NOVARTIS

Global Clinical Development – General Medicine

CQVM149B (QMF149: Indacaterol acetate / Mometasone furoate)

CQVM149B2303/ NCT02892344

A multi-center, randomized, 12-week treatment, double-blind study to assess the efficacy and safety of QMF149 (150/80 microgram) compared with MF Twisthaler® (200 microgram) in adult and adolescent patients with asthma

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List of abbreviations

ACQ	Asthma Control Questionnaire
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AQLQ	Asthma Quality of Life Questionnaire
b.i.d.	twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
COPD	Chronic Obstructive Pulmonary Disease
CPO	Country Pharma Organization
CRO	Contract Research Organization
DALYS	Disability-Adjusted Life Years
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemology
eCRF	Electronic Case Report/Record Form
eDiary	Electronic Diary
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
ER	Emergency Room
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FEF	Forced Expiratory Flow
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GTL	Global Trial Leader
hCG	Human Chorionic Gonadotropin
HV	Healthy Volunteer
IgE	Immunoglobulin E
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroid

[redacted]

IEC	Independent Ethics Committee
i.v.	Intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra Uterine Device
IUS	Intra Uterine System
IVRS	Interactive Voice Response System
LABA	Long Acting Beta-2 Agonist
LAMA	Long Acting Muscarinic Antagonist
LFT	Liver Function Test
LTRA	Leukotriene Receptor Antagonist
LS Mean	Least squares mean
MDDPI	Multi dose dry powder inhaler
MDI	Metered Dose Inhaler
MF	Mometasone Furoate
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measurements
NYHA	New York Heart Association
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	Once a day
p.o.	Oral(ly)
PDCO	Pediatric Committee of the European Medicines Agency
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PRO	Patient Reported Outcome
PSD	Premature patient discontinuation
QTc	Corrected QT interval
REB	Research Ethics Board
SABA	Short Acting Beta-2 Agonist
SAE	Serious Adverse Event
SAMA	Short Acting Anticholinergics
SCS	Systemic Corticosteroids
SDDPI	Single Dose Dry Powder Inhaler
SoC	Standard of Care
SMQ	Standard MEDRA Query
WHO	World Health Organization
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Dosage	Dose of the study treatment given to the patient in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g., prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Patient ID	A unique number assigned to each patient upon signing the informed consent
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.
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), placebo/comparator active drug Run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Patient Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 2

Amendment rationale

The assumptions for CQVM149B2303 key secondary endpoint, Asthma Control Questionnaire-7 (ACQ-7) treatment difference, were originally based on data from CQMF149A2210. In study CQMF149A2210, the observed mean difference after 12 weeks of treatment (indacaterol acetate and mometasone furoate (QMF) combination therapy versus mometasone furoate (MF) monotherapy) was -0.21 with 95% confidence interval (-0.28, -0.15). Based on the upper limit of the confidence interval, a treatment difference of -0.15 was chosen as a conservative estimate, which was used to determine the sample size of CQVM149B2303. However, upon recent evaluation of the treatment difference of CQMF149A2210, it was decided to adopt an ACQ-7 treatment difference of -0.18. This treatment difference is the upper limit of the one-sided 80% confidence interval and more appropriately reflects the expected improvement in ACQ-7 for the patient population of CQVM149B2303. Reflecting the revised assumptions, the sample size re-estimation has allowed for a reduction from 1000 to approximately 750 patients.

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:

1. Section 3.1, clarified that starting with the Run-in epoch (Visit 101), patients will record Peak Expiratory Flow Rate (PEF) twice daily; clarified enrolled patients are randomized patients; clarified Visit 204 (Week 12) should take place within a 4 day window and if this is not possible, the sponsor should be notified.
2. Section 4, updated sample size to approximately 750 males and females with a diagnosis of asthma ≥ 12 and ≤ 75 years of age; updated adolescent sample size to approximately 50 patients [redacted]; clarified that adolescents are ≥ 12 and < 18 years of age; updated anticipated number of patients to be screened to reach updated sample size with 1:1 randomization in the two treatment groups.
3. Section 4.1, updated inclusion criterion 5 to clarify that adults must be symptomatic at V101 and V102.
4. Section 4.2, updated exclusion criterion 2 for adolescents (≥ 12 and < 18) [redacted] to exclude adolescents that have had an asthma attack/exacerbation requiring systemic steroids or hospitalization (> 24 hours) or emergency room visit (≤ 24 hours) requiring systemic corticosteroids within 6 months, prior to Visit 1.
5. Section 4.2, updated exclusion criterion 33 due to template changes for highly effective contraception.; this no longer includes barrier methods of contraception.
6. Section 6, clarified that sponsor should be notified if Visit 204 (Week 12) should take place outside of the 4 day window; clarified PEF measurements are recorded twice daily.

[redacted]

7. Table 6-1, clarified Visit 204 (Week 12) should take place within a 4 day window and if this is not possible, the sponsor should be notified.
8. Table 6-2, clarified that timed assessment windows are approximate.
9. [redacted]
10. Section 6.3 & Section 6.4.4, clarified that the data from the electronic Diary (eDiary) will be reviewed by study site personnel at each visit.
11. Section 6.4.2, clarified that the ACQ-7 should be completed at the study site.
12. Section 6.5.5, clarified that electrocardiograms (ECG) should be recorded after 10 minutes rest in the supine position to ensure a stable Baseline. Also clarified that only one printed copy needs to be kept by the study site.
13. [redacted]
14. Section 9, updated dosing time window to dosing time for clarity throughout this section.
15. Section 9.2, clarified that percentage of predicted forced expiratory volume in one second (FEV_1) [redacted] will be summarized by treatment group.
16. Section 9.4.2, clarified that the between-treatment comparison will be carried out using the adjusted mean (least squares mean (LS mean)) difference based on the treatment main effect and the coefficient for the treatment-by-visit interaction for Day 85.
17. Section 9.4.5, updated section title from 'supportive' to 'supplementary' analysis and clarified that the same mixed model for repeated measure (MMRM) used in the primary analysis will be also performed on the Per-Protocol Set (PPS) to assess the treatment effect in protocol adherers.
18. Section 9.6.1.1, clarified that trough FEV_1 at Day 2 visit will be analyzed using the same MMRM as specified for the primary analysis, i.e., the visit factor will include all available visits as a factor and between-treatment comparison will be carried out using the adjusted mean (least-square mean) difference based on the treatment main effect and the coefficient for the treatment-by-visit interaction for the respective visit and treatment.
19. Section 9.6.1.2, clarified that the analysis results for all post-baseline visits, obtained from the MMRM for the key secondary endpoint ACQ-7, will be displayed. In addition, analysis for change from baseline in the ACQ-7 will be performed.
20. [redacted]
21. Section 9.7, updated secondary endpoint ACQ-7 treatment difference to -0.18 between QMF149 versus MF, assuming a standard deviation of 0.80 based on study CQMF149A2210; updated sample size and power accordingly.
22. Section 9.7, clarified sample size calculation is performed in PASS Software.
23. Section 9.7, removed reference to CQMF149E2201 and CQMF149E2203
24. Section 9.7 and References Section, removed references to Kerstjens HAM et al 2012 and Kerstjens et al 2015.

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.

[redacted]

Summary of amendments issued before this amendment:

Amendment 1

Amendment rationale

1. Adjust the approach to asthma worsening eDiary alerts during the Run-in epoch (Section 6.4.8). Currently, it is stated in the protocol, that if an asthma worsening alert is observed during the Run-in epoch, the patients must be discontinued regardless of clinical context and investigator judgment. This protocol amendment will allow investigators to use their discretion in determining the clinical significance of asthma worsening eDiary alerts during the Run-in epoch. This will allow the investigator to make the most appropriate decision as to whether patients may continue in the study or be discontinued. If asthma worsening alert is confirmed as clinically significant by the investigator, patients should be discontinued. A combination of eDiary alerts and investigator judgment will help ensure that the most appropriate patients are enrolled in the study, while maintaining rigorous monitoring and assessment of patient safety.
2. Provide additional opportunity for patients to achieve reversibility. This includes a change to the text to allow spacer use for reversibility testing as well as increasing the time period for historical reversibility from 1 year to 2 years.
3. Provide more clarity in various sections of the protocol to address queries raised by various countries and health authorities.

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:

- Updated “Other Secondary Objectives” for exacerbations to retain only the highest level endpoints (Section 2.3).
- Reference to GINA 2015 guidelines updated to GINA 2016 guidelines (Section 1.1, Section 3.1, Section 3.6, inclusion criterion 7 in Section 4.1, and exclusion criterion 20 in Section 4.2) to allow repeat spirometry retest at both Visit 101 and 102, modified timing for reversibility and modified the use of historical reversibility from 1 year to 2 years.
- Added clarification to inclusion criterion 7 that if patient fails spirometry repeatability at Visit 102, patient can be re-screened (Section 4.1).
- Specified “severe” narcolepsy and/or insomnia in exclusion criterion 24 (Section 4.2).
- Clarified spacer devices not permitted “for rescue medication” in exclusion criterion 28 (Section 4.2), however spacer devices are only permitted during reversibility testing based on investigator discretion (inclusion criterion 8, Section 4.1).
- Adjusted wording from “completion” to “stopping” in exclusion criterion 33 (Section 4.2).

[redacted]

- Clarified LAMA exclusion criteria: LAMA washout criteria in Table 5-1 removed and replaced with a new exclusion criterion 34 (Section 4.2) to exclude patients who were treated with LAMA 3 months prior to Visit 1.
- Updated exclusion criterion 5 (Section 4.2) to clarify patient would be excluded if having respiratory tract infection or asthma worsening "as determined by investigator".
- Added clarification on myocardial infarction in exclusion criteria 13 and 16 (Section 4.2).
- Updated exclusion criterion 16 (Section 4.2) to clarify that patients having clinically significant abnormality in ECG at unscheduled visits between Visit 1 and Visit 102 will be excluded.
- Clarified that countries who do not have fluticasone 100 µg b.i.d delivered by Accuhaler® or 125 µg b.i.d by MDI can use fluticasone propionate in an alternative formulation at an equivalent dose strength.
- The word masterscope was replaced with "equipment provided by spirometry vendor".
- Clarified 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.
- Updated Section 5.5.4 for the purpose of drug accountability and clarified that study medication can be taken regardless of time of sleep, meals, and other activities.
- Clarified wording and provided differentiation between monoclonal antibodies and IL-5 inhibitors in Table 5-1.
- Added a new safety criteria in Discontinuation of study treatment (Section 5.6.2).
- Updated the visits where Survival Status eCRFs are visible (Table 5-4 and Table 6-1) to be in line with the clinical database.
- Provided clarification in Section 5.6.3 regarding early study discontinuation visits for patients who withdrew consent from the study.
- Provided clarification on ACQ-7 questionnaire (Section 6.4.2) regarding the questions that needs to be completed by the patient and those that need completion by investigator.
- Clarified both exclusion criterion 5 (Section 4.2) and Section 6.4.8 to indicate that discontinuation is at the investigator's discretion when the eDiary asthma worsening alert criteria are met during Run-in epoch in accordance with Section 6.4.8. This amendment will allow the investigator to incorporate clinical judgment into the context of eDiary alerts during Run-in epoch to assess clinical significance of the asthma worsening alert and decide on best course of action and the treatment for patient.
- Aligned 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).

[redacted]

Protocol summary

Protocol number	**CQVM149B2303**
Title	A multi-center, randomized, 12-week treatment, double-blind study to assess the efficacy and safety of QMF149 (150/80 microgram) compared with mometasone furoate (MF) Twisthaler® (200 microgram) in adult and adolescent patients with asthma
Brief Title	Efficacy and safety of low dose QMF149 (150/80 microgram) compared with MF Twisthaler® (200 microgram) in patients with asthma
Sponsor and Clinical Phase	Novartis - Phase III
Investigation Type	Drug
Study Type	Interventional
Purpose and Rationale	The purpose of this study is to demonstrate superiority of QMF149 vs. MF monotherapy in terms of trough FEV_1 at Week 12 in patients with asthma to demonstrate the contribution of the LABA component in the low dose QMF149 fixed dose combination.
Primary Objective	The primary objective of this study is to demonstrate the superiority of QMF149 150/80 microgram o.d. (in the evening) delivered via Concept1 compared with MF 200 microgram o.d. (in the evening) delivered via Twisthaler® in terms of trough FEV_1 after 12 weeks of treatment in patients with asthma, who are on low dose ICS monotherapy or low dose ICS/LABA.
Secondary Objectives	The key secondary objective of this study is to demonstrate the superiority of QMF149 150/80 microgram (µg) to MF 200 microgram (µg) o.d. in terms of ACQ-7 after 12 weeks of treatment. The other secondary objectives include: lung function parameters (e.g., trough FEV_1 at additional time points, peak FEV_1, PEF) rescue medication use, days without symptoms, and asthma quality of life (AQLQ).
Study Design	A 12-week multi-center, randomized, double-blind, double-dummy, parallel-group, active controlled study.
Population	The study population will consist of approximately 750 males and females with asthma (approximately 50 adolescents). Patients will be stratified according to prognostic factors of age and region.
Key Inclusion Criteria	**Adult** patients with asthma who are symptomatic at screening despite treatment with existing therapy. Patients must have ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (i.e., inadequately controlled).

