NOVARTIS

Global Clinical Development - General Medicine

QVM149B (QMF149: Indacaterol acetate/Mometasone furoate)

CQVM149B2301 / NCT02554786

A multi-center, randomized, 52 week treatment, double-blind, triple-dummy, parallel-group study to assess the efficacy and safety of QMF149 compared with mometasone furoate in patients with asthma

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List of abbreviations

ACQ	Asthma Control Questionnaire
AE / SAE	Adverse event / Serious adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification
AQLQ	Asthma Quality of Life Questionnaire
b.i.d.	Twice a day
BMI	Body Mass Index
BUN	Bilirubin Unit Normalized
CFR	US Code of Federal Regulations
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
FVC	Forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HV	Healthy volunteer
[redacted]	[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
Pbo	Placebo
PEF	Peak expiratory flow
PI	Post inhalation
PK	Pharmacokinetics
PPS	Per protocol set
PRO	Patient reported outcome
p.o.	Oral (ly)
RAN	Randomization set
SABA	Short acting beta-2 agonist
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 5

Amendment Rationale:

Conduct primary analysis after all patients have completed at least 26 weeks treatment (V207):

The primary and key secondary endpoints of CQVM149B2301 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.

Modification of analysis of key secondary endpoint, ACQ-7: The key secondary objective has been modified to demonstrate the benefit of indacaterol (QAB149) 150 µg monotherapy on ACQ-7. This will be achieved by demonstrating superiority of combined medium and high QMF149 doses to combined medium and high MF doses, respectively in terms of ACQ-7 after 26 weeks of treatment. The analysis will be performed only if the individual treatment comparisons are significant for the primary endpoint, trough FEV_1 at week 26 (i.e., there is an evidence of efficacy of both doses of QMF149 over respective MF doses in terms of trough FEV_1). Sample size has been re-calculated based on updated objective and multiplicity adjustment. Assuming 10% dropout, the calculation shows that a sample size of approximately

[redacted]

2000 patients (i.e., 400/arm) will provide 94% power for primary endpoint trough FEV_1 and 85% power for key secondary endpoint ACQ-7.

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:

- Add an explanation for primary read-out when all patients have completed 26 weeks of treatment as above (Section 3.5, Section 5.3, Section 8.2 and Section 9.6)
- Revise the key secondary objective to demonstrate the superiority of add-on indacaterol (QAB149) 150 µg by demonstrating superiority of QMF149 (150/160 and 150/320 µg combined) to mometasone furoate doses (MF, 400 µg and 800 µg combined) in terms of ACQ-7 after 26 weeks of treatment (Section 2.2, Section 9.4).
- Changed the multiple testing strategy to reflect updated key secondary objective.
- Reduction in sample size to approximately 2000 (Section 4, Section 9.8)
- Add the clarification that the treatment for adverse events (including asthma exacerbations) is permitted (Section 5.4.8)
- 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)
- [redacted]
- 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 4); however, the text deletion was not done
- Revised targeted number of adolescents from 10% of sample size to approximately 5%.

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).

Additional changes were made in the protocol to reflect the US local amendment which took place between the global amendment 4 and amendment 5 in Section 5.4.13.

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 4 (14-Feb-2017)

Amendment rationale:

1. Modification of inclusion criteria for baseline ICS and ICS/LABA requirements and upper limit of FEV1 threshold. This is based on investigator feedback of real world asthma populations and intended to address variability in baseline FEV1 as well as 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 medium to high fixed dose combination of ICS/LABA.
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 (Section 4 and Section 9.7).

Changes to the protocol

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

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

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

- Change in inclusion 3 the required pre-treatment period of ICS or LABA /ICS from 1 year to 3 months prior to Visit 1 in inclusion criteria 4 (Section 4.1)
- Update inclusion criteria 6, inclusion criteria 7 in Section 4.1, and exclusion criteria 19 in Section 4.2 to allow repeat spirometry retest at Visit 101 and 102, modify timing for reversibility and modify the use of historical reversibility from 1 year to 2 years
- Update inclusion criteria 6 on the FEV1 upper range limit from <80% to <85%, allow a one-time rescreen in Section 4.1 and enhance the importance of complying with the asthma medication wash-out as per protocol
- Take out LAMA wash-out on criteria 6 of Section 4.1 and Table 5-2 in Section 4.2. Add an exclusion criteria to exclude any patients treated with LAMA within the last 3 months before Visit 101
- Add a clarification on myocardial infarction (MI) in exclusion criteria 13 and 16 (Section 4.2)
- Change the condition of spacer use for reversibility testing in inclusion 7 in Section 4.1 and excluding spacer use for rescue medication in exclusion criterion 27 in Section 4.2
- Update the definition of repeatability in the spirometry guidance in Appendix 4
- Add for run in medication that countries who do not have fluticasone 100 µg b.i.d by Accuhaler® or 125 µg b.i.d by MDI can use fluticasone low dose equivalent as per Appendix 11
- Add fluticasone furoate in Appendix 11, definition of dose of ICS

[redacted]

- Enhance importance of alert to have appropriate actions taken in Section 6.4.4
- Clarify in Section 3.1 that screening period is to ensure wash-out of prior asthma medication as per protocol and that therefore the time between Visit 1 and Visit 101 may be shorter than 2 weeks depending on the wash-out required.
- Clarify wording on Table 5-2
- Align Section 9 with the statistical analysis plan

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.

Amendment 3 (08-Sep-2016)

The amendment rationale was to modify the e-diary alert handling during the run-in.

In addition, the following clarifications or updates from Standards were included in this protocol amendment

- Clarify that smoking exclusion also pertains to the use of e-cigarettes in the exclusion criteria #01.
- Removing GINA reference from inclusion # 03 and # 05 as it is reflected in inclusion # 04
- Clarify the exclusion criteria #05 and in 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 that the FEV1 assessment in inclusion criteria #06 also needs to comply to ATS/ERS criteria
- Clarify the ECG prior to randomization (Visit 102) in exclusion criterion #16, although no ECG is scheduled at Visit 102, any clinically significant abnormal ECG before Visit 102 (including unscheduled ECG) should lead to exclusion.

[redacted]

- Include lactose as an example of hypersensitivity in the exclusion #18 since study drug is formulated using lactose blended dry powder.
- Clarify that repeat spirometry is permitted in cases where the spirometry did not meet ATS/ERS criteria at Visit 101 in inclusion #07 and exclusion #19.
- Specify "severe" narcolepsy and/or insomnia in exclusion criteria #23.
- Exclusion criteria #32
  - 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.
- Add IL-5 inhibitor (e.g., mepolizumab) in the Prohibited asthma-related medications (Table 5-2).
- Clarify the conditions in which anti-histamine use is permitted in Table 5-4.
- Clarify when pregnancy test is required in Section 6.5.7.
- Add the maximum duration of device usage in Appendix 1 (to address questions received in some countries).
- Specify that time between Visit 1 and Visit 101 can be adapted according to the required wash-out from previous medication as per Table 6-1.
- Clarify timing of urine analysis in Table 6-2.
- Numbering on exclusion criteria was entered.
- Update in Section 7.4 the follow-up period "up to 3 months after birth" in case a female patient is pregnant during the study.
- As Visit 299 does not have a specific eCRF 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".
- Update of Section 7.2.1 for Serious Adverse Event reporting.

Amendment 2 (01-Oct-2015)

The amendment rationale was to modify ACQ score inclusion from ACQ>2 to ACQ≥1.5

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

- 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)
- Differentiate the reversibility and the pre-bronchodilator spirometry assessments on Table 6-1 to clarify that the reversibility is only done at Visit 101

[redacted]

- 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 of the best of the three daily PEF efforts over the past 14 days.
- Clarify the wording for ECG timing to be done at Visit 210 in Section 6.5.5
- Add footnote on Table 6-1 to specify that historical reversibility or bronchoprovocation are acceptable as inclusion criteria.
- [redacted]
- 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
- Insert the whole questionnaire on Appendix 7
- [redacted]
- Add clarification on analysis timepoint in Section 9.4.6, Section 9.5.1.3, Section 9.5.1.4 and statistical method used in Section 9.5.1.6.

Amendment 1 (30-Jul-2015)

This amendment is in order to comply with the Health Authorities requirements received after finalization of the protocol version 00 regarding the pediatric population before finalization of the Pediatric Investigational Plan.

As this protocol includes adolescent patients, the following changes were made:

- Modify the Section 5.4.9 in order to permanently discontinue study drug for any adolescent patients after one asthma exacerbation requiring hospitalization.
- Modify inclusion criteria number 4 and 5 in Section 4.1 and in the protocol summary to change the requirement of previous treatment of "any" dose of LABA/ICS to "low" dose of LABA/ICS. Also patients should qualify for treatment with medium or high dose LABA/ICS (GINA 2015 step≥ 3). The Section 9.4.6 was modified accordingly for the subgroup analysis.

The opportunity was taken to also make the following changes and revisions:

- Change ACQ-5 to be given to the patients and site to ACQ-7 on Table 5-5, Table 6-1, Section 6.4.2 and Section 9.5.1.2. Derivation of rescue medication from e-diary (6th item on ACQ) and FEV1 (07th item on ACQ) will not be performed
- Specification in Section 6.3 that the patient will have to enter on the e-diary the compliance of study drug once a week.
- Update on Section 6.4.3 in order to be aligned with Section 6.3.
- Update on Section 6.4.3.1 in order to clarify the PEF measurement start and update Table 6-1 accordingly

[redacted]

[redacted]

- Update of the questions of Appendix 8 for the Patient Asthma diary in order to align to the exacerbations definitions.

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

The following minor omission and clarification are additionally included in this protocol amendment:

- Specifying on Section 4 the recruitment of approximately 10% adolescents in the trial to be consistent with the Protocol Summary
- Adding the ACQ-7 in Appendix 5 and AQLQS+12 questionnaire in Appendix 6

[redacted]

Protocol summary

Protocol number	CQVM149B2301
Title	A multi-center randomized 52-week treatment, double-blind, triple-dummy, parallel-group study, to assess the efficacy and safety of QMF149 compared with mometasone furoate in patients with asthma
Brief title	Safety and Efficacy study of QMF149 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 QMF149 (QMF149 150/160 µg and QMF149 150/320 µg via Concept1) over two respective MF doses (MF 400 µg and MF 800 µg via Twisthaler® (total daily dose)) in poorly controlled asthmatic patients as determined by pulmonary function testing and effects on asthma control.
Primary Objective(s)	The primary objective is to demonstrate the superiority of QMF149 delivered via Concept1 to MF delivered via Twisthaler® in terms of trough FEV_1 after 26 weeks of treatment in patients with asthma.
Key Secondary Objective	The key secondary objective is to demonstrate the superiority of QMF149 (150/160 and 150/320 µg combined) to mometasone furoate doses (MF, 400 and 800 µg combined)in terms of ACQ-7 after 26 weeks of treatment in patients with asthma.
Study design	52 weeks Multi-center, randomized, double-blind, triple-dummy, parallel-group, active controlled study
Population	The study population will consist of approximately 2000 males and females with asthma (5% adolescents) and patients will be stratified according to prognostic factors of age (12 to 17 years or ≥ 18) and region.
Key Inclusion criteria	• Patients with a diagnosis of asthma for a period of at least 1 year prior to Visit 1 (Screening) • Patients who have used medium or high dose ICS (please refer to Appendix 11 for guidance) or low dose of LABA/ICS combinations for asthma for at least 3 months and at stable doses for at least 1 month prior to Visit 1 • Patients must be symptomatic at screening despite treatment with mid or high stable doses of ICS and/or low dose combinations of ICS with long-acting beta adrenergic agent. Patients must have ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (prior to double-blind treatment) and qualify for treatment with medium or high dose LABA/ICS • In case that the spirometry is repeated due to a failure of meeting criterion 7, ACQ-7 should be repeated as well. • Pre-bronchodilator ≥ 50% FEV_1 and < 85 % of the predicted normal value for the patient after withholding bronchodilators (see Table 5-2) at both Visit 101 and 102. Withholding period of bronchodilators prior to spirometry: • SABA for ≥ 6 hours

[redacted]

	• FDC or free combinations of ICS*/LABA for ≥ 48 hours • SAMA for ≥ 8 hours • Xanthines ≥ 7 days Washout period of each drug should be kept as close as possible as above and should not be longer. If wash-out period is considered to be longer, please contact your Novartis Medical Monitor A one-time repeat of percent predicted FEV_1 (pre-bronchodilator FEV_1) is allowed at Visit 101 and/or Visit 102 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 at Visit 101. * in case of combination LABA/ICS, ICS should be continued. A one time rescreening is allowed provided the patient returned to the required treatment as per inclusion 4. • 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: • 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. Spacer devices are permitted during reversibility testing only. The Investigator or delegate may decide whether to use spacer or not for the reversibility testing.
Key Exclusion criteria	• Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of Visit 1 (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 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

[redacted]

	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: • QMF149 (indacaterol acetate/MF) 150/160 µg o.d. (in the evening) delivered as powder in hard capsules via Concept1 inhaler. • QMF149 (indacaterol acetate/MF) 150/320 µg o.d. (in the evening) delivered as powder in hard capsules via Concept1 inhaler. The Comparative treatments are: • MF 400 µg o.d. (in the evening) delivered via Twisthaler® • MF 800 µg total daily dose (administered as 400 µg b.i.d.) delivered via Twisthaler®) • Salmeterol/fluticasone 50/500 µg b.i.d. delivered as powder via Accuhaler® In addition the following placebo will be provided to enable the triple-dummy design of the study: • Placebo, b.i.d. or o.d. delivered via Twisthaler® • Placebo o.d. delivered as powder in capsules via Concept1 inhaler (evening)Placebo b.i.d. delivered as powder via Accuhaler®
Efficacy assessments	• Spirometry • Health Status (PROs) • e-Diary • Peak Expiratory Flow • Rescue Medication Use
Safety assessments	• Medical history and physical examination oropharyngeal examination and height measurements for adolescents • Vital signs • Hematology, Blood chemistry, Urinalysis • Evening plasma cortisol • ECG • Adverse events including asthma exacerbations and serious adverse events • Pregnancy (female patients) • Serious asthma outcomes (asthma-related hospitalizations, intubations or deaths)
Other assessments	• Asthma exacerbation [redacted] • PROs (ACQ-7, AQLQ-S+12, [redacted])
Data analysis	**The primary objective** is to demonstrate the superiority of either QMF149 150/160 µg delivered via Concept1 o.d. (in the evening) to MF 400 µg delivered via Twisthaler® or QMF149 150/320 µg delivered via Concept1 o.d. (in the evening) to MF 800 µg delivered via Twisthaler® (delivered as 400 µg b.i.d.) in terms of trough FEV_1 after 26 weeks of treatment in patients with asthma.

