NOVARTIS

Clinical Development

QVM149B (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

Statistical Analysis Plan (SAP)

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30-May-2018	Before DB lock	Creation of amendment 1	Notable value for magnesium included	Section 6.4
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List of abbreviations

ACQ	Asthma Control Questionnaire
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AQLQ	Asthma Quality of Life Questionnaire
b.i.d	twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CCV	Cardio-/Cerebro-vascular
CRF	Case Report/Record Form (paper or electronic)
DMC	Data Monitoring Committee
eDiary	Electronic Diary
ECG	Electrocardiogram
ER	Emergency Room
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FEF	Forced Expiratory Flow
FVC	Forced Vital Capacity
IgE	Immunoglobulin E
ICS	Inhaled Corticosteroid
LABA	Long Acting Beta-2 Agonist
LFT	Liver Function Test
MF	Mometasone Furoate
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measurements
o.d.	Once a day
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PPS	Per protocol set
QTc	Corrected QT interval
RAN	Randomized set
SAE	Serious Adverse Event
SAF	Safety analysis set
SCS	Systemic Corticosteroids
SOC	System Organ Class
SMQ	Standard MEDRA Query
TD	Study Treatment Discontinuation
TFL	Table Figure Listing

1 Introduction

This document contains details of the statistical methods that will be used in the phase III clinical trial CQVM149B2303. This study is designed to evaluate the efficacy and safety of QMF149 150/80 microgram o.d. delivered via Concept1 compared with MF 200 microgram o.d. delivered via Twisthaler® in patients with asthma as determined by pulmonary function testing and effects on asthma control.

Data will be analyzed according to Section 9 of the study protocol.

Important information is given in the following sections and details are provided, as applicable, in section 6: Appendix.

1.1 Study design

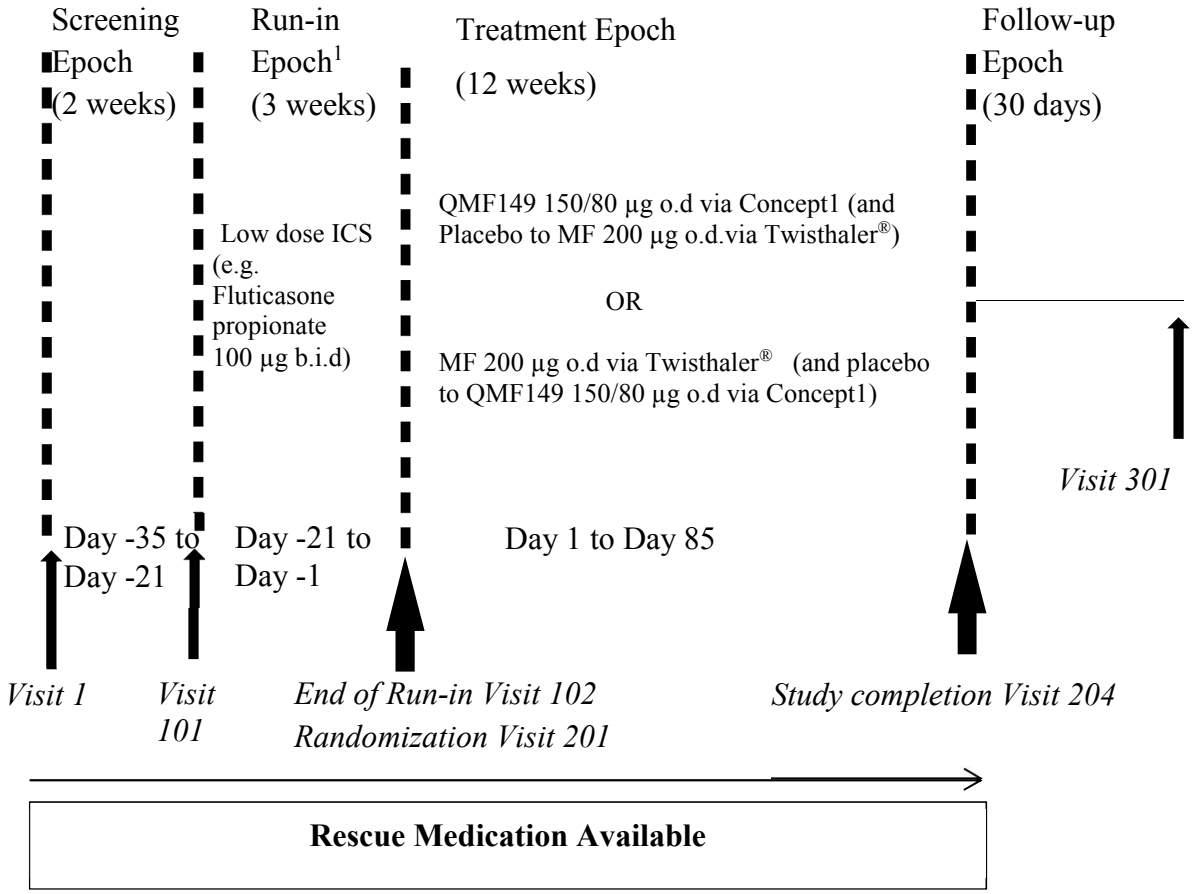
This study uses a randomized, double-blind, double-dummy, parallel-group design to assess the efficacy and safety of QMF149 150/80 microgram o.d. delivered via Concept1 compared with MF 200 microgram o.d. delivered via Twisthaler® in adult and adolescent patients with mild asthma (figure 1)