[redacted]

	Adolescent (≥ 12 to < 18 years old) patients with asthma: • Patients taking low dose ICS (without LABA), who are symptomatic at screening despite treatment with low dose ICS. These patients must have ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (i.e., inadequately controlled). • Patients taking low dose ICS / LABA, may be included only if ACQ-7 score ≥ 1 and < 1.5 at Visit 101(i.e., adequately controlled). However, ACQ-7 score must be ≥ 1.5 at Visit 102. Pre-dose FEV_1 ≥ 60% and < 90% of the predicted normal value. FEV_1 reversibility ≥ 12% and ≥ 200 mL.
Key Exclusion Criteria	Pregnant women/nursing mothers. Women of child bearing potential (unless using adequate contraception). History of chronic lung diseases other than asthma, including (but not limited to) chronic obstructive pulmonary disease, sarcoidosis, interstitial lung disease, cystic fibrosis, clinically significant bronchiectasis and active tuberculosis. Current smokers who smoked or inhaled tobacco products (including electronic cigarettes) within the 6 month period prior to Visit 1 or ex-smoker with ≥ 10 pack years smoking history. Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization (> 24 hours) or emergency room visit (≤ 24 hours) as follows: • For adults: 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. • For adolescents: Severe asthma attack/exacerbation requiring systemic corticosteroids in the last 6 months, OR hospitalization (>24 hours) due to severe asthma attack/exacerbation requiring systemic corticosteroids in the last 6 months, OR emergency room visit (≤ 24 hours) due to severe asthma attack/exacerbation requiring systemic corticosteroids within the last 6 months Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption or with known intolerance to lactose or milk products.

[redacted]

Study Treatment	• QMF149 150/80 µg Concept1 once-daily/ and Placebo to MF 200 microgram Twisthaler® once-daily • MF 200 µg Twisthaler® once-daily/ and Placebo to QMF149 150/80 microgram Concept1 once-daily
Key Efficacy Assessments	Spirometry ACQ-7 AQLQ Asthma symptoms based on electronic diary (eDiary) Peak expiratory flow Rescue medication use Worsening of asthma Asthma exacerbations
Key Safety Assessments	Physical examination, oropharyngeal examination Vital signs Hematology, blood chemistry, urinalysis Evening plasma cortisol Electrocardiogram (ECG) Adverse events (AEs) including asthma exacerbations and serious adverse events (SAEs) Pregnancy (female patients) Serious asthma outcomes (asthma-related hospitalizations, intubations or deaths)
[redacted]	
Data Analysis	The primary variable is trough FEV_1 after 12 weeks of treatment. The key secondary variable is ACQ-7 after 12 weeks of treatment. The primary variable will be analyzed using a mixed model for repeated measurement (MMRM) on the Full Analysis Set. The model will contain treatment, age (≥ 12 to < 18 or ≥ 18 years), region, visit (Days 2 and 85), 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 short acting beta-2 agonist reversibility) as covariates, and center nested within region as a random effect. The within-patient correlation will be

[redacted]

	modeled using an unstructured covariance matrix in the mixed model. The same MMRM will be used for ACQ-7 except to include the appropriate baseline covariate. A hierarchical testing procedure will be applied to control the type-I error rate for the primary and the key secondary endpoints, i.e., the key secondary endpoint ACQ-7 will be tested only if the primary endpoint (trough FEV_1) is significant at the 2-sided 0.05 level.
Key Words	QMF149, Mometasone furoate (MF), Asthma, GINA

[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 2016).

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 guidelines recommend use of low dose ICS (inhaled corticosteroid) controller treatment for step ≥ 2 while preferred controller treatment for step ≥ 3 is the combination of ICS/LABA (inhaled corticosteroid / long-acting beta$_2$-agonist) with a low dose ICS or mid/high dose ICS monotherapy (GINA 2016).

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 a day (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 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 (Breezhaler®). Concept1 is the approved inhalation device for use with indacaterol maleate and other Novartis COPD inhalation therapies.

[redacted]

Background data for Indacaterol and Mometasone furoate monotherapies:

Indacaterol

Indacaterol maleate, a long-acting beta$_2$-agonist, delivered via the Concept1 device in 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 mono-component (as add-on to existing ICS) as well is in the fixed dose combination QMF149 (indacaterol acetate / MF) delivered by the Twisthaler® device in asthma patients. Indacaterol acetate delivered by Twisthaler® has been

[redacted]

studied in healthy volunteers (HV), adult patients with COPD and adult and adolescent patients with asthma.

Two studies (CQMF149E2203 and CQAB149B2357) were conducted to support the selection of indacaterol 150 µg which is the proposed dose to be carried forward in the Phase III QVM program. Study CQMF149E2203 investigated two (2) 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.

A dose-ranging study CQAB149B2357 of indacaterol maleate in asthmatic patients demonstrated that a dose of 150 microgram o.d. was safe and effective. Furthermore, study CQAB149B2338, a 26-week study in asthmatic patients showed that indacaterol maleate at doses of 300 microgram and 600 microgram o.d. were also well-tolerated in this population.

In the QVM149 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).

Mometasone furoate

Mometasone furoate (MF) is a corticosteroid and the active ingredient in the currently marketed product Asmanex® Twisthaler® (mometasone furoate inhalation powder delivered via a multi-dose dry powder inhaler (MDDPI)).

Asmanex® Twisthaler® is currently indicated for the once or twice-daily maintenance treatment of persistent asthma in adults and adolescents > 12 years and, in the US, in children aged > 4 years. Asmanex® Twisthaler® is approved at doses of 100 µg, 200 µg and 400 µg (per delivered dose) up to a maximum daily dose of 800 µg for patients with severe disease, with preferred administration in the evenings. Merck is the Marketing Authorization Holder in 60 countries worldwide.

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 three 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.

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Comparison of MF doses in Asmanex® Twisthaler® and Concept1

The fixed dose combination of mometasone and indacaterol, QMF149 will be delivered by Concept1 device in the current study. Based on existing data for the MF component in the Twisthaler® device, a 3-Step bridging approach was conducted to determine MF dose for Concept1 which is comparable to each of the registered daily doses of Asmanex® Twisthaler® (mometasone furoate, inhalation powder). Pharmacokinetic bridging utilizing pharmacokinetic characterization in study CQMF149E2101 (Step 1) (Vaidya 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 Steps 1 and 2, the data of study CQMF149E2101 (Vaidya et al, 2012), along with in-vitro fine particle mass adjustments have determined that doses of 80, 160, and 320 microgram of MF in Concept1 device are comparable in strength to the approved doses of 200 microgram, 400 microgram and 800 microgram (2 x 400 microgram) MF in Twisthaler®.

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

Comparable MF Doses via Twisthaler® and Concept1

MF dose level	MF dose in Asmanex® via Twisthaler®	MF dose in QMF149 via Concept1 (Breezhaler®)
Low	200 µg	80 µg
Mid	400 µg	160 µg
High	800 µg	320 µg

1.2 Purpose

The purpose of the trial is to evaluate efficacy and safety of QMF149 150/80 microgram o.d. delivered via Concept1 compared to MF 200 microgram o.d., delivered via Twisthaler® in terms of lung function and symptom control in poorly (i.e., inadequately) controlled asthma patients. This study will assess contribution of LABA as an add-on therapy to low dose ICS monotherapy.

2 Study objectives and endpoints

2.1 Primary objective

The primary objective of this study is to demonstrate the superiority of QMF149 150/80 microgram o.d. (in the evening) delivered via Concept1 compared with MF 200 microgram o.d. (in the evening) delivered via Twisthaler® in terms of trough FEV_1 after 12 weeks of treatment in adults and adolescents.

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2.2 Key Secondary objective

The key secondary objective is to demonstrate the superiority of QMF149 150/80 microgram to MF 200 microgram o.d. in terms of ACQ-7 after 12 weeks of treatment.

2.3 Other secondary objectives

Other secondary objectives will evaluate the efficacy of QMF149 150/80 microgram versus MF 200 microgram o.d. in terms of:

Lung function:

- Trough FEV_1 at Day 2 of treatment period (defined as the mean of 23 hours 15 min and 23 hours 45 min FEV_1 values post dose of Day 1)
- Pre-dose FEV_1 (defined as the mean of -45 min and -15 min FEV_1 values pre-evening dose) at 4 weeks
- Forced Vital Capacity (FVC) and Forced Expiratory Flow between 25% and 75% of FVC (FEF_{25-75}) over 12 weeks
- Morning and Evening Peak Expiratory Flow Rate (PEF) over 4 and 12 weeks of treatment

Symptoms and asthma control:

- Percent of patients achieving the minimal important difference (MID) in ACQ-7 (i.e., at least 0.5 improvement from baseline) at Week 12
- Percentage of asthma symptoms free days, the percentage of nights without nighttime awakenings, and the percentage of mornings without symptoms on awakening as recorded by daily electronic Diary (eDiary) over 12 weeks of treatment
- Asthma control as assessed by the Asthma Control Questionnaire (ACQ-7) at Week 4
- Rescue salbutamol/albuterol usage (mean daily, nighttime and daytime use) from eDiary recordings over 12 weeks of treatment
- Percentage of rescue medication free days over 12 weeks of treatment period

Exacerbations:

The exacerbation data collected during 12 weeks of treatment period will be assessed with respect to the parameters described below. The exacerbation categories are: All exacerbations (mild, moderate, severe) and the combination of moderate or severe:

- Time to first asthma exacerbation by exacerbation category
- Annual rate of asthma exacerbations by exacerbation category
- Quality of life as assessed by Asthma Quality of Life Questionnaire (AQLQ) over 12 weeks of treatment period

The following safety and tolerability endpoints will be evaluated:

- Cumulative incidence of the composite endpoint of serious asthma outcomes (i.e., asthma-related hospitalization, asthma-related intubation, or asthma-related death) over 12 weeks of treatment
- AEs, vital signs, electrocardiogram (ECG), and laboratory analysis (hematology, blood chemistry including glucose and potassium, urinalysis, evening plasma cortisol) over 12 weeks of treatment

[redacted]

[redacted]

3 Investigational plan

3.1 Study design

This study uses a 12-week treatment, randomized, double-blind, double-dummy, parallel-group design. The 12 week treatment epoch will be followed by a 30 day Follow-up epoch. 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 asthma medications are replaced with permitted asthma medications for use throughout the study.

All patients should have been on a stable dose of inhaled low dose corticosteroids (with or without LABA) for at least 1 month prior to Visit 1. Once the concurrent medications comply with the requirements of the study (Section 5.5.7 and Section 5.5.8) patients will enter a Run-in epoch at Visit 101.

At Run-in 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 propionate in an alternative formulation at an equivalent dose strength) for use throughout the Run-in epoch which will be 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 washout of prior asthma medication. Depending on prior asthma medication and washout requirements, the period between Visit 1 and Visit 101 may be shorter than 2 weeks. 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 with the Run-in epoch (Visit 101), patients will record Peak Expiratory Flow Rate (PEF) twice daily. The Run-in epoch is three (3) weeks in duration and will be used to assess eligibility of the patients prior to entering the treatment epoch and to collect baseline values for some variables.

Patient can enter the Run-in epoch provided inclusion criteria are met, including those for spirometry (pre-dose percent predicted FEV_1, ATS/ERS criteria, and reversibility) as per spirometry equipment.

Patients who meet the eligibility criteria at Visit 102 will be randomized to one of following two treatment groups with an equal (1:1) randomization ratio:

- QMF149 150/80 microgram o.d. delivered via Concept1
- MF 200 microgram o.d. delivered via Twisthaler®

[redacted]

Randomized patients must have FEV_1 between 60% and < 90% of predicted normal at **both** Visit 101 and Visit 102 and they must qualify for treatment with low dose ICS plus LABA as per GINA 2016 guidelines. At Visit 102, **all** randomized patients must have ACQ-7 ≥ 1.5. Refer to Section 4.1 Inclusion Criteria for ACQ-7 requirements.

Visit 102 (end of Run-in) and Visit 201(Randomization) must take place sequentially on the same day. The assessments at Visit 102 should be performed prior to administration of the first dose of study medication (Visit 201). Reversibility should NOT be done at Visit 102 (Table 6-1). Randomized patients will enter the 12-week Treatment epoch. All patients will receive both Concept1 and Twisthaler® inhalers (double-blind and double-dummy design). During the treatment epoch, patients will be instructed to inhale study medication once daily in the evening (between 5:00 pm and 8:00 pm).

