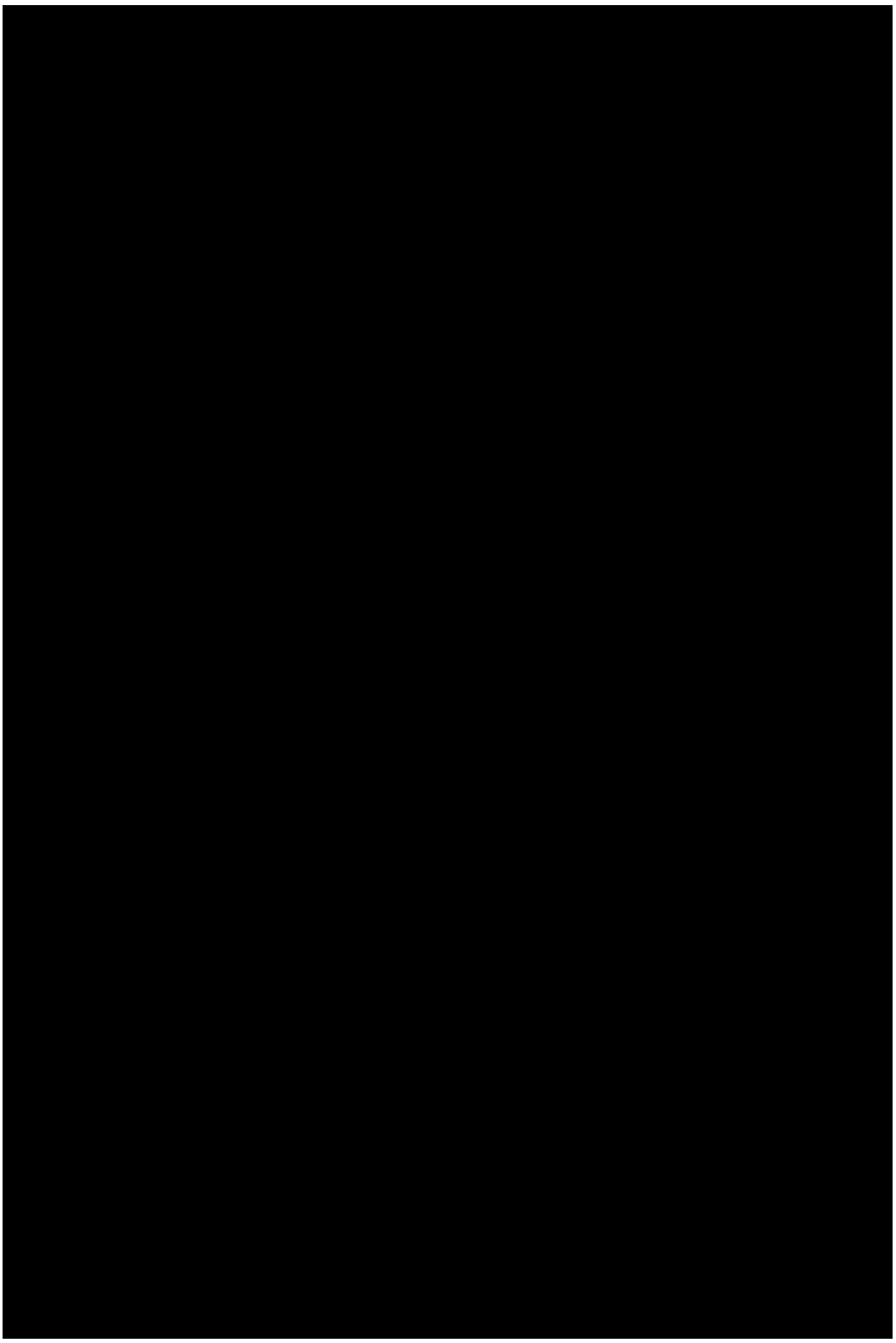
HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