[redacted]

	The comparisons of QMF149 150/160 µg versus MF 400 µg and QMF149 150/320 µg versus MF 800 µg will be evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a): H_0: QMF149 treatment group is equal to MF treatment group in trough FEV_1 at Week 26 H_a: QMF149 treatment group is not equal to MF 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, age (12 to 17 or ≥ 18 years), 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 estimated adjusted treatment difference (QMF149 – MF) will be displayed along with the associated standard error, 2-sided 95% confidence interval (CI), and p-value (2-sided). **The key secondary objective** is to demonstrate the superiority of QMF149 (150/160 and 150/320 µg combined) to mometasone furoate doses (MF, 400 µg and 800 µg combined) in terms of ACQ-7 after 26 weeks of treatment in patients with asthma. The key secondary variable ACQ-7 will be analyzed using the same MMRM model (including the appropriate visits) on the FAS as used for the primary analysis but will include baseline ACQ-7 score instead of baseline FEV_1. To demonstrate the add-on effect of indacaterol over MF, the average of following treatment contrasts will be computed: QMF149 (150/160 µg) vs. MF 400 µg QMF149 (150/320 µg) vs. MF 800 µg. **Multiplicity handling:** To control the family-wise type-I error rate at the two-sided 5% significance level, a multiple testing procedure based on the trimmed Simes test in Brannath et al (2009) is used. The family for the overall type-I error rate control contains three hypotheses including: • Two hypotheses for the primary endpoint trough FEV_1 • One hypotheses for the key secondary endpoint ACQ-7. Denote the two hypotheses for the primary endpoint as H1 and H2 for comparing QMF149 150/160 µg vs. MF 400 µg and QMF149 150/320 µg vs. MF 800 µg respectively. Similarly, denote the hypothesis as H3 for comparing QMF149 vs. MF in terms of ACQ-7. Below is a brief description of the testing procedure based on the trimmed Simes test in Brannath et al (2009). Let p_1, p_2, p_3 be the corresponding p-values (2-sided) of the three hypotheses of H1, H2, and H3. Step 1: Retain both H1 and H2 if $p_i \leq 0.05$ AND the observed treatment difference for the corresponding p_i is in the wrong direction (i.e. MF is

	performing better than QMF) for ANY i = 1, 2, stop here; otherwise go to Step 2; Step 2: Reject H1 and H2 if $p_i < 0.05$ for BOTH i = 1, 2 and go to Step 3; otherwise go to Step 4; Step 3: Reject H3 if $p_3 < 0.05$ and stop; Step 4: If neither Step 1 nor Step 2 applies, perform the Bonferroni test to H1 and H2. Thus reject H1 if $p_1 < 0.025$ or reject H2 if $p_2 < 0.025$ and stop.
Key words	QMF149, Mometasone furoate (MF), asthma

[redacted]

1 Introduction

1.1 Background

Asthma is a chronic inflammatory disorder of the airways associated with hyper responsiveness of airways 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. Although exacerbations of asthma are episodic, inflammation is chronic (GINA 2015).

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

Global Initiative for Asthma guideline (GINA 2015) recommends as preferred controller treatment for step ≥ 3 the combination of LABA/ICS with a low dose ICS in step 3, increasing the ICS dose to medium and high in step 4 and addition of monoclonal antibodies i.e. anti-IgE) or referral to specialist investigation in step 5 (GINA 2015). Alternative controller treatment for step ≥ 3 is medium/high dose ICS.

Fixed dose combination (FDC) products containing a LABA plus ICS have been shown to be safe and effective in the management of asthma. However, most of currently available FDC products (e.g. salmeterol xinafoate/fluticasone propionate) require twice-daily (b.i.d.) dosing to achieve an optimum therapeutic effect in asthma.

Novartis is developing QMF149, an inhaled FDC of indacaterol acetate, a LABA with a 24-hour duration of action and mometasone furoate (MF) an ICS, as a once daily (o.d.) maintenance treatment of asthma QMF149 is formulated as a lactose-blended inhalation powder, hard capsule, delivered by a single dose dry powder inhaler (SDDPI), referred to as the Concept1 device (also known in some regions as the Breezhaler® device), the approved inhalation device for use with indacaterol maleate and other COPD inhalation therapies.

QMF149 is developed under the QVM149 (indacaterol acetate/glycopyrronium bromide/mometasone furoate) program and therefore all the studies are coded as QVM149.

Background data for the monotherapies:

Indacaterol

Indacaterol maleate, delivered via the Concept1 device, 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. In addition to the extensive evidence for indacaterol maleate delivered via the Concept1 device in COPD, there are clinical data to support the efficacy and safety of indacaterol (as acetate salt) in asthma both as monotherapy (as add-on to existing ICS) as well is in the fixed dose combination QMF149 (indacaterol maleate/MF) delivered by the Twisthaler® device in asthma

patients. Indacaterol maleate delivered by Twisthaler® has been studied in healthy volunteers (HV), adult patients with COPD and adult and adolescent patients with asthma.

Study CQMF149E2203 investigated two doses of indacaterol acetate, 75 µg and 150 µg delivered via Concept1 in adult patients with asthma and demonstrated superiority of treatment with indacaterol acetate 75 µg and 150 µg to placebo in terms of trough FEV_1 after 12 weeks of treatment. Although the study was not powered to show a statistically significant difference between indacaterol acetate 150 µg and 75 µg for the efficacy objectives, it demonstrated positive trends in favor of indacaterol acetate 150 µg in terms of trough FEV_1 PEF and rescue medication use compared with indacaterol acetate 75 µg. Both indacaterol acetate doses 150 µg and 75 µg treatments were safe and well tolerated.

QMF149 (mometasone/indacaterol) in Twisthaler device in asthma

Phase II study CQMF149A2210 - an event driven study up to 68 weeks - 1508 asthmatic patients were treated (66 patients 12-17 years old). 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 study demonstrated that both QMF149 resulted in greater reductions in asthma exacerbations compare to MF and had beneficial effects 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 (Beasley R et al, 2015).

Mometasone furoate

Mometasone furoate (MF) is marketed in inhalation, nasal, cream, ointment and lotion formulations. MF in the Twisthaler® device, a multi dose dry powder inhaler (MDDPI), (Asmanex®) is approved for the once daily or twice daily treatment in over 55 countries world-wide in patients with asthma. 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 60 countries world-wide for the treatment of asthma in adults and adolescents ≥ 12 years of age.

In addition, MF in combination with formoterol fumarate as Dulera® (inhalation aerosol) has been approved in the United States and as Zenhale® (HFA) in Canada as a maintenance treatment for asthma in adults and children who are at least 12 years old.

In adult and adolescent patients 12 years of age and older, MF (Asmanex® Twisthaler®) was studied in 10 placebo-controlled clinical trials of 8 to 12 weeks duration with a total of 1750 patients receiving Asmanex® Twisthaler®. There were also 3 trials with a total of 475 patients receiving Asmanex® Twisthaler® for 1 year. In the 8 to 12-week clinical trials, the population was 12 to 83 years of age. In 3 long-term safety trials (two 9-month extensions of efficacy trials and one 52-week active-controlled safety trial), 475 patients with asthma received various doses of Asmanex® Twisthaler® for 1 year.

[redacted]

In pediatric patients 4 to 11 years of age, Asmanex® Twisthaler® was studied in 3 placebo controlled clinical trials of 12 weeks duration with a total of 630 patients receiving Asmanex® Twisthaler® and a 52-week, active-controlled safety trial with a total of 152 patients receiving Asmanex® Twisthaler®.

In the QMF149 program, the indacaterol acetate salt will be used. Indacaterol maleate salt has been associated with post-inhalational cough, both as a monotherapy and part of a fixed-dose combination with MF (in the Twisthaler®), without any negative impact on safety, efficacy or tolerability in patients with COPD or asthma. The acetate salt of indacaterol was chosen following demonstration of a significantly lower incidence of post-inhalational (PI) cough with acetate and xinafoate salts compared with the maleate salt without any impact on safety and comparable efficacy and systemic exposure (CQAB149D2301).

In this study, the fixed dose combination of mometasone and indacaterol, QMF149 will be delivered by Concept 1 device. Since existing data for the MF component exists in the Twisthaler® device, a 3 step bridging bridging approach was conducted to determine MF dose for Concept 1 which is comparable to each of the registered daily doses of Asmanex Twisthaler® (mometasone furoate, inhalation powder). Step 1: pharmacokinetic bridging utilizing pharmacokinetic characterization in study CQMF149E2101 (Vaidya S et al, 2012) followed by in-vitro fine particle mass adjustment (step 2) and finally pharmacodynamic evaluation of efficacy in asthma patients in study CQMF149E2201 (step 3).

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

Table 1-1 Comparable MF monocomponent doses between Asmanex Twisthaler and QMF149 Concept1

MF dose level	MF dose in Asmanex delivered by Twisthaler®	MF dose in QMF149 delivered by Concept1 (Breezhaler®)
Mid	400 µg	160 µg
High	800 µg	320 µg

In summary, over 1,700 subjects have been exposed to QMF149 in 8 completed studies in healthy volunteers or asthma patients. These clinical studies used either indacaterol maleate or QMF149 FDC (indacaterol maleate /MF) delivered by Twisthaler® at doses up to 500/800 µg (comparable with 150/320 µg in Concept1) once daily. Studies using the Twisthaler® device include component interaction (CQMF149A2102 and CQMF149A2206) in healthy volunteers, ethnic sensitivity (CQMF149A2101) in Japanese and Caucasian healthy volunteers, mechanistic disposition (CQMF149A2212) in healthy volunteers, 24 hour lung function

profiling (CQMF149A2202) in asthma patients, and efficacy, safety and tolerability (CQMF149A2203, CQMF149A2204 and CQMF149A2201) in asthma patients.

In addition to Twisthaler® data, there is clinical data for QMF149 delivered by Concept1 from the ethnic sensitivity study CQMF149E1101 and from component interaction study CQMF149E2102. PK, safety and tolerability of multiple, once daily doses of QMF149 150/80 µg (fixed-dose combination of 150 µg indacaterol acetate, 80 µg MF) and 150/320 µg orally inhaled via Concept1 were evaluated in 48 healthy Japanese and Caucasian male subjects in Study CQMF149E1101. Results showed an increase (23-30%) in exposure for indacaterol and MF in Japanese subjects that is not thought to be clinically relevant and is not expected to raise any safety concerns.

Study CQMF149E2102 in which 64 healthy volunteers were exposed to repeated doses of QMF149 (indacaterol acetate/MF) 150/320 µg showed similar systemic exposure was noted for the free vs. mono comparison for both analytes, indicating a lack of PK interaction.

The efficacy and safety available data for QMF149 and its monocomponents supports progress to Phase III to evaluate further the efficacy and safety in asthma.

1.2 Purpose

The purpose of the trial is to evaluate efficacy and long term safety of two different doses of QMF149 (QMF149 150/160 µg and QMF149 150/320 µg via Concept1) over two respective MF doses (MF 400 µg and MF 800 µg via Twisthaler® (total daily dose)) in poorly controlled asthmatic patients as determined by pulmonary function testing and effects on asthma control.

2 Study objectives

2.1 Primary objective

The primary objective is to demonstrate the superiority of either QMF149 150/160 µg delivered via Concept1 o.d. (in the evening) to MF 400 µg o.d (in the evening) delivered via Twisthaler® or QMF149 150/320 µg delivered via Concept1 o.d. (in the evening) to MF 800 µg delivered via Twisthaler® (delivered as 400 µg b.i.d.) in terms of trough FEV_1 after 26 weeks of treatment in patients with asthma.

2.2 Key Secondary objective

The key secondary objective is to demonstrate the superiority of QMF149 (150/160 and 150/320 µg combined) to mometasone furoate doses (MF, 400 µg and 800 µg combined) in terms of ACQ-7 after 26 weeks of treatment in patients with asthma.

2.3 Secondary Objectives

The secondary objectives will consider the following 2 comparison groups:

- QMF149 150/160 µg o.d. delivered via Concept1 compared to MF 400 µg o.d. delivered via Twisthaler®
- QMF149 150/320 µg o.d. delivered via Concept1 compared with MF 400 µg b.i.d. delivered via Twisthaler®

[redacted]

The secondary objectives will evaluate the efficacy in terms of:

- Trough FEV_1 at Week 52
- Pre-dose FEV_1 (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) at Week 4, Week 12 and Week 52
- Percentage of patients achieving the minimal important difference (MID) ACQ $\geq$ 0.5 at Week 26 and Week 52
- Daily e-Diary recordings of the percentage of asthma symptoms free days , no day-time symptoms, the percentage of nights with no night-time awakenings and the percentage of mornings with no symptoms on awakening over 52 weeks of treatment
- e-Diary recordings of rescue salbutamol/albuterol usage (mean daily, nighttime and daytime use) over 26 and 52 weeks of treatment
- To evaluate the efficacy of 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 asthma exacerbation by exacerbation category
  - Time to first hospitalization for asthma exacerbation
  - Annual rate of asthma exacerbations by exacerbation category
  - Duration in days of asthma exacerbations by exacerbation category
  - Percentage of patients with at least one asthma exacerbation by exacerbation category
  - 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, an additional secondary comparison, QMF149 150/320 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*

  *Trough FEV_1 will be tested for non-inferiority versus salmeterol/fluticasone 50/500 µg. If non-inferiority criteria are met, this will be tested for superiority.