Patients will be followed at regular intervals throughout the 12 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, and 12 weeks. All clinic visits should occur as scheduled per Table 6-1. 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 12 weeks of treatment (Clinic Visit 204). In case of logistical issues, Visit 204 (Week 12) should take place within a 4 day window. If this is not possible, the sponsor should be notified.

Pre-dose FEV_1 measurements will be assessed at Week 4. Telephone reviews of patients' status will be conducted after 8 weeks of treatment. Telephone contact 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 12 weeks).

The first dose of study medication will be administered at the clinic in the evening (between 05:00 pm 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.

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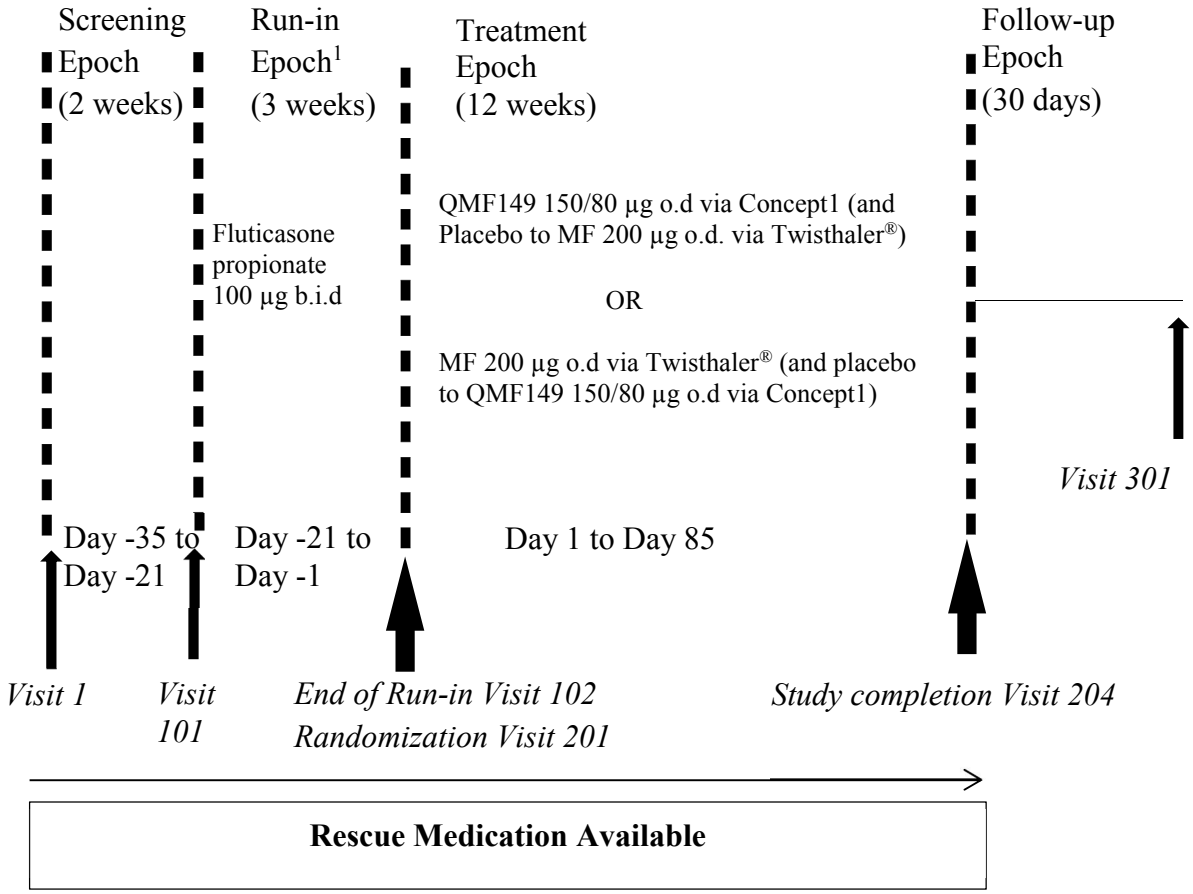
Figure 3-1 Study Design



[1] Please refer to Table 5-1 for details of adjustments to concomitant asthma medications and specified minimum washout periods prior to Run-in (Visit 101) and/or Randomization (Visit 201). For Run-in medication, fluticasone propionate 100 µg b.i.d should be delivered via Accuhaler® or fluticasone propionate 125 µg b.i.d. via Metered Dose Inhaler (MDI) will be accepted. In case it is not available in a particular country, fluticasone propionate in an alternative formulation at an equivalent dose strength may be used.

3.2 Rationale for study design

In order to optimize the rigor of the study and minimize bias, a randomized, double-blind parallel group design is used. This design is appropriate to determine the benefit of the addition of a LABA in a fixed dose combination with low dose ICS as compared to low dose ICS monotherapy. The study design does not include a placebo control, as this would not be considered ethical in this population of asthmatic patients who are symptomatic.

The primary objective of the trial is to evaluate the efficacy and safety of QMF149 150/80 microgram o.d. via Concept1 compared to MF 200 microgram via Twisthaler® in poorly (i.e., inadequately) controlled symptomatic patients as measured by trough FEV_1. In addition, secondary endpoints will provide data related to asthma control (ACQ), rescue medication use,

asthma exacerbations, quality of life, and safety of the studied QMF149 dose in this specific asthma patient population.

The analyses will be performed in a sample size of approximately 750 patients. The patient population will be described in more detail in the Section 4.

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

This study is a pivotal, multi-center, randomized, double-blind, double-dummy, parallel-group, Phase III study with a 12-week treatment epoch which is required to assess the safety and efficacy of QMF149 in asthma. The primary endpoint will be evaluated over 12 weeks. The dose regimen/route of administration of QMF149 selected (150/80 microgram delivered via Concept1) is based on the findings of previous studies identifying effective and safe doses of the individual components of the FDC, indacaterol and MF) (Section 1.1).

The 12 week duration is considered adequate 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.

3.4 Rationale for choice of comparator

MF was selected as the comparator as it is the ICS monocomponent in QMF149 combination formulation and is necessary in order to demonstrate the additional benefit of a LABA (indacaterol acetate 150 microgram) in the QMF149 combination (Appendix 9) as compared to MF monotherapy in patients whose asthma is inadequately controlled with ICS alone. Furthermore, MF in Twisthaler® formulation is approved for treatment in asthma.

The MF inhalation powder formulation is marketed as a MDDPI called Asmanex® Twisthaler® for the treatment of asthma and is currently approved in the Unites 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 old. The MF 200 microgram o.d. delivered via Twisthaler® is comparable to MF 80 microgram o.d. delivered via Concept1 (Section 1.1).

3.5 Purpose and timing of interim analyses/design adaptations

No interim analysis for efficacy is planned. It is planned that the independent Data Monitoring Committee (DMC) will review semi-blinded (i.e., treatment groups names as A and B) safety data (Section 8.4). The details of the information flow, confidentiality and specific analysis will be available from the DMC Charter.

3.6 Risks and benefits

ICS/LABA fixed dose combinations are frequently used as controller medications and are foundation therapy in GINA step ≥ 3 (GINA 2016).

QMF149 (indacaterol 150 microgram as an FDC with three doses of MF: 80 microgram, 160 microgram or 320 microgram) is a new once daily ICS/LABA FDC in development for asthma for which a Phase II development was recently successfully completed.

[redacted]

There is evidence of efficacy and safety of the mono components indacaterol and MF in asthma and COPD (indacaterol). In addition, supportive efficacy and safety information was gained from the early QMF149 development in the Twisthaler® device (see Section 1.1) and QMF149 Investigator Brochure. To further investigate the overall risk and benefit evaluation of QMF149 FDC delivered by Concept1, an MF 80 microgram dose in combination with indacaterol acetate (QMF149) is selected for further evaluation in Phase III.

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 of age), indacaterol/mometasone 500/400 microgram delivered by Twisthaler® comparable to indacaterol 150/160 microgram delivered by Concept1 showed a favorable efficacy and safety profile over MF alone (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 (QMF149E2203), 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 (QMF149F2202). 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 this Phase III study, randomized patients will receive either QMF149 or MF throughout the treatment epoch (12 weeks). Throughout the trial, patients will be given access to rescue medication (i.e., short acting beta-2agonist (SABA)), thus limiting the risk of significant asthmatic AEs. At no time during the study will any patient be without treatment for asthma.

The risk to the patients in participating in this study is that QMF149 is under development and therefore unexpected safety issues may be possible in patients randomized to QMF149 treatment (Section 5.6.2). This risk will be minimized by adherence to the patient eligibility criteria as stated in the study protocol and by close clinical monitoring of all patients. 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 most current QMF149 Investigator's Brochure.

There is evidence that LABA treatment used alone in asthma might cause asthma exacerbations (FDA warning, Advair® Diskus® prescription information). This risk is mitigated by the fact that all patients will have a minimum background therapy of low dose ICS (monotherapy or in combination with LABA, depending on treatment arm).

The potential benefit for the patient includes an improvement in the pulmonary function testing and a potential translation into better asthma control, such as reductions in symptoms and rescue medication use, and improved quality of life. A thorough medical evaluation of the patient's disease and close clinical monitoring for the duration of the study may be considered as additional benefit to the patient.

Frequent and regular contacts between the patient and site staff will occur in terms of clinic visits and telephone contacts to each patient throughout the 12-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 (twice daily)

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measurements at regular intervals throughout the study will help assess status of the patient's asthma symptom control. eDiary data will be transmitted electronically from the device to the investigator daily. Therefore, investigators will be able to monitor the patients closely throughout the study in case of an early indication of worsening symptoms.

In the event of worsening asthma symptoms, guidance to manage potential worsening of asthma symptoms is available to the investigators in accordance with 6 guideline recommendations. Patients will be provided with clear written instructions on contacting the investigator in case of worsening of their symptoms.

The investigator must discontinue study treatment 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. Patients will be followed up for safety for 30 days after they have stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later)

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 150/80 microgram will have a favorable benefit to risk profile in this patient population with asthma.

4 Population

The study population will consist of approximately 750 males and females with a diagnosis of asthma ≥ 12 and ≤ 75 years of age. Approximately 50 patients enrolled in the study will be adolescents (≥ 12 and < 18).

Adolescent patients with a diagnosis of asthma should be symptomatic on low dose ICS (ACQ-7 ≥ 1.5). Patients more adequately controlled taking low dose ICS/LABA (ACQ-7 score ≥ 1 and < 1.5) may also be included, however they can only be enrolled to double-blind treatment if ACQ-7 score is ≥ 1.5 at the time of randomization. The ACQ-7 thresholds for level of control are consistent with published literature (Juniper 2006). Although Juniper does not specifically define 'adequate control', it can be reasonably estimated to be around 1, which is considered the crossover point between 'well controlled' and 'not well controlled' asthma (Juniper 2006); therefore a range of ≥ 1 to < 1.5 is considered acceptable as an appropriate range for 'adequately' controlled asthma.

Adult patients with a diagnosis of asthma should be symptomatic on low dose ICS or low dose ICS/LABA with ACQ-7 score ≥ 1.5.

It is anticipated 1370 patients will need to be screened in order to randomize approximately 750 patients into the two treatment groups with a randomization ratio of 1:1 (i.e., approximately 375 patients per treatment group). At least 676 randomized patients (338 per treatment group) are needed to complete the study.

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 < 18 years or ≥ 18) 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. Written informed consent must be obtained from all patients before any study-related assessment is performed. Patients below the legal age of consent are required to have the Parental Informed Consent signed by the patient's parent/legal guardian; adolescents are required to sign the Assent Form.
2. Male and female adolescents aged ≥ 12 to < 18 years old (depending upon regulatory and/or institutional Review Board (IRB)/Independent Ethics Committee (IEC)/REB approval and/or country participation) and male and female adults aged ≥ 18 years and ≤ 75 years old.
3. Patients with a documented diagnosis of asthma for a period of at least 3 months prior to Screening (Visit 1).
4. Patients who have used low dose ICS (Appendix 9), with or without another controller therapy (i.e., LABA, Leukotriene Receptor Antagonist (LTRA)) at stable dose for at least 1 month prior to Screening (Visit 1).
5. **Adult** patients must be symptomatic despite treatment with existing therapy. Patients must have ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (i.e., inadequately controlled).
6. **Adolescent** patients:

   If taking low dose ICS (without LABA), patients must be symptomatic despite treatment with low doses of ICS. These patients must have ACQ-7 score ≥ 1.5 at Visit 101 and at Visit 102 (i.e., inadequately controlled).

   If taking low dose ICS / LABA, patients may be included only if ACQ-7 score ≥1 and <1.5 at Visit 101 (i.e., adequately controlled). However, ACQ-7 score must be ≥1.5 at Visit 102, directly prior to randomization.
7. Pre-bronchodilator FEV_1 ≥ 60% and < 90% of the predicted normal value for the patient according to ATS/ERS criteria after withholding bronchodilators at both Visits 101 and 102.