Approximately 750 patients (including approximately 50 adolescent patients) will be randomized 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 treatment. Detailed information regarding sample size calculation is provided in section 3.

This study will enroll multi-nationally and patients will be stratified according to prognostic factors of age (12 to 17 years or ≥ 18) and non-prognostic factor region to achieve improved homogeneity within each stratum.

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 T01 and T02) safety data (as described in Section 8.4 of the protocol). The details of the information flow, confidentiality and specific analysis will be available from the DMC Charter.

Figure 1 Study design



1.2 Study objectives and endpoints

Section 2 of the study protocol lists the following primary, key secondary, other secondary [redacted] objectives.

1.2.1 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.

1.2.2 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.

1.2.3 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 h15 min and 23 h 45min FEV1 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 decrease 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 (e-Diary) 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 e-Diary recordings over 12 weeks of treatment
- Percentage of rescue medication free days over 12 weeks of treatment period.

Exacerbations:
- To evaluate the efficacy in terms of asthma exacerbation-related parameters described below during 12 weeks of treatment. The analysis will be performed by exacerbation category wherever specified. The exacerbation categories are: All (mild, moderate, severe) and the combination of moderate or severe:
  - 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 12weeks of treatment.

[redacted]

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by [redacted]. The most recent version of SAS available in the statistical programming environment of [redacted] will be used for the analysis.

2.1.1 General definitions

The terms ‘study treatment’ which has been used in this document actually refer to ‘double-blind treatment’.

2.1.1.1 Study day

Study day will be defined as the number of days since the date of first dose of study treatment. The date of first dose of study treatment will be defined as Day 1 and the day before the first dose of study treatment will be defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the first date of study treatment,

  Study day = Assessment date – Date of first dose of study treatment + 1;

- for dates prior to the first date of study treatment,

  Study day = Assessment date – Date of first dose of study treatment.

If a patient has no study treatment, the randomized date will be used instead of the date of first dose of study treatment. Then, the randomized date is defined as Day 1 and the day before the randomization was defined as Day -1.

2.1.1.2 Baseline definition

In general, baseline is defined as the last measurement before the first dose of study treatment at the evening of Day 1.

Parameter	Baseline assessment	Detail
Post-dose **FEV_1**, Pre-dose trough **FEV_1**, Trough **FEV_1**	45 min and 15 min pre-dose FEV_1 at Day 1	The average of the values taken at -45 and -15 min
Post-dose **FVC,** Pre-dose trough **FVC**, Trough **FVC**	45 min and 15 min pre-dose FVC at Day 1	The average of the values taken at -45 and -15 min
Post-dose **FEF_{25-75},** Pre-dose trough **FEF_{25-75}**, Trough **FEF_{25-75}**	45 min and 15 min pre-dose FEF_{25-75} at Day 1	The average of the values taken at -45 and -15 min
ACQ-7	Prior to first dose of study treatment at Day 1	The average of responses of 7 questions
ACQ-5	Prior to first dose of study treatment at Day 1	The average of responses of first 5 questions
Diary data (PEF, symptoms, and rescue medication use)	Last 21 days of run-in period between run-in Visit 101 and up to one day before first dose of study treatment	The average from all non-missing records or percentage of days free of symptoms or rescue medication use
Laboratory data (hematology, biochemistry, urinalysis, and plasma cortisol)	20 min pre-dose at Day 1	
Vital signs (pulse rate and systolic and diastolic blood pressures)	25 min pre-dose at Day 1	
Height and weight	Run-in Visit 101	
ECG	35 min pre-dose at Day 1	
[redacted]	[redacted]	

Detail descriptions for calculating baseline values are provided in the latter sections.