[redacted]

- 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) over 52 weeks of treatment
- Adverse events, vital signs, ECG and laboratory analysis (haematology, blood chemistry including glucose and potassium, urinalysis, evening plasma cortisol) over 52 weeks of treatment

[redacted]

3 Investigational Plan

3.1 Study design

This study uses a 52 week treatment, randomized, double-blind, triple-dummy, parallel-group design. The primary endpoint will be evaluated over 26 weeks. 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 medium or high dose corticosteroids and/or low dose LABA/ICS for at least 3 months and on a stable dose for at least 1 month prior to Visit 1. Once patients concurrent medications comply with the requirements of the study (Section 5.4.7 and Section 5.4.8) patients will enter a Run-In epoch at Visit 101. At this point, the patients must also have an ACQ $\geq$ 1.5 at Visit 101. At Visit 101 all patients will receive an open-label fluticasone propionate 100 µg b.i.d. delivered via Accuhaler® (if not available in a specific country, open-label fluticasone propionate 125 µg b.i.d. via MDI inhaler or fluticasone low dose equivalent as per Appendix 11) which will be used throughout the Run-In epoch and stopped at Visit 102 (end of Run-In epoch) (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 medication the time between Visit 1 and Visit 101 may be shorter than 2 weeks. (i.e.If the patient was on ICS only, the Visit 1 and Visit 101 may be scheduled the same day).

At Visit 1 (Screening), all patients will be given salbutamol/albuterol to use as rescue medication throughout the study. They will be issued 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 record PEF. The Run-In epoch is 2 weeks in 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 only when spirometry assessment meet the inclusion criteria (FEV1 predicted normal values, ATS/ERS criteria and reversibility) as per spirometry 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) randomization ratio:

- QMF149 150/160 µg delivered via Concept1 o.d.
- QMF149 150/320 µg delivered via Concept1 o.d.
- MF 400 µg o.d. delivered via Twisthaler®
- MF 800 µg (as 400 µg b.i.d.) delivered via Twisthaler®
- 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 Twisthaler® or 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 week 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 day window. All patients will be required to attend the clinic visits 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 Visit (CV) 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, concomitant medications review and unscheduled laboratory exams as appropriate).

A final telephone contact must be conducted at 30-days after last treatment date (telephone visit 301 or unscheduled visit safety call for patients who discontinue treatment earlier than 52 weeks).

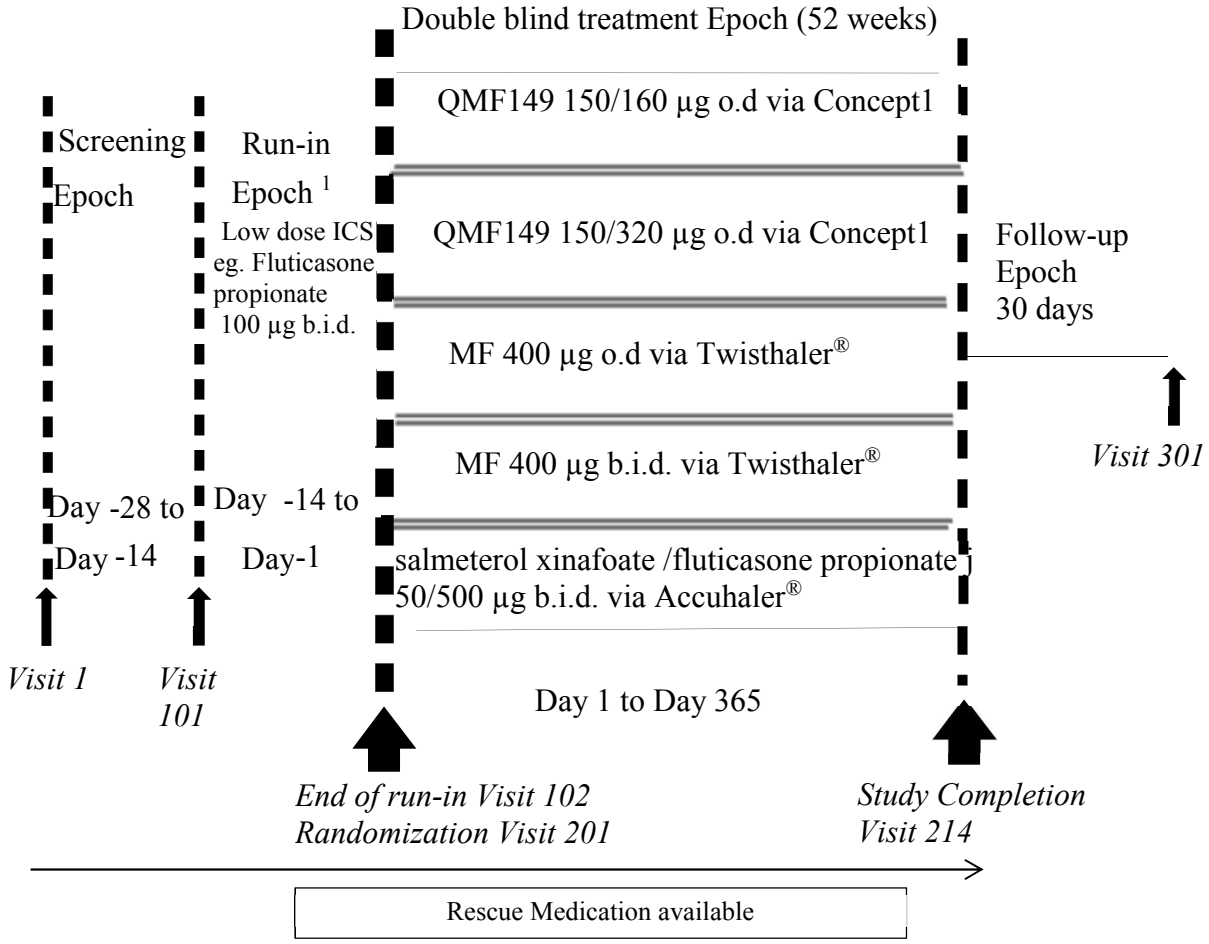
The first dose of study medication will be administered at the clinic in the evening (between 05:00 and 08:00 pm) at Visit 201 (Day 1). Subsequent clinic visits will be scheduled so that patients will be reassessed as close as possible to the same time relative to the evening doses. Patients will be 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]

Evening plasma cortisol will be measured on all patients only at Visit 201, 207 and 214.

[redacted]

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. For run-in medication, Fluticasone propionate 100 µg b.i.d. should be delivered via Accuhaler®. In case it is not available in a particular country, 125 µg b.i.d by MDI inhaler will be accepted. If fluticasone 125 µg b.i.d by MDI inhaler is not available in a particular country, an equivalent low dose fluticasone may be used (Appendix 11).

3.2 Rationale of study design

This study is a pivotal, multi-center, randomized, double-blind, triple-dummy, parallel-group, phase III study with a 52 week treatment epoch which is required to assess the safety and efficacy of QMF149 in asthma. The primary endpoint will be evaluated over 26 weeks. This is considered an adequate duration to demonstrate improvements in the primary endpoint based on the known pharmacodynamic properties of the components of each fixed-dose combination and precedent of other inhaled combination products in asthma.

In order to preserve the integrity of the study, a randomized, double-blind study design is used. This design 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 with GINA step 3 (GINA, 2015).

The primary objective of the trial is to evaluate the efficacy and long term safety of two different doses of QMF149 (QMF149 150/160 µg o.d. and QMF149 150/320 µg o.d. via Concept1) over two respective MF doses (MF 400 µg and MF 800 µg via Twisthaler® total daily dose) in poorly controlled (i.e. not optimally controlled) asthmatics as determined by pulmonary function testing, effects on asthma control and rescue medication use. In addition secondary endpoints will provide data on asthma exacerbations, quality of life, [redacted] and will establish the long term safety of the studied QMF149 doses in this specific asthma patient population. Furthermore the study will compare QMF 150/320 µg with an active comparator (salmeterol/fluticasone via Accuhaler®) as a secondary endpoint. This will provide a perspective on how QMF149 compares with a widely used treatment for asthma.

The analyses will be performed in a sample size of approximately 2000 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 patient safety throughout the study.

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

The dose regimens of QMF149 selected in this study (150/160 µg o.d. and 150/320 µg o.d. delivered via Concept1) are based on the findings of previous studies identifying effective and safe doses of the individual components of the FDC, indacaterol and MF.

Indacaterol maleate at a dose of 150 µg o.d. is approved in various countries for the maintenance treatment of COPD. A dose-ranging study CQAB149B2357 of indacaterol maleate in asthmatic patients demonstrated that a dose of 150 µg o.d. was safe and effective and furthermore, a 26 week study in asthmatic patients showed that indacaterol maleate at doses of 300 µg and 600 µg o.d. were also well-tolerated in this population (Study CQAB149B2338).

A 12-week study (CQMF149E2203) investigated indacaterol acetate 75 µg and 150 µg delivered via Concept1 in adult patients with persistent asthma. The study demonstrated superiority of indacaterol acetate 75 µg and 150 µg over placebo in most of the efficacy endpoints and showed positive trends in favor of indacaterol acetate 150 µg regarding trough FEV_1, PEF and rescue medication use compared with indacaterol acetate 75 µg. Both indacaterol acetate doses 150 µg and 75 µg treatments were safe and well tolerated.

In summary, the totality of Phase II data support the selection of indacaterol acetate 150 µg o.d. as the most appropriate dose to move forward in Phase III for the development of QMF149.

MF at a dose of 400 µg b.i.d. administered via a multi-dose dry powder inhaler (MDDPI) is approved as Asmanex® Twisthaler® for the treatment of asthma. A single-dose, pharmacokinetic study (QMF149E2101, Vaidya S et al, 2012) conducted in healthy volunteers compared systemic exposure to MF following oral inhalation from the registered Twisthaler® inhaler and the Concept1 inhaler and found that the mean dose of MF in the Concept1 that provided comparable systemic exposure to 400 µg delivered via Twisthaler® was 160 µg (after in vitro fine particle mass adjustment). Based on dose proportional changes in MF systemic exposure following administration via both devices, 800 µg MF delivered via Twisthaler® was expected to be comparable to 320 µg delivered via Concept1. In a 4-week Phase II study in patients with persistent asthma (Study CQMF149E2201), MF doses of 80 µg and 320 µg

[redacted]

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), respectively delivered once daily via Twisthaler® confirming the selected doses for MF Concept1 are appropriate for further QMF149 Concept1 development.

This study QVM149B2301 will compare two doses of QMF149 (indacaterol acetate 150 µg/ MF 160 µg and indacaterol acetate 150 µg /MF 320 µg) via Concept1 with the respective two doses of MF 400 µg and MF 800 µg (administered as 400 µg b.i.d.) delivered via Twisthaler®. The purpose is to investigate whether the QMF149 doses in Concept1 provide additional benefits over the respective MF doses in Twisthaler® in asthma patients whose asthma is inadequately controlled (symptomatic patients with an ACQ-7≥ 1.5) and who are qualified for treatment with LABA/ICS (GINA 2015, Step 3).

This study is designed to provide efficacy and safety data over a 52 weeks treatment epoch which is considered to be sufficient duration to demonstrate treatment differences of the two QMF149 doses, QMF149 150/160 µg and QMF149 150/320 µg o.d. delivered via Concept1, vs the two respective MF doses, MF 400 µg o.d. and MF 800 µg (administered as 400 µg b.i.d.) delivered via Twisthaler® in terms of lung function, symptom control and other endpoints. However, the primary endpoint, trough FEV_1 will be assessed at 26 weeks, which is an appropriate timepoint based on known pharmacodynamics of the monocomponents and is consistent with endpoints used in pivotal studies of other fixed dose combinations in asthma.

3.4 Rationale for choice of comparator

The MF inhalation powder formulation is marketed as a 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.

In addition, MF in combination with formoterol fumarate as Dulera® has been approved in the United States and as Zenhale® in Canada as a maintenance treatment for asthma in adults and children who are at least 12 years old.

MF was selected as a marketed comparator for QMF149 in this study in order to demonstrate the additional benefit of a LABA (indacaterol acetate 150 µg) on top of a medium and high dose ICS (see Appendix 11) in patients whose asthma is inadequately controlled with ICS alone or combination.

The two approved daily doses of MF (400 µg o.d. and 400 µg b.i.d.) delivered via Twisthaler®) are comparable to MF 160 µg o.d. and to MF 320 µg o.d. delivered via Concept1.

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

3.5 Purpose and timing of interim analyses/design adaptations

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.

[redacted]

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 26The primary and key secondary endpoints of CQVM149B2301 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.

3.6 Risks and benefits

LABA/ICS FDCs are frequently used as controller medications and are foundation therapy in GINA step≥ 3 (GINA 2015).

QMF149 (indacaterol 150 µg as a FDC with MF 160 µg or 320 µg) is a new once daily LABA/ICS FDC whose phase II development was recently completed.

There is an extensive evidence of the efficacy and safety of the mono components indacaterol and MF in asthma and COPD (indacaterol). There is in addition supportive efficacy and safety information from the early QMF149 development in the Twisthaler® device (see section 1.1 Background and QMF149 Investigator Brochure). To further investigate the overall risk and benefit evaluation of QMF149 FDC delivered by Concept1, two different MF doses in combination with indacaterol acetate (QMF149) are selected for further evaluation in Phase III.

[redacted]

In one large Phase II event driven trial with a duration up to 68 weeks in over 1500 moderate to severe asthma patients including adolescents (12-17 years old), QMF149 (indacaterol/mometasone 500/400 µg delivered by Twisthaler comparable to indacaterol 150/160 µg delivered by Concept1) showed a favorable efficacy and safety profile over MF (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 (QMF149 E2203), a device bridging study with MF in Concept1 (QMF149E2201) and an efficacy and safety study with QMF149 in Concept1 in moderate to very severe COPD patients (QMF149 F2202). The studies showed statistically significant improvements in lung function and symptomatic endpoints including exacerbations and confirmed a favorable and robust efficacy and safety profile in phase II.