   Withholding period of bronchodilators prior to spirometry: SABA for ≥ 6 hours and FDC or free combinations of ICS/LABA* for ≥ 48 hours (14 days for once daily combinations, i.e., indacaterol), short acting anticholinergics (SAMA) for ≥ 8 hours, xanthines ≥ 7 days.

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

   Washout period of each drug should be kept as close as possible as above and should not be longer. If washout 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 (preferably within 5 days of original Visit 101) 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.

[redacted]

A one-time re-screen is allowed in case the patients fail to meet the criteria at the repeat, provided the patients return to their previous treatment until re-screened. In this circumstance, patients are not required to go back on prior medication for 1 full month duration as outlined in inclusion criterion 4.

8. Patients who demonstrate an increase in FEV_1 of ≥ 12% and ≥ 200 mL within 15 to 30 minutes after administration of 400 microgram salbutamol / 360 microgram albuterol (or equivalent dose) at Visit 101. Spacers may be used for reversibility testing.
    - All patients must perform a reversibility test at Visit 101.

   If reversibility is not demonstrated at Visit 101:
    - Reversibility should be first repeated once.
    - If the retest does not show reversibility, patients may be permitted to enter the study with documented historical evidence of reversibility that was performed according to American Thoracic Society (ATS) / European Respiratory Society (ERS) guidelines within 2 years prior to Visit 1.
    - Alternatively, patients may be permitted to enter the study with a historical positive broncho-provocation 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 / broncho-provocation not available (or not performed according to ATS/ERS guidelines) patients will be noted as screen failure.

Spacer devices are ONLY permitted during reversibility testing. The decision whether or not to use a spacer for the reversibility testing will be taken by the study investigator.

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 (including electronic cigarettes) within the 6 month period prior to Visit 1, or who have a smoking history of greater than or equal to 10 pack years *(Note:1 pack is equivalent to 20 cigarettes. 10 pack years = 1 pack /day x 10 years, or ½ pack /day x 20 years.)*.
2. Patients who have had an asthma attack/exacerbation requiring systemic steroids or hospitalization (> 24 hours) or emergency room visit (≤ 24 hours) as follows:

- **For adults**: within **6 weeks** of Visit 1 (Screening). If patients experience an asthma attack/exacerbation requiring systemic corticosteroids or emergency room visit between Visit 1 and Visit 102 they may be re-screened 6 weeks after recovery from the exacerbation.
- **For adolescents**: Severe asthma attack/exacerbation requiring systemic corticosteroids in the last 6 months, OR hospitalization (> 24 hours) due to severe asthma attack/exacerbation requiring systemic corticosteroids in the last 6 months, OR emergency room visit (≤ 24 hours) due to severe asthma attack/exacerbation requiring systemic corticosteroids within the last 6 months.

3. Patients who have ever required intubation for a severe asthma attack/exacerbation.

[redacted]

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 the investigator within 4 weeks prior to Visit 1 (Screening) or between Visit 1 and Visit 102. Patients may be rescreened 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 rescreened once their candidiasis has been treated and has resolved.
7. Patients with any chronic conditions affecting the upper respiratory tract (e.g., chronic sinusitis) which in the opinion of the investigator may interfere with the study evaluation or optimal participation in the study.
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.
10. Patients who have a clinically significant laboratory abnormality at Visit 101.
11. Use of other investigational drugs within 30 days of Visit 101 or 5 half-lives whichever is longer or until the expected pharmacodynamics effect has returned to baseline.
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 (clinical confirmation by the study investigator required) within the previous 12 months.
14. Concomitant use of agents known to prolong the corrected QT (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 or inability to determine the QTcF interval (these patients should not be re-screened).
16. Patients who have a clinically significant ECG abnormality at Visit 101 (Start of Run-in/Baseline epoch) and/or any time prior to randomization (Visit 102), including unscheduled ECG. ECG evidence of myocardial infarction at Visit 101 (via central reader) should be clinically assessed by the study 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.

[redacted]

18. Patients with a history of hypersensitivity or intolerance to any of the study drugs (including excipients) or to similar drugs within the class including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof. This criteria also applies to rescue and Run-in medications.
19. Patients with diagnosed rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption or with known intolerance to lactose or milk products.
20. Patients who have not achieved acceptable spirometry results at Visit 101 even after a re-test, 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 which should be scheduled as close as possible to the first spirometry attempt (but not on the exact same day) if the spirometry did not qualify due to ATS/ERS criteria at Visit 101 and/or Visit 102. Should the patient fail the repeat assessment, he/she can be re-screened once, provided the patient returns to the prior treatment until re-screened.
21. Patients receiving any asthma-related medications in the classes specified in Table 5-1 unless they undergo the required washout period prior to Visit 101 and Visit 201 and follow the adjustment to treatment program.
22. Patients receiving any medications in the classes listed in Table 5-2.
23. Patients receiving medications in the classes listed in Table 5-3 should be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met.
24. Patients with severe narcolepsy and/or insomnia.
25. Patients on Maintenance Immunotherapy (desensitization) for allergies for less than 3 months prior to Visit 101 or patients on Maintenance Immunotherapy for more than 3 months prior to Visit 101 but expected to change throughout the course of the study.
26. Patients, who are serving a custodial sentence, do not have a fixed residence or who are detained under local mental health legislation/regulations.
27. Patients who are directly associated with any members of the study team or their family members.
28. Patients unable to use the Concept1 dry powder inhaler, Twisthaler®, Accuhaler® or MDI. Spacer devices are not permitted for rescue medication.
29. History of alcohol or other substance abuse in the last 10 years.
30. 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 eDiary device.
31. Patients who do not maintain regular day/night, waking/sleeping cycles (e.g., night shift workers).
32. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human Chorionic Gonadotropin (hCG) laboratory test.
33. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 30 days after stopping medication.

[redacted]

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least 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 patients on the study, the vasectomized male partner should be the sole partner for that patients
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before Visit 201 (Randomization/Start of treatment epoch).

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

If requested by local authorities/ethics committees, additional and more frequent pregnancy testing might be performed.

34. Use of Long Acting Muscarinic Antagonist (LAMA) within 3 months prior to Visit 1.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The Study drug is as follows:

- QMF149 (indacaterol acetate/MF) 150/80 microgram o.d. (in the evening) delivered as powder in hard capsules via Concept1 inhaler

The Comparative treatment is:

- MF 200 microgram o.d. (in the evening) delivered as powder via Twisthaler®

In addition, the following placebos will enable the double-dummy design of the study:

- Placebo delivered as powder via Twisthaler® (in the evening)
- Placebo delivered as powder in capsules via Concept1 (in the evening)

[redacted]

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 treatment

The specified minimum washout periods prior to Run-in (Visit 101) are described in Table 5-1. The low dose fluticasone propionate (100 microgram b.i.d. via Accuhaler or 125 microgram b.i.d via MDI) should be used during the Run-in epoch. If these are not available in a particular country, fluticasone propionate in an alternative formulation at an equivalent dose strength can be used (Appendix 9). These will either be supplied to the investigator sites locally by Novartis or provided by the study center and reimbursed by Novartis.

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 5.5.6 for more details regarding rescue medication.

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

5.2 Treatment arms

Patients will be assigned to one of the following two treatment arms (as per randomization ratio of 1:1):

- QMF149 150/80 microgram o.d. delivered via Concept1 (in the evening) and Placebo to MF 200 microgram o.d. delivered via a Twisthaler® (in the evening)
- MF 200 microgram o.d. delivered via a Twisthaler® (in the evening) and Placebo to QMF149 150/80 microgram o.d. delivered via Concept1 (in the evening)

5.3 Treatment assignment and randomization

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

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

Randomization will be stratified by factors of age (≥ 12 to < 18 years or ≥ 18) and by region.

[redacted]

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

5.4 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 (with the exception of bio-analyst) 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, and schedule of administration, appearance, taste, and odor.

[redacted]

During the study, the individual patient unblinding can occur in the case of patient emergencies, request from the DMC if needed for the safety interim analysis (Section 8.4) or as an outcome of their evaluation and at the conclusion of the study. 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.

5.5 Treating the patient

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

5.5.1 Patient numbering

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

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

5.5.2 Dispensing the study drug

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

[redacted]

The study drug 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 study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment 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 Country Pharma Organization (CPO) Quality Assurance.

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

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

5.5.3.2 Handling of additional treatment

The following non-study drug will be monitored as follows:

The non-study drug 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-study drug 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-study drug 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 study drug for the rescue medication.

These medications are:

- Salbutamol (100 microgram) or albuterol (90 microgram) used as rescue medication from Visit 1 to Visit 204;
- Fluticasone propionate (100 microgram b.i.d. or acceptable dose equivalent as outlined in Section 3.1 used as Run-in medication from Visit 101 to Visit 102.

[redacted]

5.5.4 Instructions for prescribing and taking study treatment

The investigator must 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 must also 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 kits of study treatment assigned by the IRT will be recorded / databased 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. 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.

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

At Visit 1 all patients will be instructed how to use an MDI to administer rescue salbutamol/albuterol correctly. At Visit 101 patients will be trained to the use of the eDiary, peak flow meter and Accuhaler® (Appendix 3). At Visit 102 all patients will be fully trained in the correct use of the Concept1 and Twisthaler® 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 correct use of each device. If required, further device training should be provided. Patients will be instructed to contact the site if the device is not functioning properly.

Patients will be instructed to take their dose of study medication at approximately the same time every evening regardless of their time of sleep, meal or other activities. Patients will be instructed to rinse their mouth 2 times with approximately 30 mL of water after the last inhalation of the study drug following sequential inhalations from devices. Water used for mouth rinsing should NOT be swallowed.

The study drugs must be taken in the evening (between 5:00 and 8:00 pm), and consist of **sequential single inhalations from the following devices:**

- One inhalation from the Concept1 device containing either QMF149 or placebo
- One inhalation from the Twisthaler® device containing either MF or placebo

The 2 inhalations should be taken as close together in time as possible. Instructions for use of the Concept1 inhaler and Twisthaler® are provided in Appendix 1 and Appendix 2.

5.5.5 Permitted dose adjustments and interruptions of study treatment

The Study drug 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 eCRF.

[redacted]

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

5.5.6 Rescue medication

At Visit 1, all patients will be provided with a SABA (100 microgram salbutamol or 90 microgram 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 eCRF, 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 eCRF. From Visit 101, patient should be instructed to record daily use of rescue medication (number of puffs taken in the previous 12 hours) each morning and evening throughout the 12 week treatment epoch in her/his 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.

5.5.7 Concomitant medication

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

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

5.5.8 Prohibited medication

Prohibited medications, as listed in Table 5-1, must not be taken during the study (unless for the treatment of asthma exacerbations). The specified minimum washout periods prior to Run-in (Visit 101) and/or Randomization (Visit 201) are described in Table 5-1. The classes of medication listed in Table 5-2 are not permitted to be taken during the study. The medications in Table 5-3 are only permitted under the circumstances given. Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it is allowed. If in doubt, the investigator should contact the medical monitor before randomizing a patient or allowing a new medication to be started.

[redacted]

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 5-1 Prohibited Asthma-Related Medications

Class of medication	Minimum washout period prior to Run-in (V101) [1, 2, 3, 4]
Short acting anticholinergics (SAMA)	Must be discontinued 8 hours prior to Visit 101
Fixed combinations of β_2-agonists and inhaled corticosteroids	Must be discontinued 48 hours prior to Visit 101; Patients should 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 microgram b.i.d. (or equivalent dose) from Visit 101 to Visit 102 (Figure 3-1); all other ICS must be discontinued at Visit 101
Fixed combinations of short-acting β_2-agonist and short-acting anticholinergic	Must be discontinued 8 hours prior to Visit 101
Leukotriene Receptor Antagonist (LTRA) and leukotriene synthesis inhibitors	Must be discontinued 7 days prior to Run-in (Visit 101)
Long-acting β_2-agonists (LABAs)	LABAs b.i.d. must be discontinued 48 hours prior to Visit 101. LABAs o.d. (i.e., indacaterol) 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
Salbutamol/albuterol (SABA) provided at Visit 1 and throughout study as required for rescue medication	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 be discontinued 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 be discontinued 4 weeks prior to Run-in (Visit 101)
Intra-muscular depot corticosteroids	Must be discontinued 3 months prior to Run-in (Visit 101)
Monoclonal Antibody: IgE inhibitors and other asthma-related biologics (i.e., omalizumab), IL-5 inhibitors (e.g., mepolizumab)	Must be discontinued 4 months prior to Run-in (Visit 101)
Xanthines	Must be discontinued 7 days prior to Run-in (Visit 101)
Systemic mast cell stabilizers (e.g., cromoglycate, nedocromil, ketotifen)	Must be discontinued 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 6.4.9 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.