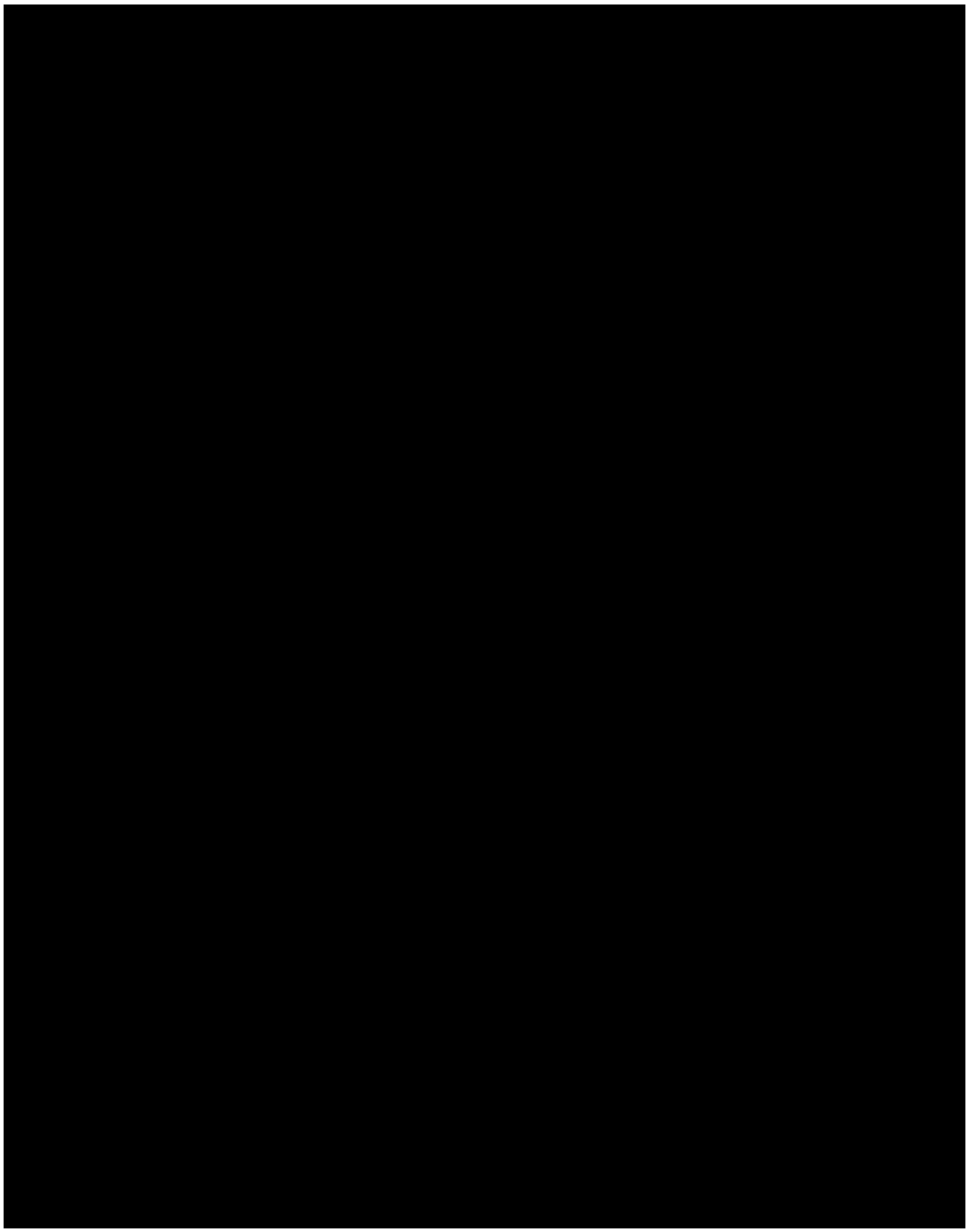
	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

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

[redacted]





Appendix 7: 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

[redacted]

Appendix 8: Liver event definitions and follow-up requirements

Table 13-1 Liver Event Definitions

	Definition/ threshold
Adverse event of special interest	
Laboratory values	ALT or AST > 3 x ULN
	ALP > 2 x ULN
	TBL > 1.5 x ULN
Medically significant event (SAE)	
Laboratory values	ALT or AST > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	ALP > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	TBL > 3 x ULN
	Potential Hy's Law cases (defined as ALT/AST > 3 x ULN and TBL > 2 x ULN [mainly conjugated fraction] without notable increase in ALP to > 2 x ULN)
Adverse events	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 x ULN accompanied by general malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any event that links to a preferred term (PT) in the MedDRA dictionary falling under the SMQ sub-module "Drug-related hepatic disorders – severe events only"* or any "Hy's law case" PT

* 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

[redacted]

Table 13-2 Liver Event Follow Up Requirements

Criteria	Event type	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Medically significant	Discontinue the study drug immediately Hospitalize, if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST			
> 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists for *more than 2 weeks*, discontinue the study drug Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 x ULN accompanied by symptoms[b]	Medically significant	Discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis Repeat LFT once or twice in the week If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 3 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
ALP (isolated)			
> 5 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, report to Novartis as an SAE Establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
> 2 to ≤5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis Repeat LFT once or twice in the weekIf elevation persists,	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

[redacted]