In summary, the QMF149 Twisthaler® program in phase II along with further phase II studies with QMF149 delivered by the Concept 1 inhaler suggest a favorable efficacy and safety profile of the compound.

In the current Phase III, one year pivotal trial (QVM149B2301), two QMF149 doses are compared to the respective MF doses and to salmeterol/fluticasone propionate (Seretide®). In this large study with a double-blind, triple-dummy, active controlled design, the patients must be symptomatic (defined by ACQ-7 mean score ≥ 1.5) despite medical care according to the current GINA guideline as of year 2015. The patients need to have moderate to severe persistent asthma with a $\geq 50\%$ $FEV_1 < 80\%$ of predicted normal (at Visit 1) under ongoing asthma medication. All patients will continue with either one of two different doses of QMF149 or one of two different doses of MF or one dose of Seretide®. Throughout the trial all patients will have free access to rescue medication (i.e. short acting beta 2-agonist), thus limiting the risk for patients with a significant asthmatic adverse events.

The potential benefit for the patient includes an improvement in the pulmonary function testing and a potential translation into better asthma control like reductions in symptoms and rescue medication use, 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. Diary data will be transmitted electronically from the device to the investigator daily. Therefore, investigators **may** have an early indication of worsening symptoms and will be able to monitor the patient closely throughout the study.

In line with current medical treatment guidelines, all patients participating in the study will receive active "controller" treatment for their asthma throughout the 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 during the study will any patient be without treatment for asthma.

[redacted]

The risk to the patients in participating in the study is that QMF149 is under development and therefore it is possible that unexpected safety issues may be identified in patients randomized to treatment with QMF149 (Section 5.4.9) and will be minimized by compliance with the eligibility criteria and close clinical monitoring. The risks of side effects from the study medication are those known for the individual compounds indacaterol and MF, and no additional risks have been identified that might occur when the two components are administered concurrently or from the same inhaler. Further information can be obtained from the 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/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), as well as to patients via written instructions to contact the investigator in the event of worsening asthma symptoms.

The investigator should discontinue study treatment for a given patient and/or withdraw the patient from the study if, 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 the available data of QMF149 and the efficacy and safety data of the marketed monotherapy components, it is anticipated that QMF149 150/160 µg and QMF149 150/320 µg will have a favorable benefit to risk profile in patients with asthma.

4 Population

The study population will consist of approximately 2000 males and females (approximately 5% of adolescents) with asthma.

It is anticipated that approximately 4000 patients will need to be screened in order to randomize approximately 2000 patients into the five treatment groups of the study with a randomization ratio of 1:1:1:1:1, (i.e. approximately 400 patients in each of the treatment groups). It is intended that at least 1800 patients (360 patients per treatment group) will have completed 26 weeks of treatment for primary and key secondary objectives.

Drop-outs after randomization will not be replaced. This study will enroll multi-nationally and patients will be stratified according to prognostic factors of age (12 to 17 years or ≥ 18) (Section 4.1, Inclusion Criteria 1) and non-prognostic factor region to achieve improved homogeneity within each stratum.

[redacted]

4.1 Inclusion criteria

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

1. Male and female adult and adolescent patients aged ≥ 12 years old (or ≥ 18 years old depending upon regulatory and/or IRB/IEC/REB approval and/or country participation) and ≤ 75 years

[redacted]

2. Written informed consent must be obtained before any study-related assessment is performed. Patients below the legal age of consent are required to have the Informed Consent Form signed by the patient's parent / guardian; adolescents are required to sign an assent form
3. Patients with a documented diagnosis of asthma for a period of at least 1 year prior to Visit 1 (Screening)
4. Patients who have used medium or high dose ICS (please refer to Appendix 11 for guidance) or low dose of LABA/ICS combination for asthma for at least 3 months and at stable doses 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 and/or combinations of ICS (low dose) with long-acting beta adrenergic agent. Patients must have ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (prior to double-blind treatment) and qualify for treatment with medium or high dose LABA/ICS
    - In case that the spirometry is repeated due to a failure of meeting criteria 6, ACQ-7 should be repeated as well.
6. Pre-bronchodilator FEV_1 ≥ 50 % and < 85 % of the predicted normal value for the patient according to ATS/ERS criteria after withholding bronchodilators (see Table 5-2) at both Visit 101 and 102
    - Withholding period of bronchodilators prior to spirometry:
        - SABA for ≥ 6 hours
        - FDC or free combinations of ICS*/LABA for ≥ 48 hours
        - SAMA for ≥ 8 hours
        - xanthines ≥ 7 days

Washout period of each drug should be kept as close as possible as above and should not be longer. If wash-out period is considered to be longer, please contact your Novartis Medical Monitor

A one-time repeat of percent predicted FEV_1 (pre-bronchodilator FEV_1) is allowed at Visit 101 as well as at Visit 102. Repeat of Visit 101 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. Run in medication should be dispensed only once the repeat spirometry was qualified by spirometry equipment, if all inclusion at visit 101 are successful in case of necessary repeat of Visit 101.

A one-time rescreening is allowed in case the patients fail to meet the criteria at the repeat, provided the patients return to their previous treatment until rescreened.

*** in case of combination LABA/ICS, ICS should be continued**.

7. 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:
    - Reversibility should be repeated once

[redacted]

- 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 at 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 to use spacer or not 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.) or use of nicotine inhalers such as e-cigarettes at the time of Visit 1.
2. Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization (> 24 hours) or emergency room visit (≤ 24 hours) within 6 weeks of Visit 1 (Screening). If patients experience an asthma attack/exacerbation requiring systemic steroids 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 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.
6. 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.
7. Patients with any chronic conditions affecting the upper respiratory tract (eg. chronic sinusitis) which in the opinion of the investigator may interfere with the study evaluation or optimal participation in the study.
8. 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.
9. Patients with Type I diabetes or uncontrolled Type II diabetes.

[redacted]

10. Patients who have a clinically significant laboratory abnormality at Visit 101.
11. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
12. 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.
13. Patients with a history of myocardial infarction (this should be confirmed clinically by the investigator) within the previous 12 months.
14. Concomitant use of agents known to prolong the QTc interval unless it can be permanently discontinued for the duration of study.
15. 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).
16. Patients who have a clinically significant ECG abnormality at Visit 101 (Start of Run- In epoch) and at 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
17. 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.
18. 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
19. Patients who have not achieved an acceptable spirometry results at Visit 101 in accordance with American Thoracic Society/European Respiratory Society (ATS /ERS) criteria for acceptability and repeatability. Repeat spirometry may be 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 patients fail the repeat assessment, the patients may be rescreened once, provided the patients return to their treatment prior until rescreened
20. Patients receiving any medications in the classes listed in Table 5-3
21. 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.
22. 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.

[redacted]

23. Patients with severe narcolepsy and/or insomnia.
24. Patients on Maintenance Immunotherapy (desensitization) for allergies or 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.
25. Patients who are serving a custodial sentence, do not have a permanent residence or who are detained under local mental health legislation/regulations.
26. Patients who are directly associated with any members of the study team or their family members.
27. Patients unable to use the Concept1 dry powder inhaler, Twisthaler®, Accuhaler® or a metered dose inhaler. Spacer devices are not permitted for rescue medication.
28. History of alcohol or other substance abuse.
29. 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.
30. Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers).
31. 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.
32. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment and for 30 days after stopping of study treatment

Only the following highly effective contraception methods are permitted:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject) if allowed as effective method of contraception according to local regulations. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male 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

[redacted]

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.

33. LAMA use within 3 months prior to visit 101

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

The Investigational treatments are as follows:

- QMF149 (indacaterol acetate/MF) 150/160 µg o.d. (in the evening) delivered as powder in hard capsules via Concept1 inhaler
- QMF149 (indacaterol acetate/MF) 150/320 µg o.d. (in the evening) delivered as powder in hard capsules via Concept1 inhaler

The Comparative treatments are:

- MF 400 µg o.d. (in the evening) delivered as powder via Twisthaler®
- MF 800 µg total daily dose (equivalent to 400 µg b.i.d. (in the morning and in the evening)) delivered as powder via Twisthaler®
- Salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered as powder via Accuhaler®

In addition the following placebo will be provided to enable the triple-dummy design of the study:

- Placebo, delivered as powder via Twisthaler® (in the morning and in the evening or in the morning only)
- Placebo delivered as powder in capsules via Concept1 inhaler (in the evening)
- Placebo delivered as powder via Accuhaler® (in the morning and in the evening)

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

5.1.2 Additional study treatment

At Visit 1 (Screening) patients will be provided with SABA (salbutamol/albuterol) inhaler to use as rescue medication on an "as needed" basis throughout the study. Please refer to Section 5.4.6 for more details regarding rescue medication.

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.

During the run-in, low dose fluticasone propionate 100 µg b.i.d. (or , if not available in a specific country, 125 µg b.i.d. MDI or fluticasone low dose equivalent as outlined in Section 3.1) will

[redacted]

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 assigned to one of the following five treatment arms in a ratio of 1:1:1:1:1

- QMF149 150/160 µg o.d. delivered via Concept1 inhaler (in the evening), placebo to MF 400 µg o.d. delivered via a first Twisthaler®(in the evening), placebo to MF 400 µg o.d. delivered via a second Twisthaler® (in the morning), 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 inhaler (in the evening), placebo to MF 400 µg o.d. delivered via a first Twisthaler®(in the evening), placebo to MF 400 µg o.d. delivered via a second Twisthaler® (in the morning), placebo to salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler®
- MF 400 µg o.d. delivered via a first Twisthaler® (in the evening), placebo to QMF149 delivered via Concept1 inhaler (in the evening), placebo to MF 400 µg o.d. delivered via a second Twisthaler® (in the morning), placebo to salmeterol/fluticasone 50/500 µg b.i.d. (in the morning and in the evening) delivered via Accuhaler®
- MF 400 µg b.i.d. delivered via Twisthaler® (400 µg o.d. from one Twisthaler® in the morning, and 400 µg o.d. from another Twisthaler® in the evening), placebo to QMF149 delivered via Concept1 inhaler (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 QMF149 delivered via Concept1 inhaler (in the evening), placebo to MF 400 µg o.d. delivered via a first Twisthaler® (in the evening), placebo to MF 400 µg o.d. delivered via a second Twisthaler® (in the morning)

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).

[redacted]

Randomization will be stratified by factors of age (12 to 17 years or ≥ 18) (Section 4.1, Inclusion Criteria 2) and region.

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

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 QMF149 and MF Twisthaler® arms of the study to facilitate indacaterol/MF bioanalysis. [redacted]

Unblinding for 26 week 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.

[redacted]

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.

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 follow:

[redacted]

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

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

These medications are:

- Salbutamol (100 µg) or albuterol (90 µg) used as rescue medication from Visit 1 to Visit 214
- Fluticasone propionate (100 µg b.i.d. or acceptable dose equivalent as outlined in Section 3.1) 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 101 patients will be trained to the use of the peak flow meter and e-diary and at Visit 102 all patients will be fully trained in the correct use of the Concept1, Twisthaler®, 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 inhalational devices to ensure that he/she is 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 2 times with approximately 30 mL of water after the last inhalation of the study drug which is in the evening after sequential inhalations of study drugs from three devices and in the morning after sequential inhalations of study drugs from two devices. Water used for mouth rinsing should be spat out and should NOT be swallowed.

The morning dose (to be taken between 05:00 and 08:00 am) will consist of a **single inhalation** from the morning Twisthaler® device (label colored in yellow) containing either MF or placebo

[redacted]

and a single inhalation from Accuhaler® device containing either salmeterol/fluticasone or placebo.

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

- One inhalation from the Concept1 device containing either QMF149 or placebo
- One inhalation from the evening Twisthaler® device (label colored in blue) containing either MF or placebo
- One inhalation from the Accuhaler® device containing either salmeterol/fluticasone or placebo

Inhalations from the two devices (in the morning) and three devices (in the evening) should be taken as close together as possible. Instructions for use of the Concept1 inhaler, Accuhaler® and Twisthaler® devices are given in Appendix 1, Appendix 2 and Appendix 3, respectively.

Table 5-1 Study Treatments

Treatment arm	Morning		Evening	
QMF149 150/160 µg o.d.	Pbo to MF 400 µg Pbo to salmeterol/ fluticasone 50/500 µg	Twisthaler * Accuhaler	*QMF149 150/160 µg* Pbo to MF 400 µg Pbo to salmeterol/fluticasone 50/500 µg	Concept 1 Twisthaler * Accuhaler
QMF149 150/320 µg o.d.	Pbo to MF 400 µg Pbo to salmeterol/ fluticasone 50/500 µg	Twisthaler * Accuhaler	*QMF149 150/320 µg* Pbo to MF 400 µg Pbo to salmeterol/fluticasone 50/500 µg	Concept 1 Twisthaler* Accuhaler
MF 400 µg o.d.	Pbo to MF 400 µg Pbo to salmeterol/ fluticasone 50/500 µg	Twisthaler * Accuhaler	*MF 400 µg* Pbo to QMF149 Pbo to salmeterol/fluticasone 50/500 µg	Twisthaler* Concept 1 Accuhaler
MF 400 µg b.i.d.	*MF 400 µg* Pbo to salmeterol/ fluticasone 50/500 µg	Twisthaler * Accuhaler	*MF 400 µg* Pbo to QMF149 Pbo to salmeterol/fluticasone 50/500 µg	Twisthaler* Concept 1 Accuhaler
Salmeterol/ fluticasone 50/500 µg b.i.d.	*Salmeterol/ fluticasone 50/500 µg* Pbo to MF 400 µg	Accuhaler Twisthaler *	*Salmeterol/fluticasone 50/500 µg* Pbo to QMF149 Pbo to MF 400 µg	Accuhaler Concept 1 Twisthaler*

* In order to keep the blind, 2 Twisthaler devices will be given to the patient. One to be used in the morning (yellow label), one to be used in the evening (blue label). Each of them will have either active or placebo (Pbo) treatment, depending on the arm the patient is randomized into.