[redacted]

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

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

Table 5-2 Prohibited Medications

Class of medication	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 (tetracyclics which are similar in class with regards to drug interaction are also to be excluded)	14 days
Other investigational drugs	30 days or 5 half-lives, whichever is longer
Noradrenaline reuptake inhibitors	7 days
Live attenuated vaccine	30 days

Table 5-3 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 as needed, providing an established pattern of use has been documented
Antihistamines (e.g., loratadine, cetirizine)	If stabilized for at least 4 weeks prior to Visit 1 and throughout the trial; in the case of as needed, providing an established pattern of use has been documented
Topical corticosteroids for the treatment of eczema	In recommended doses and dosage regimens

[redacted]

Class of medication	Condition
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 asthma exacerbation, any treatment deemed necessary for the safety of the patient is allowed from the start of the asthma exacerbation event (Section 6.4.9) until the asthma exacerbation event is resolved.

5.5.9 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 (TD) 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 Novartis Clinical Trial Head that the code has been broken.

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

- protocol number
- study drug name (if available)
- patient number

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

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

5.6 Study completion and discontinuation

5.6.1 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 safety follow-up at Day 114 for serious adverse events (SAEs).

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

5.6.2 Discontinuation of study treatment

Patients may voluntarily discontinue study drug (discontinue double-blind study medication but continue with study participation) at any time. Patients who wish to discontinue double-blind study medication will be asked to remain in the study **and complete all study visits for**

[redacted]

assessment of safety and vital status. Patients withdrawn from study drug will receive standard of care (SoC) asthma therapy according to investigator judgment.

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.

Study treatment must be discontinued under the following circumstances:

- Patients who experience one "severe" asthma exacerbations (**as defined** in Section 6.4.9) during the 12 week treatment epoch that requires treatment with systemic corticosteroids or hospitalization (including intubation).
- 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 that requires consistent use of prohibited treatment as per Section 5.5.8 or if patient is not compliant because of use of prohibited medications. Any other protocol deviation that results in a significant risk to the patient's safety.
- If a patient experiences paradoxical bronchospasm, as recommended in the QMF149 Investigator Brochure
- 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 (TD) 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 eCRF. The investigator and study staff must discuss with the patient the continued participation in the study by maintaining regular telephone contact with him/her or with a person pre-designated. 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 should be discontinued from the double blind study medication. Patients can voluntarily stay in the study and complete all study visits for assessment of safety and vital status. The survival status also needs to be collected until the end of the study Follow-up visit (Visit 301)

Patients who discontinue study treatment should NOT be considered withdrawn from the study. He/she should return for the assessments indicated in Table 5-4. If he/she fails to return for

[redacted]

these assessments for unknown reasons, every effort (e.g., telephone, e-mail, and letter) should be made to contact them as specified in Section 5.6.4.

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

Table 5-4 Table of Assessment for Patients who Discontinue Study Treatment Prematurely

Assessment	Early Study Treatment Discontinuation Visit	Unscheduled Safety Follow-Up Visit	At time of Scheduled Visit	Premature study discontinuation *	Follow-up Visit 301
Clinic/Telephone	C	T	T	T	T
Week	Disc. Date	Disc.date +4 weeks			16
Day	Disc. Date	Disc.date +30 days			114
IRT TD call	S				
IRT Call for visit confirmation	S		S	S	S
Vital Signs	X				
Physical exam	S				
Record Height (Adolescent only)	X				
Record Weight	X				
Oropharyngeal examination	S				
Pregnancy test (serum)	X				
Collect study medication	S				
Concomitant medication	X	X	X	X	X
Record interruption/changes in Drug Administration to assess compliance	X				
Download/review eDiary	S				
Review rescue medication use	S				
Review AEs	X	X	X	X	X
Review SAEs	X	X	X	X	X
Review asthma exacerbations	X	X	X	X	

[redacted]

Assessment	Early Study Treatment Discontinuation Visit	Unscheduled Safety Follow-Up Visit	At time of Scheduled Visit	Premature study discontinuation *	Follow-up Visit 301
Review surgery and procedures	X	X	X	X	X
Safety Lab assessments (hematology, clinical chemistry, urinalysis, [redacted])	X				
Spirometry[1]	X				
ECG	X				
[redacted]					
ACQ-7 [2]	X				
Evening Plasma cortisol	X				
Survival Status		X			X
Record Healthcare visit for asthma worsening	X			X	
Record end of Study Treatment page	X				
Record end of treatment epoch disposition				X	

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

X assessment to be reported in the clinical database

*Applicable for patients who withdrew consent or lost to follow-up or dead

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

[2] PRO assessments should be done before all other assessments. When a scheduled visit is planned on 2 consecutive days the PROs are to be completed on the first day.

[redacted]

5.6.3 Withdrawal of informed consent

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

Withdrawal of consent 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, and 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

[redacted]

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 TD visit and enter on the eCRF as Early Study Discontinuation visit provided the patient gives consent for these assessments. The patient disposition status should be entered on the eCRF. 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.

The investigator must also notify the IRT (Interactive Voice Response System(IVRS)/ Interactive Web Response System(IWRS)) of the premature discontinuation of study treatment.

Patients who prematurely discontinue study treatment and withdraw from the study will not be replaced.

5.6.4 Lost to follow up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw the investigator should allow “due diligence” by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study based on the Data Monitoring Committee advice, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, the patient should be seen as soon as possible and treated as a prematurely discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient’s interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial, unless otherwise required by local country regulations.

In addition, a Data Monitoring Committee will be used, which will evaluate safety data on a regular basis and can recommend adjustment to study conduct (including stoppage) at any time. Please see Section 8.4 for more details

6 Visit schedule and assessments

The study will consist of a Screening epoch, a Run-in epoch, a 12-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 days or as close as possible to those dates. While Visit 102 (end of Run-in) and Visit 201(Randomization) must take place on the same day, a visit window of 4 days is allowed at Visit 204 as described in Section 3.1 (if this is not possible, the sponsor should be notified). All data obtained for these assessments must be supported in the patients' source documentation.

At Visit 1, all patients will be issued an electronic diary to record asthma symptoms and rescue medication use and at Visit 101, a Peak Flow meter to record Peak Expiratory Flow Rate (PEF) twice daily. The Run-in epoch will be used to assess eligibility of the patients to enter the treatment epoch and to collect baseline values for some variables.

Once patient's eligibility is confirmed (at Visit 102), patient will be randomized to one of the two treatment groups with an equal (1:1) randomization ratio:

- QMF149 150/80 microgram o.d delivered via Concept1
- MF 200 microgram o.d. delivered via Twisthaler®

Visits 102 and 201 should take place sequentially on the same day and Visit 102 assessments should be performed prior to administration of the first dose of study medication (Visit 201).

The scheduled assessments should be performed in the following order: Patient reported outcomes (PROs) (i.e., ACQ, AQLQ), ECG, radial pulse rate, blood pressure and blood /urine samples followed by spirometry (as per Table 6-2).

The details of spirometry assessments are indicated in Table 6-2. An approximate 3 min rest from start of ECG to the start of spirometry manoeuvres should be given. When an ECG is needed to be taken after spirometry, a 10 minute rest from the end of spirometry to start of ECG assessments should be considered.

If other assessments are scheduled at the same time-point, spirometry will take precedence (with the exception of PROs and blood tests) so that it occurs at/or as close as possible to the scheduled time points.

[redacted]

Table 6-1 Assessment schedule

Visit Number	**1**	**101**	**102**	**201**	**202**	**203[5]**	**204[10]**	**Early treatment discontinuation (TD)**	**Premature study discontinuation (PSD)**	**301[9]**
Epoch	**Screen**	**Run-in**		**Treatment**					**PSD**	**Follow-up**
Clinic (C) /Telephone (T)	C	C	C	C	C	T	C	C	T	T
Week – Start of Week	-5 to -3	-3	0	0	4	8	12			16
Day Number	-35 to -21	-21	1	1/2	30	57	84/85[6]			114
Obtain Informed Consent and/or assent (including for sub-group)	X[11]									
Current medication review/ adjustment	X									
Inclusion/exclusion criteria	X	X	X							
Randomization via IRT				S						
Medical History, Demography	X									
History of Asthma exacerbation	X									
Smoking history and status	X									
Run-in medication		X								
Pregnancy test (serum)[1]		X			X		X	X		
Pregnancy test (urine) [1]	X		X							

[redacted]

Visit Number	**1**	**101**	**102**	**201**	**202**	**203**[5]	**204**[10]	**Early treatment discontinuation (TD)**	**Premature study discontinuation (PSD)**	**301**[9]
Epoch	**Screen**	**Run-in**		**Treatment**					**PSD**	**Follow-up**
Clinic (C) /Telephone (T)	C	C	C	C	C	T	C	C	T	T
Week – Start of Week	-5 to -3	-3	0	0	4	8	12			16
Day Number	-35 to -21	-21	1	1/2	30	57	84/85[6]			114
Urine analysis (dipstick)		S		S			S	S		
Device training[4]	S	S	S							
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Physical examination		S					S	S		
Oropharyngeal examination		S	S	S	S		S	S		
Record height (for adult patients only at Visit 101) and weight		X					X[12]	X[12]		
ECG[2]		X		X			X	X		
Vital signs[2]		X	X	X	X		X	X		
Issue rescue medication as necessary	S	S		S	S					
Review rescue medication use		X	X	X	X		X	X		
Spirometry Practice (optional)	S									

[redacted]

Visit Number	**1**	**101**	**102**	**201**	**202**	**203[5]**	**204[10]**	**Early treatment discontinuation (TD)**	**Premature study discontinuation (PSD)**	**301[9]**
Epoch	**Screen**	**Run-in**		**Treatment**					**PSD**	**Follow-up**
Clinic (C) /Telephone (T)	C	C	C	C	C	T	C	C	T	T
Week – Start of Week	-5 to -3	-3	0	0	4	8	12			16
Day Number	-35 to -21	-21	1	1/2	30	57	84/85[6]			114
Screening spirometry and FEV_1 reversibility test (SABA)		X								
Spirometry[2]			X	X	X		X	X		
Issue eDiary[5]	X									
Issue Peak Flow meter		S								
Review and upload eDiary recordings[5]			S		S		S	S		
Administer study drug at visit				X	X		X			
Dispense study medication via IRT				X	X					
Call IRT for visit confirmation	S	S		S	S		S	S	S	S
Collect unused study medication					S		S	S		
Record interruption/changes in Drug Administration to assess compliance					X	X	X	X		
AE recordings	X[14]	X	X	X	X	X	X	X	X	X

[redacted]

Visit Number	**1**	**101**	**102**	**201**	**202**	**203**[5]	**204**[10]	**Early treatment discontinuation (TD)**	**Premature study discontinuation (PSD)**	**301**[9]
Epoch	**Screen**	**Run-in**		**Treatment**					**PSD**	**Follow-up**
Clinic (C) /Telephone (T)	C	C	C	C	C	T	C	C	T	T
Week – Start of Week	-5 to -3	-3	0	0	4	8	12			16
Day Number	-35 to -21	-21	1	1/2	30	57	84/85[6]			114
SAE recording	X	X	X	X	X	X	X	X	X	X
Review Surgery and Procedures		X	X	X	X	X	X	X	X	X
Study Disposition (Screening)	X									
Study disposition (Run-in)[13]		X	X							
Study disposition End of Treatment epoch (end of study)							X		X	
Study disposition (Follow-Up)										X
Survival Status										X
Review asthma exacerbations	X	X	X		X	X	X	X	X	
Safety Lab assessments (hematology, clinical chemistry, urinalysis, [redacted]		X		X			X	X		

[redacted]

Visit Number	**1**	**101**	**102**	**201**	**202**	**203**[5]	**204**[10]	**Early treatment discontinuation (TD)**	**Premature study discontinuation (PSD)**	**301**[9]
Epoch	**Screen**	**Run-in**		**Treatment**					**PSD**	**Follow-up**
Clinic (C) /Telephone (T)	C	C	C	C	C	T	C	C	T	T
Week – Start of Week	-5 to -3	-3	0	0	4	8	12			16
Day Number	-35 to -21	-21	1	1/2	30	57	84/85[6]			114
Evening plasma cortisol [2]				X			X	X		
[redacted]										
ACQ-7[3]		X	X		X		X	X		
AQLQ-S+12[3]			X				X			
Telephone patient 1 day in advance of visit				S	S		S			
Record healthcare visits for asthma worsening					X	X	X	X	X	

TD = Study treatment discontinuation

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

X assessment to be reported in the clinical database

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

[2] Details of timed assessments for randomized patients are provided in Table 6-2.

[3] PROs must be assessed before all other assessments. When a scheduled visit is planned on 2 consecutive days the PROs are to be completed on the first day.

[4] Device training for peak flow meter and eDiary (electronic device for questionnaires and assessments based on asthma symptoms) and Accuhaler® at Visit 1 and/or 101 and for Concept1 and Twisthaler® devices at Visit 102.

[5] Site to call patient at specified time points in between clinic visits to check if patient asthma symptoms have worsened, any treatment required and eDiary completed accordingly. In case of an asthma exacerbation, the patient should be encouraged by the site to contact 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.