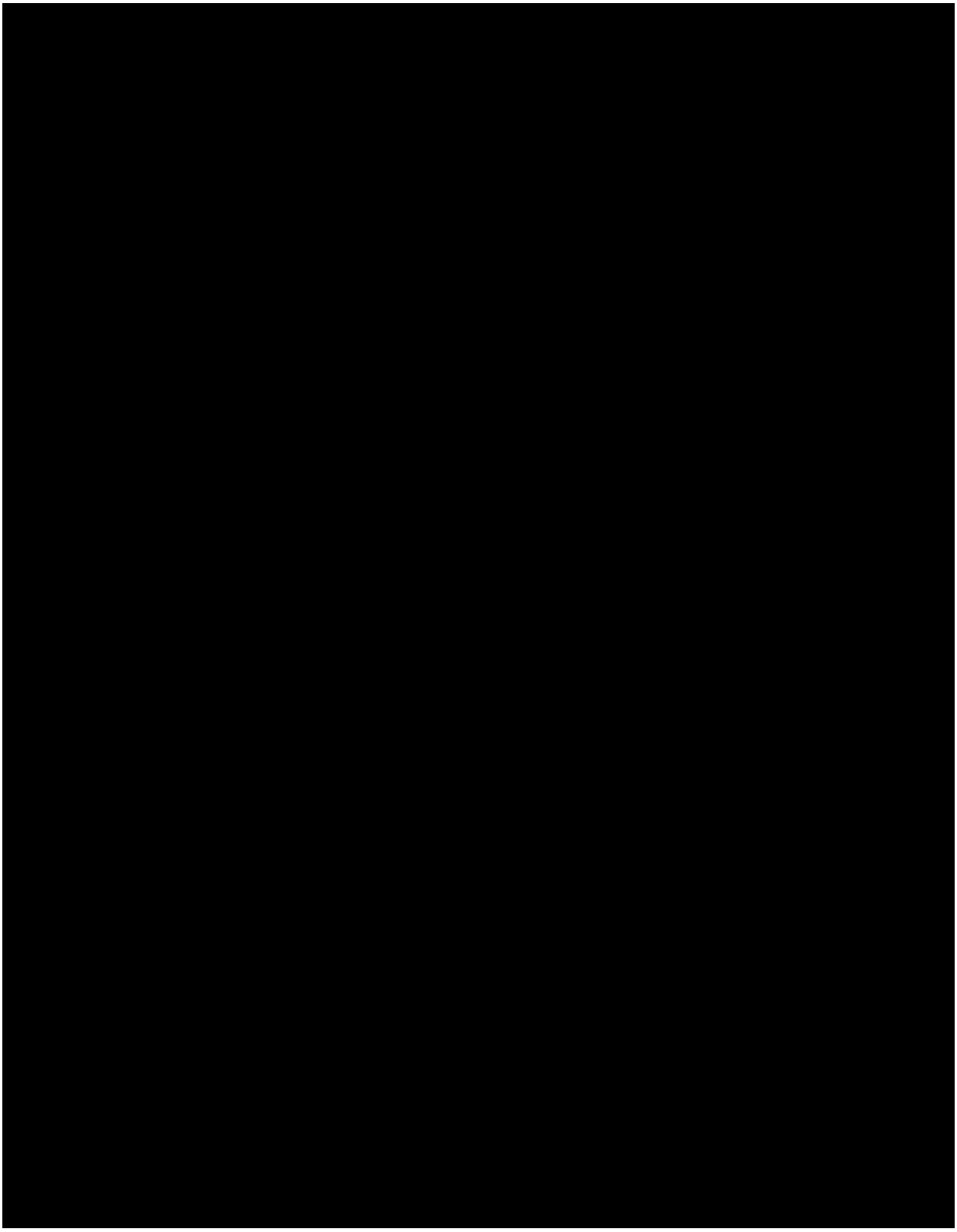
Criteria	Event type	Actions required	Follow-up monitoring
		establish causality	
≤ 2 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
TBL (isolated)			
> 3 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 3 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Novartis Repeat LFT once or twice in the weekIf elevation persists, establish causality	investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 1.5 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
Preferred terms			
Jaundice	Medically significant	Discontinue the study drug immediately Hospitalize the patient Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
"Drug-related hepatic disorders - severe events only" SMQ AE	Medically significant	Discontinue the study drug hospitalization if clinically appropriate Report to Novartis as an SAE Establish causality	Investigator discretion

[a] Elevated ALT/AST > 3 x ULN and TBL > 2 x ULN but with no notable increase in ALP to > 2 x ULN

[b] General malaise, fatigue, abdominal pain, nausea, or vomiting, rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: return to baseline values, stable values at three subsequent monitoring visits at least 2 weeks apart, remain at elevated level after a maximum of 6 months, liver transplantation, and death.

[redacted]



Appendix 10: Low, medium and high Daily Doses of Inhaled Glucocorticosteroids for Adults*

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

*GINA 2015, Summary of Product Characteristics of Relvar Ellipta for Fluticasone Furoate

** Beclomethasone dipropionate CFC is included for comparison with older literature.

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

Patients treated with ICS mono-therapy in addition to combination of ICS/LABA are not eligible for the study

[redacted]