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.

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

The 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 SABA (100 µg salbutamol or 90 µg albuterol via MDI) which they will be instructed to use throughout the study as rescue medication. Nebulized salbutamol/albuterol is not allowed as rescue medication throughout the entire trial. No other rescue treatment is permitted and use of 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/albuterol) within 6 hours of the start of each visit where spirometry is being performed unless absolutely necessary. If rescue medication is taken within 6 hours prior to spirometry assessments, then the visit should be rescheduled to the next day if possible.

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 his/her 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 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.

If a patient takes systemic corticosteroids within 7 days prior to a study visit, the visit must be rescheduled to allow a washout of 7 days.

Table 5-2 Prohibited asthma-related medications

Class of medication	Minimum washout period prior to screening visit (visit 1) Run-in (Visit 101) and Randomization (Visit 201) [1,2,3,]
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 48 hours prior to Visit 101. Patients can continue with an ICS until Visit 101 when patients will be switched to fluticasone propionate 100 µg b.i.d. (or equivalent dose) for run-in. The last dose of run-in medication will be taken in the morning of visit 102.
Inhaled corticosteroids[1]	All patients must be treated for asthma with fluticasone propionate 100 µg b.i.d. (or equivalent dose) from Visit 101 to Visit 102 (Figure 3-1). All other ICS must not be used at Visit 101.
Fixed combinations of short-acting β_2-agonist and short-acting anticholinergic	Must not be used within 8 hours prior to Visit 101.
Leukotriene Antagonist and leukotriene synthesis inhibitors	Must not be used within 7 days prior to Run-In (Visit 101)
Long-acting β_2-agonists (LABAs)	LABAs b.i.d. not be used within 48 hours prior to Visit 101. Indacaterol (LABA o.d.) must be discontinued at Visit 1 (14 days prior to visit 101). All patients will be provided with SABA at Visit 1 for use throughout the study.

[redacted]

Class of medication	Minimum washout period prior to screening visit (visit 1) Run-in (Visit 101) and Randomization (Visit 201) [1,2,3,]
Salbutamol/albuterol (SABA) provided at Visit 1 and throughout study as required for rescue medication prn	Must be withheld 6 hours prior to Visit 101 and Randomization (Visit 201)[4]
Short acting β_2-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 or oral 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)
Monoclonal antibody: IgE inhibitors (e.g., omalizumab), IL-5 inhibitors (e.g., mepolizumab)	Must not be used within 4 months prior to Run-In (Visit 101)
Xanthines	Must not be used within 7 days prior to Run-In (Visit 101)
Systemic mast cell stabilizers e.g cromoglycate, nedocromil, ketotifen	Must not be used within 7 days prior to Run-In (Visit 101)

[1] ICS must be discontinued at Visit 101. Treatment for recorded asthma exacerbation as defined in Section 6.4.5 is allowed ONLY until the asthma exacerbation is resolved (minimum wash-out of 7 days is required before scheduling a visit including spirometry assessment).

[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

Patients using LAMA within 3 months prior to Visit 101 are not allowed in the trial as per exclusion 33

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
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

[redacted]

Class of medication[1]	Minimum cessation period prior to Run-in (Visit 101)
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. Treatment for AEs including asthma events are permitted if required. However if it is transitioning to chronic treatment, the investigator should contact Novartis Medical Monitor.

Table 5-4 Medications allowed under certain conditions

Class of medication	Condition
Mucolytic agents not containing bronchodilators	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, pneumococcal vaccination or any other inactivated vaccine	Not administered within 48 hours prior to a study visit.
Intra-nasal corticosteroids	Stable dose for at least 4 weeks prior to Visit 101 In the case of prn, 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 prn, 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.

If indicated for the treatment of an adverse event including asthma exacerbation, any treatment deemed necessary for the safety of the patient is allowed from the start of the event (defined as per protocol Section 6.4.5 for asthma exacerbation) until the event is resolved. If it is required as chronic treatment, the investigator should contact/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.

5.4.9 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time. In the case that the patients would want to discontinue the treatment, it is particularly important to ask if they would be willing to remain in the trial and share his/her 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.

[redacted]

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.
- Adolescent patients (12 to 17 years old) who experience one asthma exacerbation requiring hospitalization
- Patients with > 50% decrease in FEV_1 from baseline (e.g Visit 101) confirmed by a repeat measurement the same day during the run-in or during the treatment epoch (baseline being then Visit 201).
- 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 he/she completes 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. 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 the patients discontinuing study treatment) are adverse event and serious adverse events for up to 30 days after drug discontinuation and survival status until the end of the 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. He/she should return for the assessments indicated in Table 5-5. If he/she fails 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 5.4.9

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

[redacted]

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
IRT treatment discontinuation call	X				
Vital Signs	X				
Physical exam	X				
Record Height (Adolescent only)	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	

[redacted]

[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 of 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.

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).

[redacted]

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 will be when the last patient has completed Visit 301 and as close as possible to SAE follow-up at day 395.

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.

QMF149 has not been approved by the US Food and Drug Administration (FDA) for the treatment of asthma.

In the US, QMF149 will not be available to patients once they complete the study. There are currently no plans to make this medication commercially available in the US. However, there are several alternative treatments in the same medication class (LABA/ICS) as QMF149 that are widely available in the US for treatment of asthma

Upon completion of the study (including pre-mature discontinuation), the investigator should evaluate patient's condition to assess the best treatment option for the patient. Should combination LABA/ICS be clinically indicated, the investigator should consider treatment with one of these alternative LABA/ICS combinations.

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

[redacted]

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

The study will consist of a screening epoch, a run-in epoch, a 52 week blinded treatment epoch and a follow-up epoch of 30 days after the last treatment.

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: PROs (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). A minimum 3 min rest period from the beginning of 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 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. If necessary other assessments (excluding PROs) 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 treatment discontinuation**	**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	1/2	30	57	86	113	141	183/ 184	197	225	254	281	309	337	364/ 365[6]			395
Obtain Informed Consent and/or assent (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																			

[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 treatment discontinuation**	**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	1/2	30	57	86	113	141	183/184	197	225	254	281	309	337	364/365[6]			395
Run-in medication		X																		
Pregnancy test (serum)[1]		X															X	X		
Pregnancy test (urine)[1]	X		X							X										
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 (adult patients to record it ONLY at Visit 101) and weight		X								X							X	X		
ECG[2]		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 treatment discontinuation**	**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	1/2	30	57	86	113	141	183/184	197	225	254	281	309	337	364/365[6]			395
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		
Spirometry Practice (optional)	X																			
Screening spirometry			X																	
FEV_1 reversibility test (SABA)[10]		X																		
Spirometry[2]				X	X		X			X							X	X		
Issue e-Diary[5]	X																			
Issue Peak Flow meter	X																			
Review and upload e-Diary recordings[5]			S		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 treatment discontinuation**	**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	1/2	30	57	86	113	141	183/184	197	225	254	281	309	337	364/365[6]			395
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		
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																			

[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 treatment discontinuation**	**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	1/2	30	57	86	113	141	183/ 184	197	225	254	281	309	337	364/ 365[6]			395
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	
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		

[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 treatment discontinuation**	**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	1/2	30	57	86	113	141	183/ 184	197	225	254	281	309	337	364/ 365[6]			395
AQLQ-S+12[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	

Visit early study discontinuation should be used for Premature study withdrawal (please refer to Section 5.4.10 and Section 5.4.11)

*: 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

[redacted]

[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.

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

[redacted]

[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 [5]	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					
	- 30 min						
	-25 min						
	-15 min	X					X
	0 min	Evening dosage					
	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					
	5 min	X					
	15 min						
	30 min	X					
	55 min						
	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 [5]	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 time 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

[6] It is baseline for the evening plasma cortisol

[redacted]

**Assessments are to be completed within a ± 5 mn window from Table 6-2 schedule

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)

[redacted]

- Sex
- 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 an 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 the recording of the dose counter number of remaining doses in Twisthaler® and Accuhaler®.

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

[redacted]

6.4.1 Spirometry

The following spirometric assessments will be made:

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

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

Trough FEV_1 is defined 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 4 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 5) will be used to assess improvements in asthma symptom control. The ACQ-7 (Juniper 1999; Juniper 2005 and 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. ACQ-7 will be provided to the site. All seven items are then scored on a 7-point Likert scale, with 0 indicating total control and 6 indicating no 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.

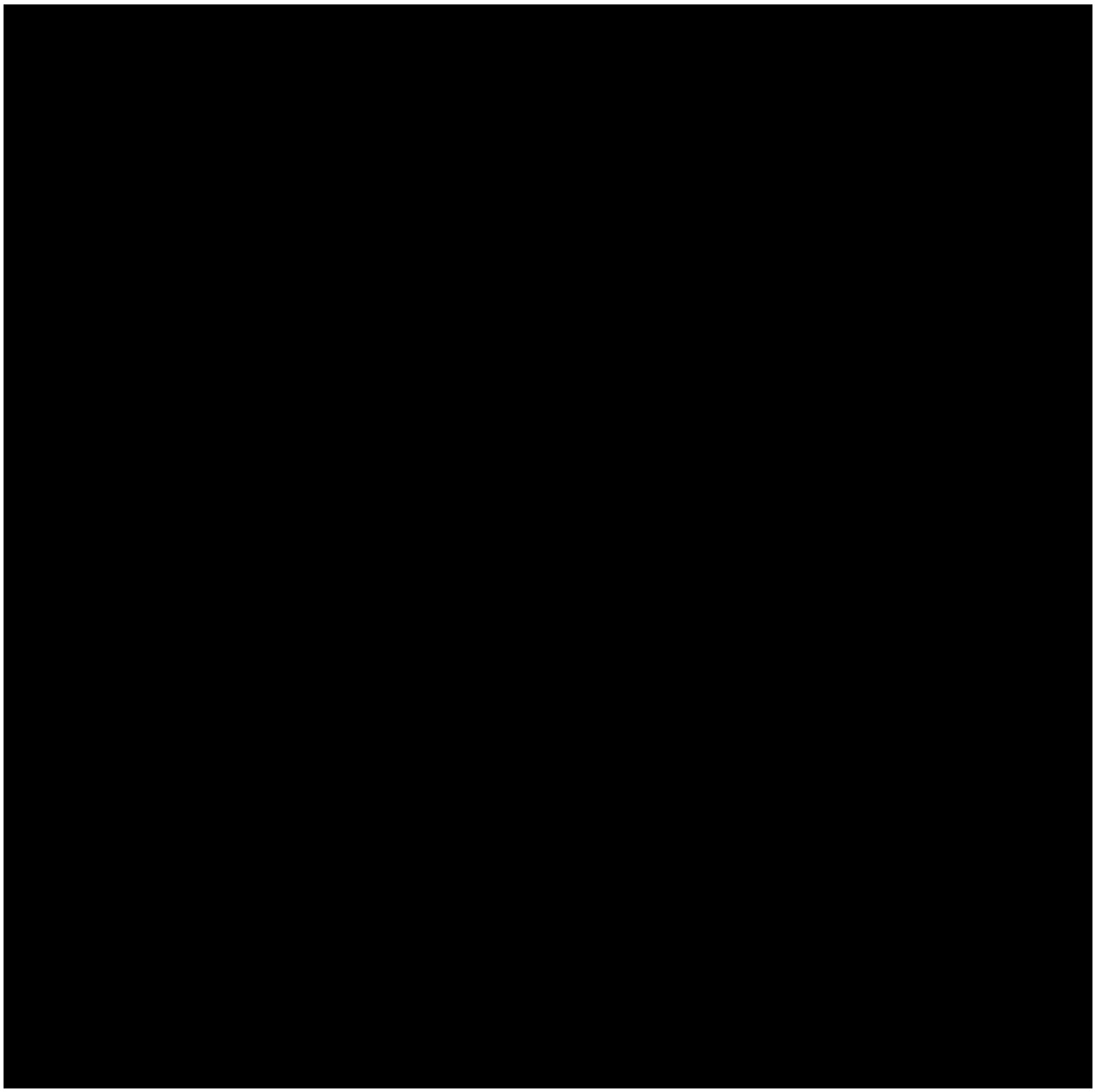
The ACQ-7 should be completed by the patient (first 6 questions) and investigator (for the last ACQ question – airway caliber FEV1% predicted based on the equipment provided by spirometry vendor at the investigators site at Visits 101, 102, 202, 204, 207, 214 and EOT if applicable.

6.4.2.2 Asthma Quality of Life Questionnaire (AQLQ-S +12)

The AQLQ-S +12 is a 32-item disease specific questionnaire designed to measure functional impairments that are most important to patients with asthma (Appendix 6) 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. The overall AQLQ score is the mean response to all 32 questions (Juniper 1992, Juniper 1993). Clinically important differences in scores between any two assessments have been determined by the authors of the AQLQ. Changes in scores of 0.5 are considered clinically meaningful; changes of 1.0 are considered as moderate and > 1.5 as large changes for any individual domain or for the overall summary score (Juniper 1994).

AQLQ should be completed 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 and clinical symptoms, and from Visit 101 on, the PEF and compliance with the study treatment. 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 asthma control e-Diary questions is provided in Appendix 8.

6.4.3.1 Peak Expiratory Flow (PEF)

An electronic Peak Flow Meter part of the e-diary device will be provided to each patient at Visit 1 for the measurement of morning and evening PEF during the run-in and treatment periods.