[redacted]

[6] The last dose of study medication will be taken on Day 84 (Visit 204).

[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] Clinic Visit 204 (Week 12) should take place within a 4-day window. If this is not feasible, the sponsor should be notified.

[11] Patients below the legal age of consent are required to have their parent/guardian sign the parental Informed Consent; adolescents must sign the Assent Form.

[12] Height will be measured for adult patients only at Visit 101. Height will be measured for adolescent patients at Visits 101, 204 (or TD Visit if applicable). Weight will be measured for all patients at Visits 101, 204 (or TD if applicable).

[13] Visit 101 disposition eCRF page should be completed in case the patient is a Run-in failure at Visit 101. Visit 102 disposition eCRF page should be completed if the patient is a Run-in failure at this visit or if the patient is randomized in the study.

[14] For randomized patients all AEs must be collected in the eCRF, however for screen failure patients, AEs that are not SAEs must be collected in the source data

Table 6-2 Timed Assessment**

Visit (Day)	Time point[1]	Spirometry (FEV_1, FVC)[4]	[redacted]	Hematology Chemistry Urinalysis [5]	Plasma cortisol	ECG[3]	Vital signs[2]
Visit 201 (Day 1)[7]	-45 min	X					
	-35 min					X	
	-25 min						X
	-20 min			X	X[6]		
	-15 min	X					
	0 min	Evening dosage (between 5:00 - 8:00 pm)					
	5 min	X					
	15 min	X					
	20 min						X
	30 min	X		X[5]			
	1 h	X				X	X
Visit 201 (Day 2)	23h15 min	X					
	23h45 min	X					
	0 min	Evening dosage (between 5:00 - 8:00 pm)					
Visit 202 (Day 30)	-45 min	X					
	-30 min						
	-25 min						
	-15 min	X					X
	0 min	Evening dosage (between 5:00 - 8:00 pm)					
	5 min	X					
	15 min						

[redacted]

Visit (Day)	Time point[1]	Spirometry (FEV_1, FVC)[4]	[redacted]	Hematology Chemistry Urinalysis [5]	Plasma cortisol	ECG[3]	Vital signs[2]
	30 min	X					
	1 h	X					
Visit 204 (Day 84)	-45 min	X					
	-35 min					X	
	-25 min						X
	-20 min			X	X		
	-15 min	X					
	0 min	Evening dosage (between 5:00 - 8:00 pm)					
	5 min	X					
	15 min						
	20 min						X
	30 min	X		X			
	1h	X				X	X
Visit 204 (Day 85)	23h15 min	X					
	23h45 min	X		X	X		

[redacted]

**It is necessary that scheduled assessments follow this order: PROs, ACQ, AQLQ, ECG, radial PR, BP, blood / urine samples and spirometry. Assessments in Table 6-2 are to be performed as close as possible to designated timeframes; however an approximate ± 5 min window is permitted.

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

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

[3] At time points requiring both spirometry and ECG, ECG should always be performed first. Approximately a 3 min rest period from the beginning of ECG assessments to the start of spirometry manoeuvres should be observed.

[4] Approximately a 10 min rest period from the end of spirometry maneuvers to the beginning of ECG assessments should be observed.

[5] Blood/urine samples must always be taken in advance of spirometry measurements planned at the scheduled time points. Urine analysis is only to be performed if the urine dipstick is abnormal.

[6] Baseline for the evening plasma cortisol

[7] Assessments prior to randomization will be part of Visit 101 reporting.

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the Screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. AEs 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

[redacted]

- Gender
- Race and ethnicity
- Height and weight
- Body mass index (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 (asthma and non-asthma related)
- Pre and post-bronchodilator spirometry (screening spirometry and reversibility testing).
- [redacted]

6.3 Treatment exposure and compliance

The time of study treatment administration at each in-office dosing visit will be collected on the eCRF as well as any dosing interruptions. For assessments where spirometry is performed, the time of dosing is to be taken from the spirometer. While at home, the time of study treatment administration will be recorded by the patient in the eDiary once a week. The data from the eDiary will be reviewed by study site personnel 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 and 204 (or TD Visit or Study Withdrawal Visit if applicable). Compliance will be assessed based on the number of days where study drug was administered "As per protocol" as recorded on the Dosage Administration Record (DAR) Summary eCRF.

6.4 Efficacy

The following assessments of efficacy will be performed:

- Spirometry
- ACQ-7
- AQLQ
- Asthma symptoms based on eDiary
- Peak expiratory flow
- Rescue medication use
- Asthma exacerbations

[redacted]

6.4.1 Spirometry

The following spirometry 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 and TD Visit (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 hours 15 min and 23 hours 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 measured 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 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 et al 1999; Juniper et al 2005, and Juniper et al 2006) is a seven-item disease-specific instrument developed and validated to assess asthma control in patients in clinical trials as well as in individuals in clinical practice. 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 first 6 questions of the ACQ-7 are to be completed by the patient while the last question (question 7) is to be completed by the study investigator using spirometry data generated by the spirometry equipment. The ACQ-7 should be completed at the study site at Visits 101, 102, 202, 204 and TD Visit if applicable.

6.4.3 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 et al 1992, and Juniper et al 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 et al 1994).

AQLQ should be completed at Visits 102 and 204.

[redacted]

6.4.4 Electronic Diary

At Visit 1, all patients will be provided with an electronic diary (referred to as an eDiary) to record rescue medication (salbutamol/albuterol) use and clinical symptoms, the PEF and compliance with the study treatment (starting in Visit 101). The patients will be instructed to routinely complete the eDiary twice daily – at the same time each morning and again approximately 12 hours later in the evening. The eDiary is to be reviewed by study site personnel at each clinic visit until study completion. Sites and patients will receive appropriate training and guidance on the use of the eDiary device. A list of the asthma control eDiary questions is provided in Appendix 7.

6.4.5 Peak Expiratory Flow (PEF)

An electronic Peak Flow Meter part of the eDiary device will be provided to each patient at Visit 101 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 204 and TD Visit (if applicable). The measurements will be performed using an e-Peak Flow Meter provided to the patients at Visit 101. PEF will be measured twice a day; once in the morning and once approximately 12 hours later in the evening (prior to evening dose) from Run-in throughout the study. Patients should be encouraged to perform morning and evening PEF measurements BEFORE taking rescue medication. At each time point, the patient should be instructed to perform 3 consecutive maneuvers within 10 minutes. These PEF values are captured in the e-PEF/diary. The best of 3 values will be used.

6.4.6 Rescue Medication Usage

The use of rescue salbutamol/albuterol should be recorded by patients in their eDiary twice each day in the morning and evening. 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.

6.4.7 Investigational Medication Usage

In order to ensure compliance and safety follow-up, the patients will be requested to record once per week in the eDiary whether he/she missed any dose and from which inhalation device.

6.4.8 Worsening of asthma

Investigators and patients will be instructed how to deal with worsening of asthma symptoms. The data captured in the eDiary 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 develop:

[redacted]

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
- Nighttime awakenings requiring SABA use on at least 2 out of any 3 consecutive nights
- 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 Run-in period.

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

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:

- Review alert trends over time, in particular PEF decreases.
- Call the patient promptly to assess the clinical status when any specific alert type (e.g., PEF < 60%) is received on consecutive days. This may include urgent clinic visits as appropriate and/or immediate treatment.
- Implement prompt clinical treatment as deemed necessary by the investigator.

If patient believes that his/her symptoms are worsening and/or has received alerts as outlined above the patient should notify the investigator in order to be evaluated and treated as clinically appropriate. Patient should be instructed to visit emergency room / hospital if deemed necessary.

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

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

6.4.9 Asthma Exacerbation

A **severe asthma** exacerbation (Draft note for guidance on clinical investigation of medicinal products for treatment of asthma: CHMP/EWP/2922/01 Rev.1) is defined as an aggravation of

[redacted]

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 or hospitalization due to asthma or death due to asthma.

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

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

   Nighttime 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 SCS or hospitalization.

This deterioration would be defined by:

> 20% decrease in FEV_1 from baseline value.

Or

[redacted]

≥ 20% decrease in am or pm PEF from baseline on 2 out of any 3 consecutive days compared to Baseline.

Or

< 60% of PEF compared to Baseline.

"Start and end dates" of each reported event in the eCRF 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.

6.4.10 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
- AEs including asthma exacerbations and serious AEs
- Pregnancy (female patients)
- Serious asthma outcomes (asthma-related hospitalizations, intubations or deaths)

ECG and laboratory assessments will be centralized.

Additional pregnancy testing might be performed if requested by local requirements.

6.5.1 Physical examination

A physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and 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, 204 or TD visit (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

[redacted]

eCRF. Significant findings made after informed consent (Visit 1) is given which meet the definition of an AE must be recorded on the AE screen of the patient's eCRF.

6.5.2 Vital signs

Systolic and diastolic blood pressure and radial pulse rate (over a 30 second interval), performed in the sitting position, will be recorded at each scheduled clinic visits as detailed in Table 6-2. (at Visits 101, 102, 201, 202, 204 or TD Visit, 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. In adolescents the height will additionally be measured at Visit 204 (or TD Visit if applicable). Body weight (to the nearest 0.1 kilogram in indoor clothing, but without shoes) will be measured at Visit 101, 204 (or TD Visit 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, urinalysis [redacted]) will be performed at Visit 101, 201, 204 and TD Visit 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, aspartate aminotransferase (AST) or Serum Glutamic-Oxaloacetic Transaminase (SGOT), alanine aminotransferase (ALT) or Serum Glutamic Pyruvic Transaminase (SGPT), bilirubin, creatinine, gamma-glutamyl transferase (γ-GT), glucose, potassium, magnesium, blood urea nitrogen (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 Visits 101, 201, and 204, or TD (if applicable).

[redacted]

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

6.5.4.4 Hepatotoxicity

Any liver event which meets the criteria for "**medically significant**" event as outlined in Table 8-1 in Appendix 8 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, 204 and TD Visit if applicable. The sampling point is as shown in Table 6-1 and Table 6-2.

6.5.5 Electrocardiogram (ECG)

ECGs should 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 201, and 204, ECGs will be measured at -35min pre-dose (evening dose) and post dose 1 hour, as indicated in Table 6-2. All ECGs 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 trace should be printed. Each ECG will be sent electronically for central review directly from the ECG machine. One print-out will be generated and kept at the investigator site as source documentation and will be dated and signed. The patient'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 study drug.

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.

[redacted]

Clinically significant abnormalities should be recorded on the relevant section of the medical history/current medical conditions/AE eCRF page as appropriate.

6.5.6 Serious asthma outcomes

Asthma-related hospitalizations, asthma-related intubations or asthma-related deaths over the 12-week treatment epoch will be recorded and will all be reviewed by the Adjudication Committee. Hospitalization is defined as an inpatient stay or a ≥ 24 hour stay in an observation area in an emergency department or other equivalent facility.

6.5.7 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. A plasma and urine pregnancy test will be performed (tests provided by the Central Laboratory) per Assessment Table 6-1. A positive urine pregnancy test at Visit 1, Visit 102 and positive serum pregnancy test at Visit 101 or Visit 202 or Visit 204 or TD Visit if applicable or at any time during the study requires the patient to be discontinued from the study treatment. Refer to Section 5.6.2 and Section 7.4 for more details.

Additional pregnancy testing might be performed if requested by local authorities.

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 patient or clinical investigation patient after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs 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 AEs only if they fulfill at least one of the following criteria:

- induce clinical signs or symptoms,
- considered clinically significant,
- 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 AEs.

AEs must be recorded in the AE eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information.

- The severity grade:
  Mild: usually transient in nature and generally not interfering with normal activities
  Moderate: sufficiently discomforting to interfere with normal activities
  Severe: prevents normal activities
- Its relationship to the study treatment (Yes or No):
  "No Relationship to study treatment or other investigational treatment" or
  "Relationship to study treatment" or
  "Relationship to other investigational treatment" or
  "Relationship to both study treatment and other investigational treatment or indistinguishable".
- Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.

[redacted]

- Whether it constitutes a SAE, as defined in Section 7.2 and which seriousness criteria have been met.
- Action taken regarding the study treatment. All AEs should be treated appropriately. Treatment may include one or more of the following:
    - no action taken (e.g., further observation only)
    - [investigational] treatment dosage increased/reduced
    - [investigational] treatment interrupted/withdrawn
    - concomitant medication or non-drug therapy given
    - patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
    - its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an AE 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). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient. Investigators should be familiar with known potential adverse events outlined in the IB as well as local labelling. If patients experience such AEs (or any AE), they should be treated as considered clinically appropriate. This may include discontinuation from treatment medication.

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 AE (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

[redacted]

- 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 (Annex IV, ICH-E2D Guideline 2003).

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 (Annex IV, ICH-E2D Guideline 2003).

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 eCRF. SAEs are also required for individual reporting to Drug Safety & Epidemiology 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 the investigator learning of its occurrence / receiving follow up information. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

[redacted]

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

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study drug a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study drug 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 European Union (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 a by radiologist's interpretation of a chest 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/AEs have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

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

[redacted]

Please refer to Table 8-1 in Appendix 8 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 8-1 in Appendix 8 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 8-2 in Appendix 8.

For the liver laboratory trigger:

- Repeating the liver function test (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 eCRF 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 eCRF pages, including the liver event overview eCRF pages.

7.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing of the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to 3 months following the birth of your child 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 follow up period can be increased if requested by health authorities.

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 eCRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (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 Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data and identify risks and 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, ECGs, and the results of any other tests or assessments. All information on eCRFs 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 eCRF 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 eCRFs 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 eCRFs are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff (or a designated Contract Research Organization (CRO)) staff will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the

[redacted]

investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

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

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

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

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).

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

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

8.4 Data Monitoring Committee

An independent, external data safety monitoring committee (DMC) will be set up to review all SAEs (including deaths and all hospitalizations). 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 need to recommend modification or termination of the study.

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

The DMC is the autonomous data and safety advisory group for Novartis. The DMC charter will be developed as a separate document. The charter will define:

1. Membership of DMC
2. Responsibilities of DMC and Novartis

[redacted]

3. Responsibilities of independent biostatistician and programmer
4. The relationship of 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 DMCs.

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 may include:

- Data interpretation
- Publications
- Presentations

9 Data analysis

The analysis will be conducted on all patient data at the time the trial ends. Measurements made after patients discontinue randomized treatment (off-treatment measures) will not be used for any efficacy evaluation.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

The following analysis sets are defined for data analysis.

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

[redacted]

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 unblinding 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 assigned 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, BMI, relevant medical history, Screening spirometry parameters: (FEV_1, FVC, FEV_1/FVC and FEF_{25-75}), FEV_1 reversibility, percentage 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, radial pulse rate), QTc using Fridericia's correction and baseline ACQ-7 and AQLQ will be summarized by treatment group.

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

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

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

9.3 Treatments

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

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

[redacted]

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 the route of administration, the recorded pre-specified drug subcategories (including types of combination) and preferred terms. The summary will be repeated by showing ingredients instead of preferred terms. 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

9.4.1 Primary variable

The primary variable is trough FEV_1 after 12 weeks of treatment.

9.4.2 Statistical model, hypothesis, and method of analysis

The comparison of QMF149 150/80 microgram versus MF 200 microgram 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 12

H_a: QMF149 treatment group is not equal to MF treatment group in trough FEV_1 at Week 12

The primary variable will be analyzed using a mixed model for repeated measure (MMRM) on the FAS. The model will contain treatment, age ($\geq$ 12 to < 18 or $\geq$ 18 years), region, visit (Days 2 and 85), 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 an unstructured covariance matrix in the mixed model. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom (Kenward and Roger, 1997). If the model does not converge with unstructured covariance matrix, the compound symmetry covariance matrix will be used in the mixed model. The restricted maximum likelihood method will be used. The between-treatment comparison will be carried out using the adjusted mean (least squares mean (LS mean)) difference based on the treatment main effect and the coefficient for the treatment-by-visit interaction for Day 85.

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).

[redacted]

9.4.3 Handling of missing values/censoring/discontinuations

If any of the 23 hours 15 min and 23 hours 45 min values contributing to the trough FEV_1 is collected within 7 days of systemic corticosteroid use, within 6 hours of rescue medication, or if the actual measurement times are outside the 22-25 hour post-evening dose time 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 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 explicit imputation.

9.4.4 Multiplicity adjustment

A hierarchical testing procedure will be applied to control the type-I error rate for the primary and the key secondary endpoints, i.e., the key secondary endpoint ACQ-7 will be tested only if the primary endpoint (trough FEV_1) is significant at the 2-sided 0.05 level.

9.4.5 Supplementary analysis

As supplementary analysis, the same MMRM used in the primary analysis will be also performed on the PPS to assess the treatment effect in protocol adherers. The same primary MMRM 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 time will not be included.

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

- Age group ($\geq$ 12 to < 18 years, $\geq$ 18 years)
- Race (Caucasian, Black, Asian, Other)
- Gender (male, female)
- History of asthma exacerbation in the 12 months prior to Screening (Yes, No)
- Patients' prior therapies before Run-in period (e.g., low dose ICS without LABA, low dose ICS with LABA)
- FEV_1 response according to percent predicted FEV_1 range at Baseline (60% to < 70%, 70% to < 90%, and < 60% or $\geq$ 90% in case of protocol deviations)
- ACQ-7 Baseline (1 to < 1.5, 1.5 to < 2, 2 to < 2.5, $\geq$ 2.5)

9.5 Key secondary variable

The key secondary variable is ACQ-7 after 12 weeks of treatment.

[redacted]

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

9.6 Analysis of secondary variables

9.6.1 Efficacy variables

9.6.1.1 Spirometry

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

Spirometry measurements taken within 7 days of systemic corticosteroid use within 6 hours of rescue medication use or if the actual measurement times are outside the 22-25 hour post evening dose time, then the individual FEV_1 value will be set to missing and not be imputed, unless specified otherwise.

Spirometry data by visit

Trough FEV_1 at Day 2 visit will be analyzed using the same MMRM as specified for the primary analysis, i.e., the visit factor will include all available visits as a factor and between-treatment comparison will be carried out using the adjusted mean (least-square mean) difference based on the treatment main effect and the coefficient for the treatment-by-visit interaction for the respective visit and treatment. 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 trough FEV_1, post-dose FEV_1, pre and post-dose FVC and pre and post-dose FEF_{25-75}.

9.6.1.2 ACQ-7

Analysis results for all post-baseline visits, obtained from the MMRM for the key secondary endpoint ACQ-7, will be displayed. In addition, analysis for change from baseline in the ACQ-7 will be performed.

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 a logistic regression model. The model will include terms for treatment, age ($\geq$ 12 to < 18 years, $\geq$ 18 years) , region, visit, and treatment-by-visit interaction as fixed effects, and 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 ratio will be displayed along with the associated 95% (2-sided) confidence interval and p-value.

9.6.1.3 Rescue medication

The number of puffs of the rescue medication use in the last 12-hour is recorded twice daily (morning/evening) by the patient in his/her eDiary. The mean daily number of puffs of rescue medication use over the 12 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

[redacted]

using an (ANCOVA) model. The model will contain treatment, age (≥ 12 to < 18, 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 difference along with the corresponding two-sided 95% confidence interval and corresponding p-value will be presented. This analysis will be performed for morning (nighttime), evening (daytime), and daily (average of nighttime and 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 4 weekly (28 days) intervals and analyzed using a similar MMRM as specified for the primary analysis with the baseline FEV_1 value replaced with the appropriate baseline rescue medication use.

9.6.1.4 Peak Expiratory Flow Rate (PEF)

All the patients are instructed to record PEF twice daily using an electronic Peak Flow Meter device, once in the morning and once approximately 12 hours later in the evening (prior to evening dose), from Run-in Visit 101 and throughout the study.

PEF (liters/min) will be averaged separately for morning and evening values with means over the 12 weeks treatment phase and the 3 weeks Baseline Run-in phase.

Mean morning/evening PEF will be summarized by treatment. The between-treatment difference of the change from baseline in mean morning/evening PEF will be analyzed using the same model 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 the treatment difference.

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

9.6.1.5 Asthma symptoms based on eDiary

The eDiary data on asthma symptoms will be summarized for:

- the mean daytime asthma symptom score
- the total daily symptom score
- percentage of days with no daytime symptoms
- percentage of nights with no nighttime awakenings
- percentage of mornings with no symptoms on rising

[redacted]

- percentage of asthma symptoms free days, i.e., days with no daytime symptoms and no nighttime awakenings and no mornings with symptoms on rising

The same ANCOVA model as used for the analyses of rescue medication will be used with the appropriate baseline value as a covariate.

In addition, summarizations will be performed by 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.

9.6.1.6 Asthma exacerbations

The following asthma exacerbation-related parameters over the 12 weeks will be summarized by treatment (asthma exacerbation is defined in Section 6.4.9). The analysis will be performed by exacerbation category wherever specified. The exacerbation categories are: All (mild, moderate, severe) and the combination of either moderate or severe.

- Time to first asthma exacerbation by exacerbation category
- The annual rate of asthma exacerbations by exacerbation category

Time-to-event variables will be analyzed using a Cox regression model stratified by age (≥ 12 to < 18 years, ≥ 18 years). 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 within 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 < 18 years, ≥ 18 years), 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 within 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.

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

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.

[redacted]

For the overall score and each respective domain score measured at Week 12, treatment group comparison will be performed using the same ANCOVA model as specified for rescue medication use with baseline AQLQ as covariate.

The proportion of patients who achieve an improvement of at least 0.5 at Week 12 in the change from baseline in AQLQ (i.e., increase of AQLQ score of at least 0.5 from baseline) will be analyzed using a logistic regression model on the FAS. The model will include terms for treatment, age (≥ 12 to < 18 years, ≥ 18 years), region as fixed effects, and baseline AQLQ, FEV_1 prior to inhalation and FEV_1 within 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates.

9.6.2 Safety variables

All safety variables will be summarized for the safety set.

9.6.2.1 Serious asthma outcomes

A composite endpoint of serious asthma outcomes is defined as a) asthma-related hospitalization, b) asthma-related intubation, or c) asthma-related death. All serious asthma outcomes and deaths occurring from the time of randomization until the 30 days after permanent discontinuation of study drug will be adjudicated by an independent external committee to determine their asthma relatedness.

The composite endpoint as well as each single component of it will be analyzed for the number of patients with the event, the time to event and the annual rate of events. If a sufficient number of events will occur, similar analyses as described for asthma exacerbations will be performed. Otherwise, a purely descriptive analysis will be done only.

9.6.2.2 Adverse events

All treatment emergent AEs including asthma exacerbations will be summarized and listed. AEs starting on or after the time of the first inhalation of study drug but not later than 7 days (30 days in the case of a SAE) after the last inhalation will be classified as a treatment emergent AE. Any AEs that started during the study before the time of the first inhalation of study drug will be classified as a prior AE.

The following treatment emergent AE 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 AEs by system organ class and preferred term, SAEs by system organ class and preferred term, and AEs leading to permanent discontinuation of study-drug by system organ class and preferred term.

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

In addition, AEs will be summarized by standardized MedDRA query (SMQ) level. The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify AEs of special interest which will be summarized too.

Fatal AEs will be summarized by adjudicated reason for death.

[redacted]

9.6.2.3 Electrocardiogram (ECG) and vital signs

ECG data, vital signs (systolic and diastolic blood pressure and radial pulse rate) data, and body weight will be summarized by treatment, visit, and time point, including changes from baseline.

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

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

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

Notable values for vital signs and change from baseline will be summarized by treatment group, visit and time point. Additionally, the number and percentage of patients with notable values at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits 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*

Radial 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 in a similar way. A notable value is defined as a QTc interval of greater than *450 ms (male), 460 ms (female) and 500 ms (both)*. The number of newly occurring or worsening notable QTc values will be shown for post-baseline time points and overall (i.e., at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits). The categories used for the change from baseline in QTc are less than 30 ms, 30 to 60 ms and greater than 60 ms.

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

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

9.6.2.4 Laboratory data

The laboratory parameters (hematology, blood chemistry including glucose and potassium, urinalysis and evening plasma cortisol) will be summarized by treatment, visit and time point, including changes from baseline. The baseline measurement will be the 20 min pre-dose

[redacted]

measurement at Visit 201. The maximum blood glucose or minimum serum potassium post first dosing (i.e., post-baseline value) will also be summarized.

All laboratory data will be listed with abnormal values flagged. 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.

The number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria will be summarized by laboratory parameter, scheduled post-baseline visit and time point and additionally at any time on treatment considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits. Similar analysis will be done for newly occurring or worsening abnormalities in liver function tests (LFT).

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

9.6.2.5 Unscheduled primary and secondary care visits due to asthma worsening

Worsening of asthma symptoms may require unscheduled evaluation between visits. The on-treatment data related to asthma worsening collected will be listed and summarized descriptively.

9.6.3 Safety monitoring analysis

It is planned that the independent DMC will review semi-blinded (i.e., treatment group named as A or B) 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 (no interim analysis for efficacy has been planned) for stopping rule, there will be no alpha spent for the safety monitoring analysis. All analyses will be considered exploratory.

[redacted]

9.7 Sample size calculation

The sample size calculation takes into account the following consideration:

1. To achieve at least 90% power for the primary endpoint trough FEV_1 with a treatment difference of 100 mL between QMF149 vs. MF, assuming a standard deviation of 380 mL based on internal studies CQMF149A2210, CQMF149E2201, CQMF149E2203 and literature data, where most observed treatment effects range approximately 80 mL to 120 mL.
2. To achieve at least 75% power (with multiplicity adjustment) for the secondary endpoint ACQ-7 with a treatment difference of -0.18 between QMF149 vs. MF, assuming a standard deviation of 0.80 based on study CQMF149A2210, where observed treatment difference was -0.21 with 95% confidence interval (-0.28, -0.15);

If 10% dropout rate is assumed, then calculation shows the sample size of 750 patients (i.e., 375/arm) will provide approximately 93% power for item 1 and 77% power for item 2 with multiplicity adjustment.