PEF will be measured at consistent times for a patient, in the morning and evening each day during the study from Visit 101 to 214. The measurements will be performed using an e-Peak 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 e-PEF/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 from Visit 1 until Visit 214. 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 visit 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 e-Diary will also be used to alert the patient and/or investigator to possible signs of worsening asthma and to possible asthma exacerbation. 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 if one or more of the following criteria of worsening asthma develops:

Asthma Worsening Criteria alerts

- > 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)
- > 50% increase in SABA use and > 8 puffs per day on 2 out of any 3 consecutive days compared to baseline
- ≥ 20% decrease in AM or PM PEF from baseline on 2 out of any 3 consecutive days compared to baseline
- < 60% of PEF compared to baseline
- Night time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights

[redacted]

- Urgent unscheduled clinic visit due to asthma related deterioration

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 mean of the best of the three daily 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 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 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
- Call the patient promptly 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 any other 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 systemic corticosteroids (SCS) for at least three consecutive days and/or a need for an ER visit, 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

[redacted]

"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.

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

The treatment of asthma exacerbations including the initiation of systemic corticosteroids 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 patients require significantly longer treatment periods or chronic administration, they must be discontinued from treatment.

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 asthma exacerbations and 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 or EOT (if applicable). An oropharyngeal examination will be performed at each clinic visit.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to informed consent being granted must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's e-CRF. 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 e-CRF.

[redacted]

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 each scheduled clinic visits as detailed in Table 6-2. (At visit 101, 102, 201, 202, 204, 207, 210, 214, or EOT (if applicable) vital sign should be measured directly after the ECG assessments).

6.5.3 Height and weight

Height in centimeters (cm) will be measured at Visit 101 for all patients and will be measured only in adolescents at visit 207, 214 or EOT if applicable. Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at Visit 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 Visit 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.

6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, pH, protein, glucose and blood will be performed at Visit 101, 201, 204, 207 and 214.

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

[redacted]

6.5.4.4 Hepatotoxicity

Any liver event which meets the criteria for "**medically significant**" event as outlined in Table 13-1 of Appendix 9 should follow the **standard procedures for SAE reporting** as described in Section 7.2.

6.5.4.5 Plasma Cortisol

Evening plasma cortisol will be measured at Visits 201, 207 and 214 and EOT if applicable. The sampling time point is shown in Table 6-1 and 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, and 214, ECGs will be measured at -35min pre-dose (evening dose) and post dose 30 min/ 1 hour. At Visit 204 ECG will be measured pre-dose only as indicated in Table 6-2. At Visit 210, the ECG will be done -35min pre-dose only. All electrocardiograms should include 12 standard leads. An ECG tracing will be taken for those patients who prematurely discontinue from the study treatment.

For each ECG performed original traces and 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 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.

[redacted]

6.5.6 Serious Asthma outcomes

Asthma-related hospitalizations, asthma-related intubations or 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 plasma and urine 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 plasma pregnancy test at Visit 1, Visit 101, Visit 102,Visit 207 (Week 26) ,Visit 214 or EOT 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.

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

[redacted]

- 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.

All AEs (serious and non-serious) are captured on the e-CRF. SAEs are also required for 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 later) 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

[redacted]

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 reoccurence, 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 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

[redacted]

Please refer to Table 13-1 in Appendix 9 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 9 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 9.

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.

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 for 3 months after the birth to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy 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 investigational/study treatment.

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

[redacted]

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 eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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

8.2 Data collection

Designated investigator 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.

[redacted]

- 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.

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 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 independent 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

[redacted]

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 and CHMP guidelines on DMC's.

8.5 Adjudication Committee

An independent external adjudication committee will be established to assess serious asthma outcomes (asthma-related hospitalizations, intubations and deaths). All serious asthma outcomes, and deaths 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. 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:

- 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.

[redacted]

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.

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, 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.

[redacted]

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 administrations, the recorded pre-specified drug subcategories (including type of combinations) 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.

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

9.4.1 Variable(s)

The primary objective is to demonstrate the superiority of either QMF149 150/160 µg delivered via Concept1 o.d. (in the evening) to MF 400 µg delivered via Twisthaler® or QMF149 150/320 µg delivered via Concept1 o.d. (in the evening) to MF 800 µg delivered via Twisthaler® (delivered as 400 µg b.i.d.) in terms of trough FEV_1 after 26 weeks of treatment in patients with asthma.

The key secondary objective is to demonstrate the superiority of QMF149 (150/160 and 150/320 µg combined) to mometasone furoate doses (MF, 400 µg and 800 µg combined) in terms of ACQ-7 after 26 weeks of treatment in patients with asthma.

9.4.2 Statistical model, hypothesis, and method of analysis

The comparisons of QMF149 150/160 µg versus MF 400 µg and QMF149 150/320 µg versus MF 800 µg will be evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a):

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

H_a: QMF149 treatment group is not equal to MF 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, age (12 to 17 or ≥ 18 years), 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

[redacted]

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 (QMF149 – MF) will be displayed along with the associated standard error, 2-sided 95% confidence interval (CI), and p-value (2-sided).

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 hour 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 multiple testing procedure based on the trimmed Simes test in Brannath et al (2009) is used. The family for the overall type-I error rate control contains three hypotheses including two hypotheses for the primary endpoint trough FEV_1 and one hypothesis for the key secondary endpoint ACQ-7. Denote the two hypotheses for the primary endpoint as H1 and H2 for comparing QMF149 150/160 µg vs. MF 400 µg and QMF149 150/320 µg vs. MF 800 µg respectively. Similarly, denote the hypothesis as H3 for the key secondary endpoint ACQ-7, for comparing QMF149 vs. MF.

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

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

[redacted]

Step 1: Retain both H1 and H2 if $p_i \leq 0.05$ **AND** the observed treatment difference for the corresponding p_i is in the wrong direction (i.e. MF is performing better than QMF) for **ANY** i = 1, 2, stop here; otherwise go to Step 2;

Step 2: Reject H1 and H2 if $p_i < 0.05$ for **BOTH** i = 1, 2 and go to Step 3; otherwise go to Step 4;

Step 3: Reject H3 if $p_3 < 0.05$ and stop;

Step 4: If neither Step 1 nor Step 2 applies, perform the Bonferroni test to H1 and H2. Thus reject H1 if $p_1 < 0.025$ or reject H2 if $p_2 < 0.025$ and stop.

For each of the three hypotheses, the corresponding testing statistic (estimated least squares mean difference) follows normal distribution. Hence for H1 and H2, their corresponding testing statistics follow jointly a 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 Brannath et al (2009).

Other than the three 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.

To demonstrate the superiority of QMF149 (150/160 and 150/320 combined) to mometasone furoate (MF 400 µg and 800 µg combined), the average of following treatment contrasts will be computed:

QMF149 (150/160 µg) vs. MF 400 µg

QMF149 (150/320 µg) vs. MF 800 µg

Least squares means (95% CI) will be presented graphically to assess the interaction between indacaterol and dose levels of MF.

9.4.6 Supportive analyses

As supportive analysis, 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.The following [redacted] 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:

- Age group (12 to 17 years, ≥ 18 years)
- Race (Caucasian, Black, Asian, Other)

[redacted]

- Sex (male, female)
- History of asthma exacerbation in the 12 months prior to screening (Yes, No)
- Patients' prior therapies before Run-in period (e.g. medium dose ICS, high dose ICS and low dose ICS/LABA)
- FEV_1 response according to % predicted FEV_1 range at baseline (50% to < 60%, 60% to < 80% and <50% or > 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 QMF149 150/320 µg o.d vs. salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. (Seretide®) will be performed using the same model for the comparison of QMF149 vs. MF 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, and/or 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-squares 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.

To estimate the add-on effect of indacaterol (QAB149) to existing MF treatment (in terms of trough FEV_1), the average difference between QMF and MF will be computed across two dose levels. This difference is interpreted as an average effect of adding indacaterol to MF, under the assumption that indacaterol effect is not altered by dose of MF. To compute the difference, the QMF149 and MF 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.

Comparison of QMF149 150/320 µg vs salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d. in term of trough FEV_1 at Week 26

[redacted]

The comparison of QMF149 150/320 µg o.d. vs active control (salmeterol xinafoate /fluticasone propionate 50/500 µg b.i.d.) will be performed using the same model as specified for the primary endpoint. The result will be interpreted based on the 95% confidence interval (CI) of the treatment difference of QMF149 – active control. The lower bound of the 95% CI is the difference that can be ruled out. For example, if the lower bound of the 95% CI is larger than the non-inferiority margin -90 mL (i.e. the entire 95% CI is to the right of -90 mL), QMF149 150/320 µg can be considered non-inferior to active control, and if the lower bound of the 95% CI is greater than 0, then QMF149 150/320 µg can be considered superior to active control with regard to trough FEV_1 at Week 26. Note that the comparison versus active control is not part of the confirmatory testing strategy.

The estimation of the non-inferiority margin of -90 mL is provided in Appendix 12.

9.5.1.2 ACQ at Weeks 4, 12 and 52

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

ACQ-7 at post-baseline visits will be analyzed using the same MMRM model as specified for the primary analysis except that baseline FEV_1 will be replaced with baseline ACQ-7 and all post-baseline visits corresponding to ACQ-7 will be included.

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, age (12 to 17 or ≥ 18 years), region, visit, and treatment-by-visit interaction as fixed effects with baseline ACQ-7, 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 explore the potential interaction effect, the individual treatment contrasts will be presented.

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

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, age (12 to 17 or ≥ 18), 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 'days with no rescue use' 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 baseline 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 means 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.

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
- 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 age (12 to 17 or ≥ 18). The model will include treatment, region and history of asthma exacerbation in the 12 months prior to screening (Yes, No) 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 QMF149 over MF 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 a generalized linear model assuming the negative binomial distribution including treatment, age (12 to 17 or ≥ 18), and region and history of asthma exacerbation in the 12 months prior to screening (Yes, No) 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 age (12 to 17, or ≥18), region and history of asthma exacerbation in the 12 months prior to screening (Yes, No).

The proportion of patients with at least one asthma exacerbation will be analyzed using logistic regression. The model will include terms for treatment, age (12 to 17 or ≥ 18), region and history of asthma exacerbation in the 12 months prior to screening (Yes, No), as fixed effects with center nested within region as a random effect, and FEV_1 prior to inhalation and FEV_1 15 to 30

[redacted]

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.

The percentage of patients who permanently discontinued study drug due to asthma exacerbation will be analyzed using the same model as for the proportion of patients with at least one asthma exacerbation.

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 indacaterol (QAB149) to existing MF treatment (in terms of exacerbations), the average difference between QMF and MF will be computed for all inferential analyses mentioned above. This difference is interpreted as an average of adding indacaterol to MF, under the assumption that indacaterol effect is not altered by dose of MF. To compute the difference, the QMF149 and MF doses will be pooled using appropriate contrasts within the specified analyses. 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.

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.

[redacted]

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: $QTc = QT / \sqrt[3]{RR}$, where $\sqrt[3]{\ }$ 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. 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.

[redacted]

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 (Yes, No) 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.

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

[redacted]

[redacted]

[redacted]

9.6 Interim Analysis

The primary and key secondary endpoints of CQVM149B2301 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).

Since the analysis of primary and key secondary objectives will be performed only for CSR I, this interim analysis will not require any adjustment to the overall type I error rate.

9.7 Safety Monitoring Analyses

No interim analysis for efficacy is planned. 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. [redacted]

9.8 Sample size calculation

The sample size calculation takes into account the following consideration:

[redacted]

- To achieve at least 90% power (with multiplicity adjustment) for primary endpoint trough FEV_1 with a treatment difference of 100 mL between QMF149 vs. MF at the corresponding doses, assuming standard deviation of 380 mL based on internal studies QMF149A2210, QMF149E2201, QMF149E2203 and literature data;
- To achieve at least 80% power (with multiplicity adjustment) for key secondary endpoint ACQ-7 with a treatment difference of 0.15 between QMF149 vs. MF based on pooled doses, assuming standard deviation of 0.80 based on studies QMF149A2210, QMF149E2201, QMF149E2203 and Kerstjens (2012).

If 10 % dropout rate is assumed, then calculation shows the sample size of 2000 patients (i.e 400/arm) will provide 94% power for item 1 and 85% power for item 2, with multiplicity adjustment as given in Section 9.4.4.

The sample size calculation is performed in R 3.2.3.

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 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.

[redacted]

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 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 should be followed.

[redacted]

12 References

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[redacted]

13 Appendices

Appendix 1: Instruction for Use of Concept1

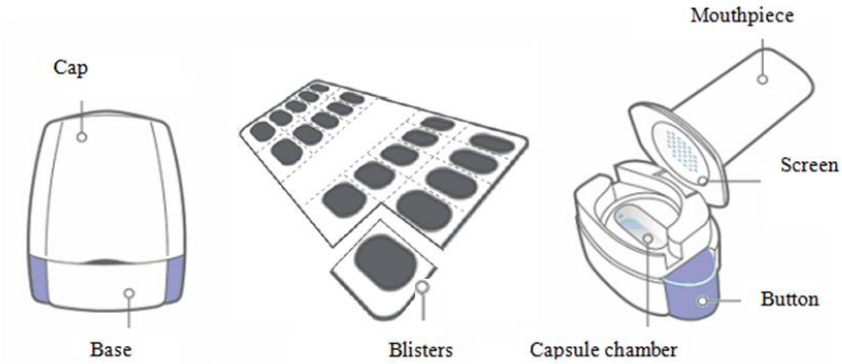
Instructions for using inhaler and capsules.

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.

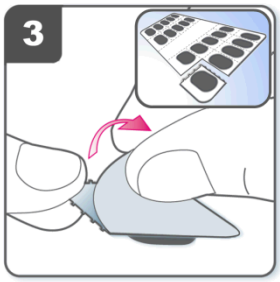
Do not use the study medication capsules with any other capsule inhaler, and do not use the inhaler to take any other capsule medicine.

[redacted]

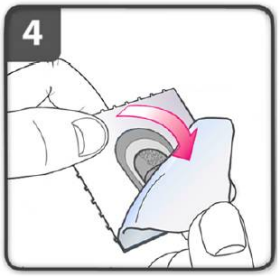
How to use your inhaler

Pull off cap.