The sample size calculation is performed in PASS Software.

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.

Participation of patients and in particular adolescent patients in this study will be based on the local regulations and ethics committee requirements in various participating countries.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents. Patients below the legal age of consent are required to have the

[redacted]

Parental Informed Consent signed by the patient's parent/guardian; adolescents are required to sign the Assent Form.

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.

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.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient 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

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

10.5 Quality control and quality assurance

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

Audits of investigator sites, vendors and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved

[redacted]

in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach

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

11 Protocol adherence

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

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

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

[redacted]

12 References

References are available upon request.

[Annex IV, ICH-E2D Guideline (2003)] Available from ich.org website

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

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

[redacted]

[FDA warning for Advair Diskus prescription information; ALERT [11/2005] Information for Healthcare Professionals - Fluticasone propionate; Salmeterol xinafoate (marketed as Advair Diskus.

[Global Initiative for Asthma (GINA) (2016)] Global Strategy for Asthma Management and Prevention. 'Available from ginasthma.org website'

[Juniper EF, et al (1992)] Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax; 47: 76-83.

[Juniper EF, et al (1993)] Measuring quality of life in asthma. Am Rev Respir Dis; 147: 832-838.

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

[Juniper EF et al (1999)] Development and validation of the questionnaire to measure asthma control. Eur Resp J; 14:'902-7'.

[Juniper EF et al (2005)] Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 99:553-8.

[Juniper EF et al (2006)] Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med; 100: 616-621.

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

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

[redacted]

13 Appendices

Appendix 1: Instructions for Use of Concept1

Instructions for using inhaler and capsules.

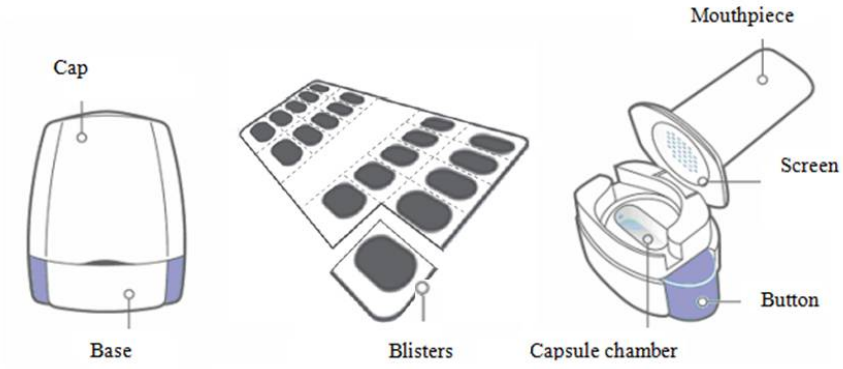
Do not swallow capsules.

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

Your inhaler and capsules

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

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



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

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

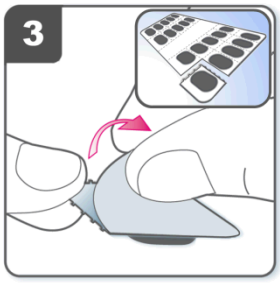
How to use your inhaler

Pull off cap.

[redacted]

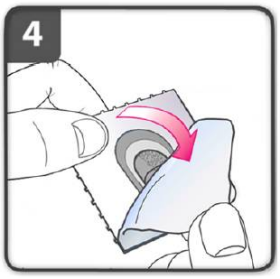
Open inhaler:

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



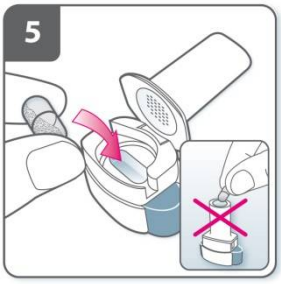
Prepare capsule:

Immediately before use, with dry hands, separate one of the blisters from the blister card by tearing along the perforations and lift the corner of the foil.



Remove a capsule:

Peel away the foil and remove the capsule from the blister.



Insert capsule:

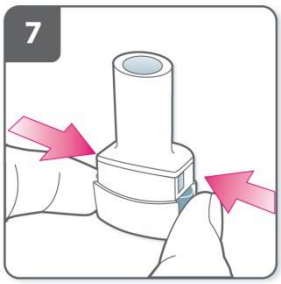
Place the capsule into the capsule chamber.

Never place a capsule directly into the mouthpiece.

Close the inhaler:

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

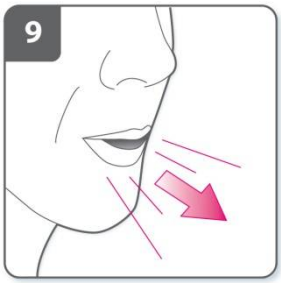
[redacted]



Pierce the capsule:

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

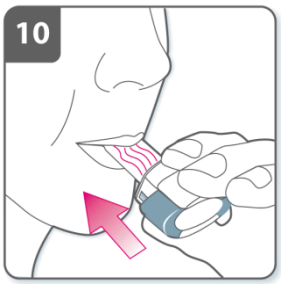
Release the side buttons fully.



Breathe out:

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

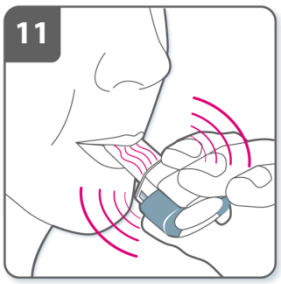
Do not blow into the mouthpiece.



Inhale the medicine

To breathe the medicine deeply into your airways:

- Hold the inhaler as shown in the picture. The side buttons should be facing left and right. Do not press the side buttons.
- Place the mouthpiece in your mouth and close your lips firmly around it.
- Breathe in rapidly but steadily and as deeply as you can.



Note:

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

Additional information

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

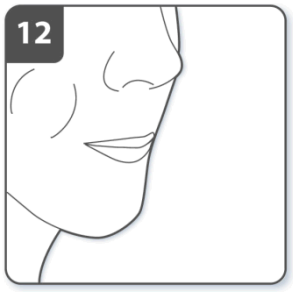
[redacted]

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:

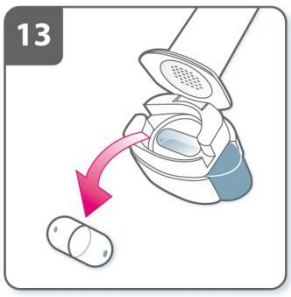
- Close the inhaler.
- Repeat steps 9, 10, 11 and 12.

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.

Always use the new inhaler that comes with your new medication pack. Dispose the inhaler after maximum 30 days of use.

- 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.

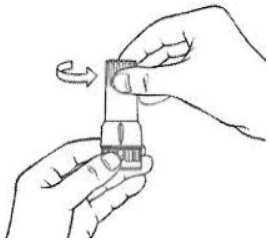


Figure 1 – Cap Removal

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).

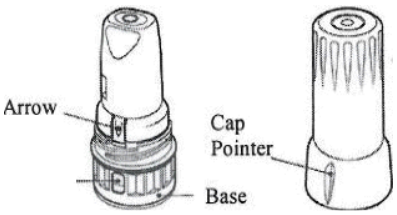


Figure 2

[redacted]

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 hold your breath for about 10 seconds or as long as you comfortable can.

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.

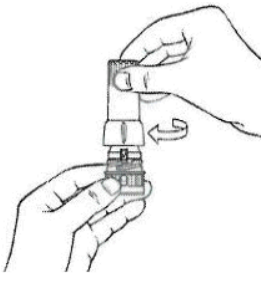


Figure 4 – Closing the Inhaler

[redacted]

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 all used TWISTHALER® device to the study site

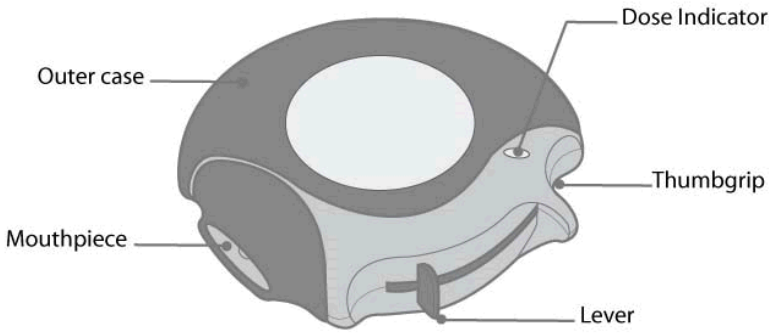
[redacted]

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).

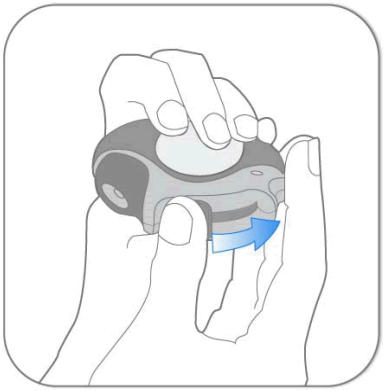
[redacted]

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:**

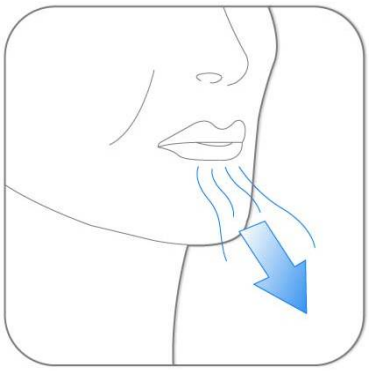
- Do not close the Diskus.
- Do not tilt the Diskus.
- Do not play with the lever.
- Do not move the lever more than once.

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.**

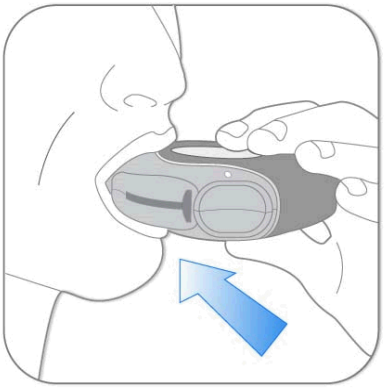
[redacted]

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



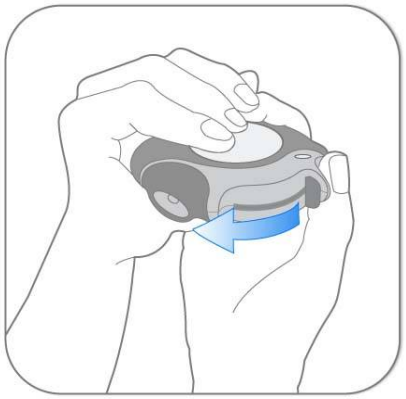
Remove the Diskus® from your mouth. Hold your breath for about 10 seconds, or for as long as is comfortable. Breathe out slowly. The Diskus® delivers your dose of medicine as a very fine powder. Most patients can taste or feel the powder. Do not use another dose from the Diskus® if you do not feel or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

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 patient'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 patient. The technician should ensure a good seal around the mouthpiece, and confirm that the patient's posture is correct. The patient 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 patient is unable to perform a single acceptable maneuver after 8 attempts, testing may be discontinued.

Acceptability

An acceptable maneuver has the following characteristics:

[redacted]

- No hesitation or false start;
- A rapid start;
- No cough, especially during the first second of the maneuver;
- No glottic closure or obstruction by tongue or dentures;
- No early termination of exhalation (minimum exhalation time of 6 seconds is recommended, and no volume change for at least 1 second) or the patient 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 microgram 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:

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

Patients 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

[redacted]

References

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

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

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

[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

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, 25, 30
Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

[redacted]

Appendix 7: Patient Asthma Control eDiary

(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

Appendix 8: Liver Event and Laboratory Trigger Definitions and Follow-up Requirements

Table 8-1 Liver Event and Laboratory Trigger Definitions

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

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

Table 8-2 Follow Up Requirements for Liver Events and Laboratory Triggers

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

[redacted]

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

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

[redacted]

Appendix 9: ICS Dose Level

Table 9-1 Low, Medium and High Daily Doses of Inhaled Glucocorticosteroids for Adults and Adolescents (12 years and older) (GINA 2016)

Drug	Total Daily Dose (microgram/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
Mometasone furoate	110 - 220	> 220 - 440	≥ 440
Triamcinolone acetonide	400 - 1000	> 1000 - 2000	> 2000
Fluticasone Furoate - DPI**	N/A	100	200

CFC: chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant
*Beclomethasone dipropionate CFC is included only for comparison with older literature
**As per Relvar SmPC

[redacted]