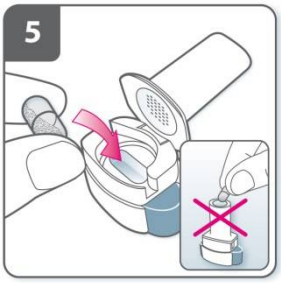
Open inhaler:
Hold the base of the inhaler firmly and tilt back the mouthpiece. This opens the inhaler.



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.



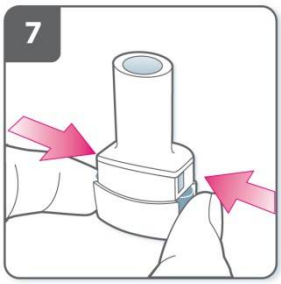
Remove a capsule:
Peel away the foil and remove the capsule from the blister.



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

[redacted]

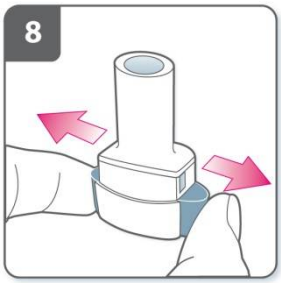
Close the inhaler:
You should hear a “click” as the mouthpiece closes onto the inhaler base.

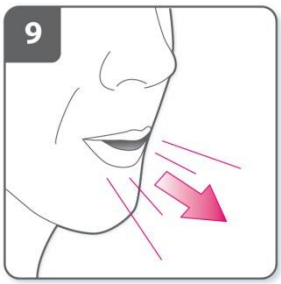


Pierce the capsule:

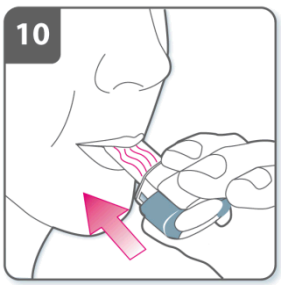
- Hold the inhaler upright with the mouthpiece pointing up.
- Pierce the capsule by firmly pressing together both side buttons at the same time. **Do this only once.**
- You should hear a “click” as the capsule is being pierced.

Release the side buttons fully.





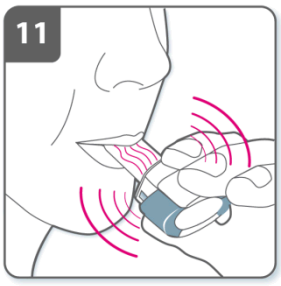
Breathe out:
Before placing the mouthpiece in your mouth, breathe out fully.
Do not blow into the mouthpiece.



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]

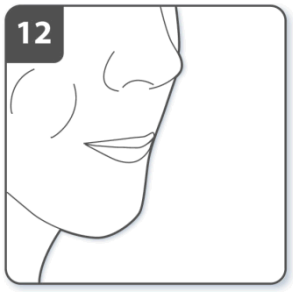


Note:
As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. You will experience a sweet flavor as the medicine goes into your lungs.

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.

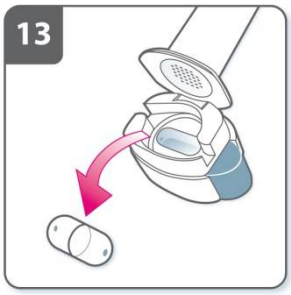
If there is powder left in the capsule:

- 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: Instructions for use of Twisthaler®

HOW TO USE

Before first use, remove the TWISTHALER® from its foil pouch.

Step 1. Open inhaler

Hold the inhaler straight up with the portion (the base) on the bottom (Figure 1). It is important that you remove the cap of the TWISTHALER® while it is in this upright position to make sure that you get the correct dose.

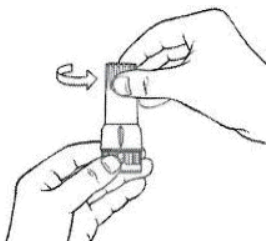


Figure 1 – Cap Removal

Holding the base, twist the cap in a counterclockwise direction to remove it. As you lift off the cap, the dose counter on the base will count down by one. (If you began with the dose counter reading "60", this action will cause it to now read "59".) This action loads the device with the dose that you are now ready to inhale.

IT IS IMPORTANT TO NOTE that the indented arrow (located on the portion of the TWISTHALER®, directly above the base) is pointing to the dose counter (Figure 2).

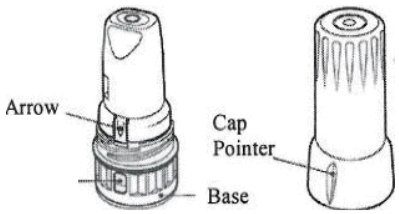


Figure 2

Step 2. Inhale dose

Exhale fully. Then bring the TWISTHALER® up to your mouth with the mouthpiece facing toward you. Place it in your mouth, holding it in a horizontal position as illustrated (Figure 3). Firmly closing your lips around the mouthpiece, take in a fast, deep breath. Since it is a very fine powder, you may not be able to feel or taste it after inhalation.

Figure 3 – Inhalation

Remove the TWISTHALER® from your mouth and for about 10 seconds or as long as you comfortable can.

[redacted]

IMPORTANT: DO NOT BREATHE OUT THROUGH THE INHALER.

After you use your inhaler, it is important that you wipe the mouthpiece dry, if necessary, and immediately replace the cap firmly closing the TWISTHALER® (Figures 4 and 5).

This is the only way to be sure that your next dose is properly loaded. Be sure that the arrow is in line with the dose-counter window. The cap needs to be put back on and turned in a clockwise direction, as you gently press down. You'll hear a distinctive "click" to let you know that the cap is fully closed.

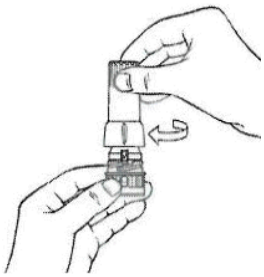


Figure 4 – Closing the Inhaler

Figure 5 – Closed inhaler

IT IS IMPORTANT TO REPEAT STEPS 1 AND 2 EACH TIME YOU INHALE. Rinse your mouth after using.

STORING YOUR INHALER
Keep your inhaler clean and dry at all times. If the device needs cleaning, gently wipe the mouthpiece with a dry cloth or tissue as needed. Do not wash the inhaler. Avoid contact with any liquids.

Store in a dry place. Avoid storing it in damp or hot conditions such as a bathroom or in your car.

Keep your inhaler out of the reach of young children.

HOW TO KNOW WHEN YOUR INHALER IS EMPTY
The inhaler has a dose indicator window on the base. It is a dose counter which displays the number of doses remaining. When the unit reads "01", this indicates the last remaining dose. After dose "01", the counter will read "00", and the cap will lock and no additional dose will be delivered.

WHAT TO DO WITH YOUR USED INHALER

Please return your used TWISTHALER® device to the study site

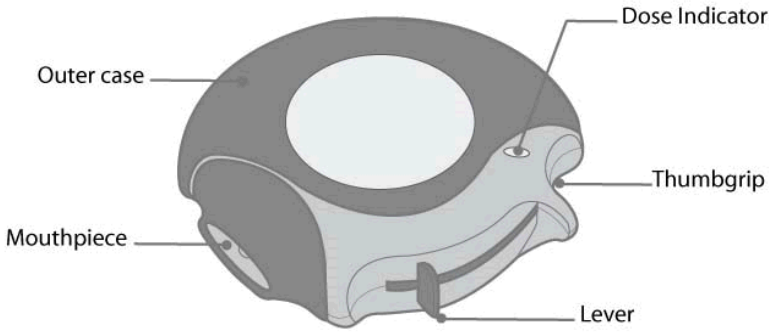
[redacted]

Appendix 3 How to Use an 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

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*)*.

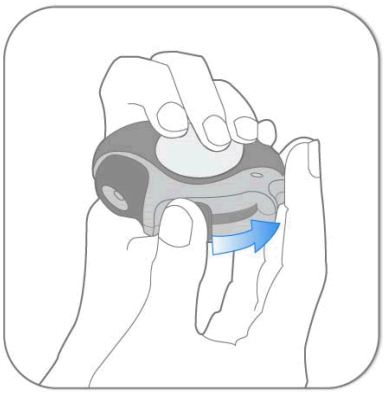
[redacted]

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:**

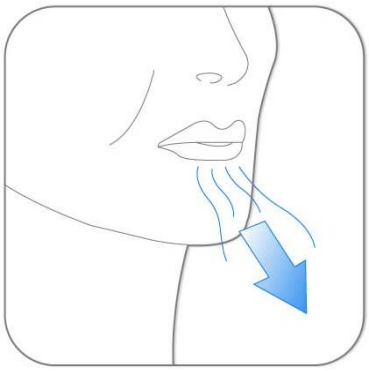
- Do not close the Diskus.
- Do not tilt the Diskus.
- Do not play with the lever.
- Do not move the lever more than once.

3. INHALE

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.**

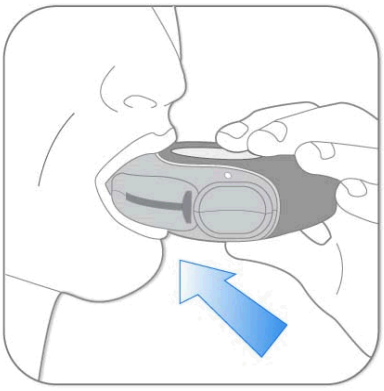
[redacted]

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



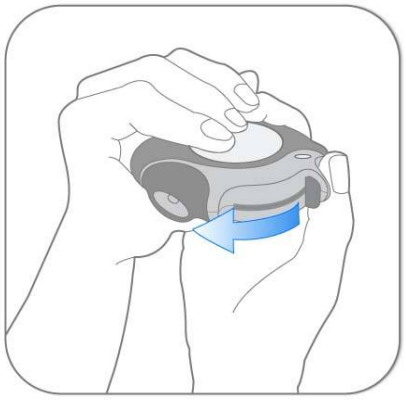
Remove the Diskus from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly. The Diskus delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the Diskus if you do not feel or taste 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 4: Spirometry Guidance

Equipment

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

Calibration

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

Preparing the test subject

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

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

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

Performing Spirometry

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

Number of trials

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

Acceptability

An acceptable maneuver has the following characteristics:

- No hesitation or false start;

[redacted]

- 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.

Predicted normal values will be calculated according to ECSC

For height measured in meters

Males: FEV_1 predicted (L)=4.30x(height(meters))-0.029xage(years)-2.49

Females: FEV_1 predicted (L)=3.95x(height(meters))-0.025xage(years)-2.60

References

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

[redacted]

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

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

[redacted]

Appendix 5: ACQ-7

For illustrative purposes only:

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

ASTHMA CONTROL QUESTIONNAIRE© PATIENT ID:_____

DATE:_____

Page 2 of 2

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 6: AQLQ-S +12

For illustrative purposes only:

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

Page 1 of 5

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

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

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

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: _____

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: _____

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

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

HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS?

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

[redacted]

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

Page 5 of 5

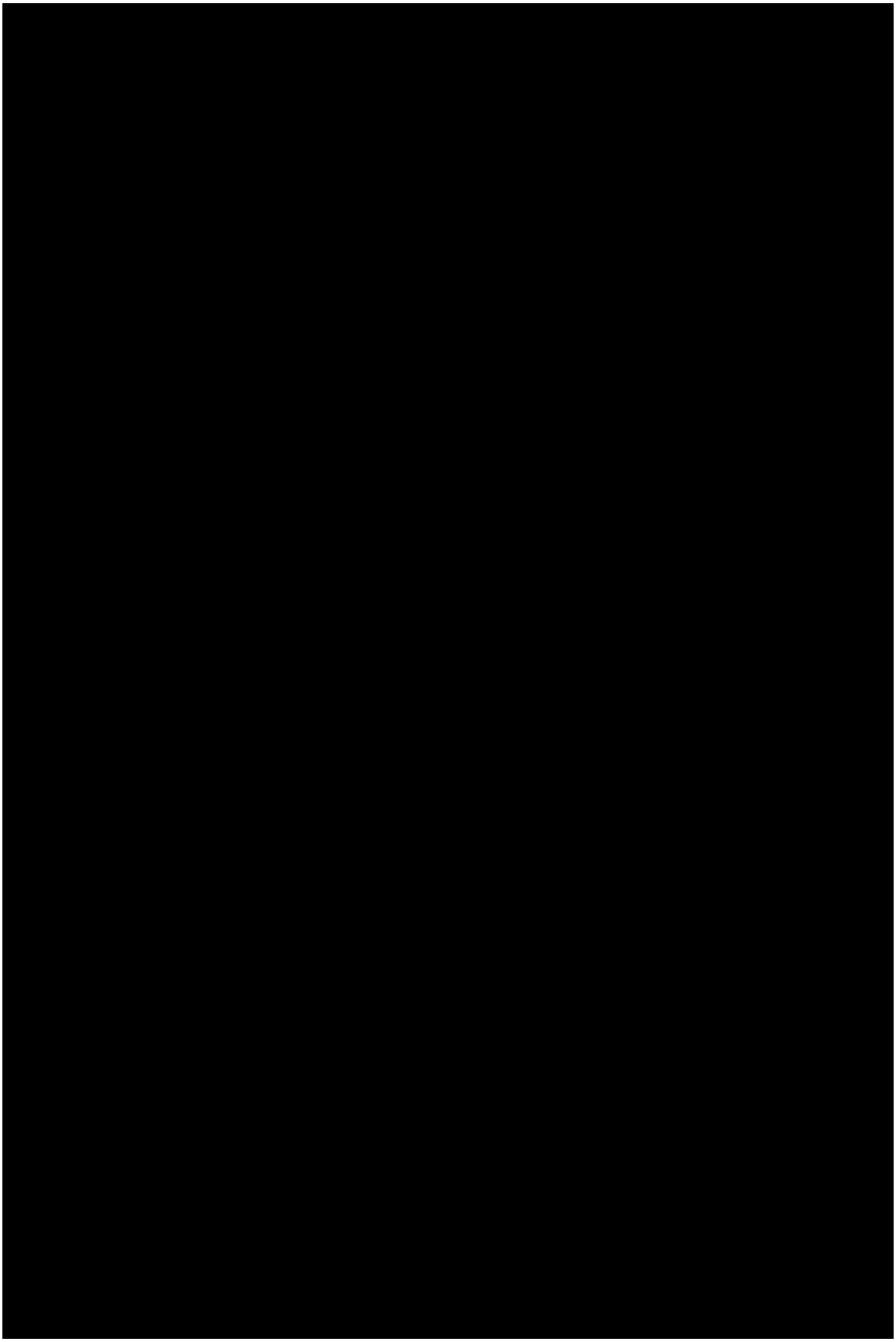
HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS?

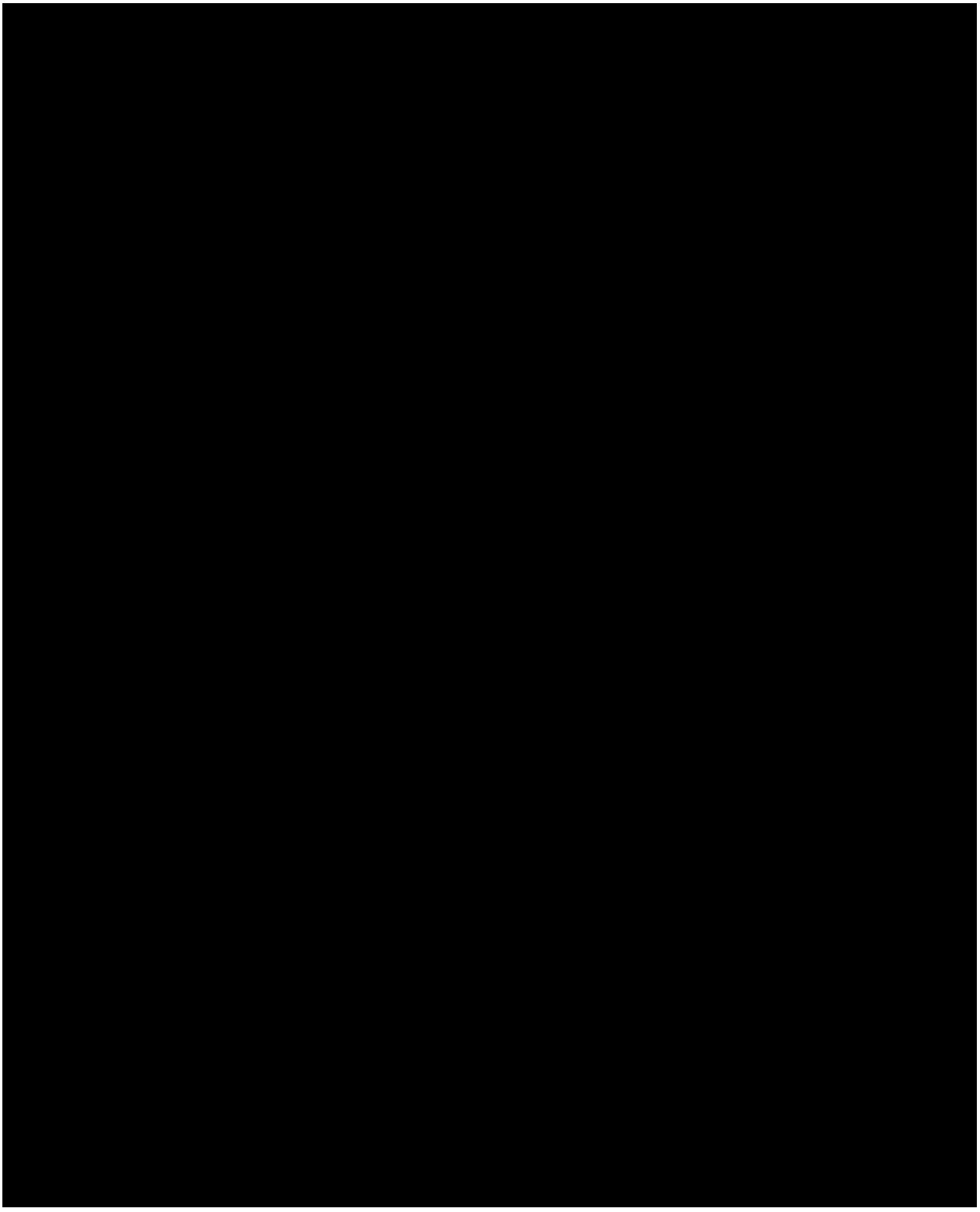
	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

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 8: Patient Asthma Control e-Diary

For illustrative purposes only:

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 rate
	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 9: 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, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 2 x ULN	N/A	Repeat LFT at next visit	

[redacted]

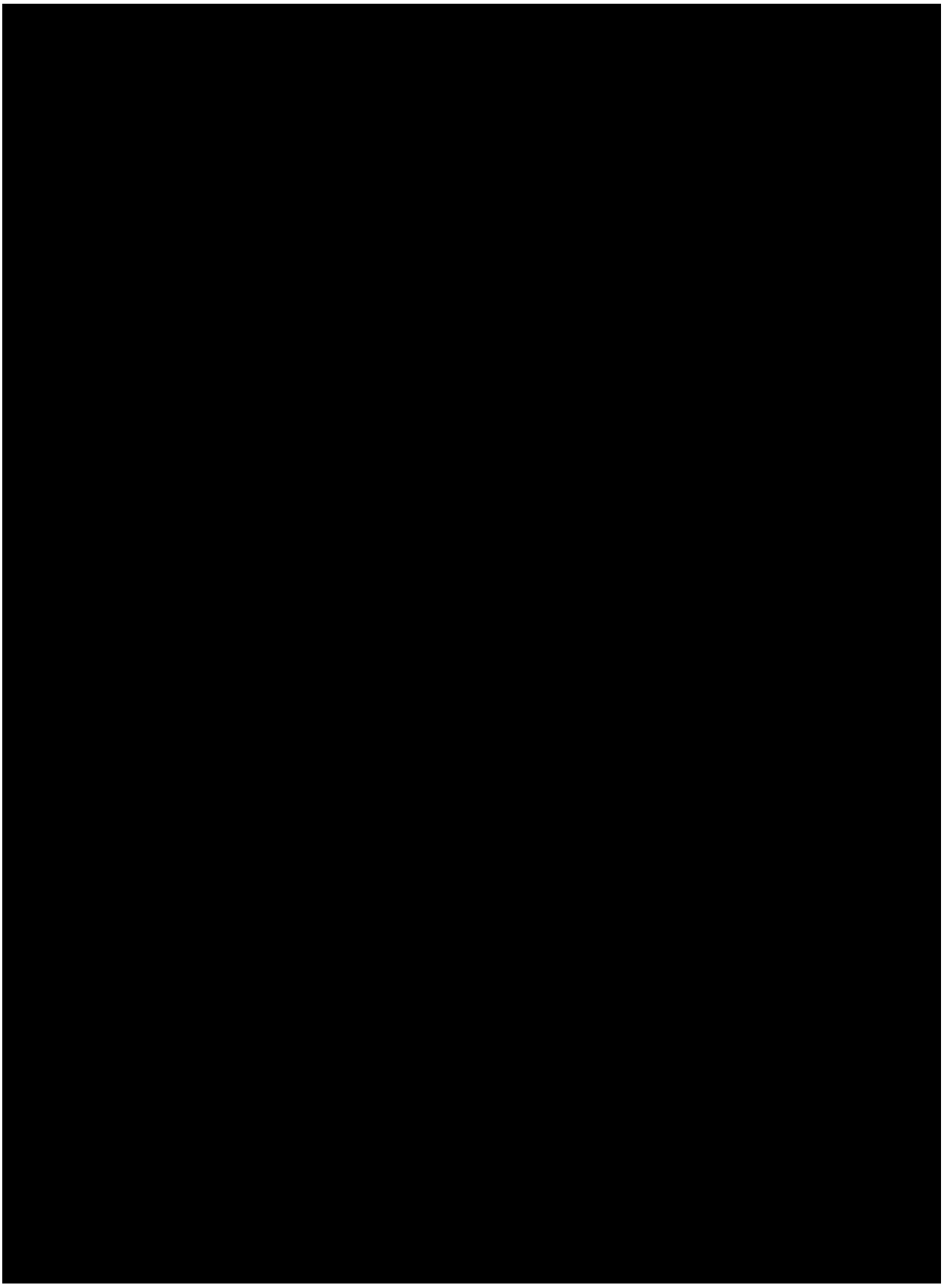
Criteria	Event type	Actions required	Follow-up monitoring
(patient is asymptomatic)			
TBL (isolated)			
> 3 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish 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 11: ICS Dose level

Table 13-3 Low, medium and high Daily Doses of Inhaled Glucocorticosteroids for Adults and adolescents (12 years and older)* (GINA 2015)

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 Furuoate**	NA	100	200
Mometasone furoate	110-220	> 220-440	≥ 440
Triamcinolone acetonide	400-1000	> 1000 –– 2000	> 2000

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant.

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

** As per SmPC

[redacted]

Appendix 12: Estimation of non-inferiority margin of comparing QMF149 versus active control (salmeterol xinafoate /fluticasone propionate)

The non-inferiority margin of QMF149 vs active control (salmeterol xinafoate /fluticasone propionate) is based on the results from Kavuru et al (2000), Nathan et al (2006), and Relvar® Ellipta's asthma studies HZA106827 and HZA113091 (GSK Breo Ellipta Advisory Committee briefing document, March 2015) on the treatment effect of the three different doses of active control over placebo. Table 13-4 summarizes the key inclusion criteria for these studies, the adjusted mean for each treatment of active control and placebo, standard error (SE) of the mean, treatment difference, and its 95% CI. In addition the table summarizes the meta-analysis based on the pooled estimates from these studies.

From Table 13-4, the historical evidence of drug effect of active control over placebo (from the meta-analysis) is 354 mL with its 95% CI from 281 mL to 426 mL. Hence based on the lower limit of the pooled estimate, 281 mL, by demonstrating the NI with the chosen NI margin of -90 mL, the treatment effect of QMF149 would be at least 191 mL over (putative) placebo with 95% confidence level, which represents 68% preservation of the treatment effect of active control over placebo.

Table 13-4 Historical evidence of sensitivity of drug effect of active control fixed-dose combination (FDC) for trough FEV_1 in patients with persistent asthma

Study (Duration)	Key Inclusion Criteria	Treatment (n)	Mean (L)* (SE)	Difference vs. placebo (95% CI)
Nathan et. al. (12 weeks)	• ≥ 12 years old with asthma requiring pharmacotherapy for at least 6 month before the study • Use of ICS therapy for ≥ 3 months before the study and at a consistent dose for the previous month • 40% < FEV_1 < 85% • ≥ 15% increase in FEV_1 from pre to post SABA	FDC 42/220 µg BID (n = 92)	0.41 (0.04)	0.53 (0.405, 0.655)
		Placebo (n = 87)	-0.12 (0.05)	
Kavura et. al. (12 weeks)	• ≥ 12 years old with asthma requiring pharmacotherapy for at least 6 month before the study • Use of ICS therapy for ≥ 3 months before the study and at a consistent dose for the previous month • 40% < FEV_1 < 85% • ≥ 15% increase in FEV_1 from pre to post SABA	FDC 50/100 µg BID (n = 87)	0.51 (0.05)	0.50 (0.319, 0.681)
		Placebo (n = 77)	0.01 (0.07)	
Relvar Asthma Program 2015	See Table 13-5	FDC 50/250 µg BID (n=389)		0.191** (0.089, 0.293)

[redacted]

(Briefing Book)		Placebo (n=193)		
Meta-Analysis***		FDC (n = 576)		0.354 (0.281, 0.426)
		Placebo (n = 357)		

* Change from baseline in pre-dose FEV_1 at week 12.

** Treatment effect is estimated based on combining studies HZA106827 and HZA113091 from Relvar® asthma program (briefing book) as summarized in Table 13-5.

*** Meta-analysis is based on pooling of the results from Nathan et al (2006), Kavuru et al (2000), and Relvar's asthma program from studies HZA106827 and HZA113091 and using the inverse variance weighting method.

Table 13-5 Summary of studies HZA106827 and HZA113091 for trough FEV_1 from Relvar® asthma program

Study (Duration)	Key Inclusion Criteria	Treatment (n)	Mean (L) (SE)	Treatment Difference (95% CI)
Relvar Asthma Program Study HZA106827 (12 weeks)	• Outpatients at least 12 years of age • Male and female; female subjects of childbearing potential must be willing to use birth control • Pre-bronchodilator FEV1 of 40-90% predicted normal • Reversibility FEV1 of at least 12% and 200 mL • Current asthma therapy includes inhaled corticosteroid use for at least 12 weeks prior to first visit	FF/VI 100/25 µg (n=200)	0.368 (0.0304)	0.172 (0.087, 0.258)
		Placebo (n=193)	0.196 (0.0310)	
Relvar Asthma Program Study HZA113091 (24 weeks)	• Clinical diagnosis of asthma • Reversibility of at least 12% and at least 200 mL within 10-40 minutes following 2-4 inhalations of albuterol • FEV1 of 40-85% predicted normal • Currently using inhaled corticosteroid therapy	FF/VI 100/25 µg (n=397)	0.281 (0.0191)	-0.019 (-0.073, 0.034)
		FP/SAL 250/50 µg BID (n=389)	0.300 (0.0193)	

Reference:

Kavuru MD et al (2000) Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: A randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol (2000); 105: 1108-16.

Nathan et al (2006) Efficacy and tolerability of fluticasone propionate/salmeterol administered twice daily via Hydrofluoroalkane 134a metered-dose inhaler in adolescent and adult patients

with persistent asthma: a randomized, double-blind, placebo-controlled, 12-week study. Clinical Therapeutics (2006); 28: 73-85.

[redacted]