2.1.1.3 Post-baseline measurement

Post-baseline measurements are defined as those assessments after the first dose of study treatment.

When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value.

Detail descriptions for calculating post-baseline values are provided in the latter sections.

2.2 Analysis sets

The following analysis sets are defined:

- The randomized (RAN) set will consist of all patients who were assigned a randomization number, regardless of whether or not they actually received study treatment. Patients in RAN will be analyzed according to the treatment they were randomized to. The RAN set will be used for a summary of patient disposition, demographics and baseline characteristics.
- The Full Analysis Set (FAS) will consist of all patients in the RAN set who received at least one dose of study treatment. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization. The FAS will be used in the analysis of all efficacy variables.
- The Per-Protocol set (PPS) will include all patients in the FAS who did not have any major protocol deviations. The list of major protocol deviations will be available in Appendix 6.7 prior database lock. Patients will be analyzed according to the treatment they received. The PPS will be used for supportive analysis of the primary analysis only.
- The Safety Set will consist of all patients who received at least one dose of study treatment including non-randomized patients who received study treatment in error. Patients will be analyzed according to the treatment they received. If patients switch double-blind treatment during the study, they will be counted and analyzed only once according to their initial treatment. The safety set will be used in the analysis of all safety variables.
- [redacted]

2.2.1 Subgroup of interest

Subgroup analyses of primary, key and other secondary, [redacted] objectives will be performed for adolescent patients (12 - 17 years old). These analyses will be identified in the TFL shells. For tables presenting results from statistical models, the treatment effects in adolescent patients will be derived from the treatment x age subgroup interaction term by including all patients in the analysis.

At week 12, the following subgroups will be used for supporting analyses of primary endpoint trough FEV1:

- Age group (12 to 17 years, ≥ 18 years)
- Race (Caucasian, Asian, Black and other)
- Gender (male, female)

- History of asthma exacerbation in the 12 months prior to Screening (Yes, No)
- Patients' prior therapies before Run-in period (eg. low dose ICS without LABA, low dose ICS with LABA)
- FEV1 response according to % predicted FEV1 range at Baseline (60 %-< 70%, 70% to < 90%)
- ACQ-7 Baseline (1.5- < 2, 2-< 2.5, ≥ 2.5)

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of patients will be summarized by region (i.e., Eastern Europe, Western Europe, India, Japan, Asia (other than India and Japan), rest of world), country and treatment group for the RAN set. Further, for each study epoch (i.e., screening, run-in, treatment phase, post treatment follow-up), the overall number of patients who entered, completed, and discontinued that phase will be summarized including the reasons for discontinuation.

Time to premature treatment discontinuation will be displayed graphically for each treatment group using a Kaplan-Meier curve for the safety analysis set. The date of premature treatment discontinuation is defined as the date of last dose of study treatment. Patients who completed the study treatment will be censored at the date of last dose of study treatment.

Number of patients with protocol deviations will be tabulated by deviation category (e.g., selection criteria not met, prohibited concomitant medication).

The number of patients included in each analysis set will be tabulated, as well as the reasons for exclusions from analysis sets.

2.3.2 Patient demographics and baseline charecteristics

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 asthma treatment (ICS low dose, ICS/LABA low dose and in case of protocol deviation ICS other than low dose, ICS/LABA other than low dose will be included), prior concurrent medications (asthma-related and non-asthma related) baseline ACQ-7, [redacted] will be summarized by treatment group using the RAN set.

Continuous variables will be summarized using descriptive statistics (number of non-missing data, mean, standard deviation, median, first and third quartiles, minimum, and maximum) and categorical variables will be summarized in terms of the number and percentage of patients in each category including a category for missing data if any.

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

In addition, the following categorizations of continuous variables will be done:

- Age into 12 – 17 years, 18 - 64 years, and ≥ 65 years;
- BMI into ≤ 30.0 kg/m2 and > 30.0 kg/m2;
- Duration of asthma into < 1 year, 1 - 5 years, > 5 - 10 years, > 10 - 15 years, > 15 – 20 years, and > 20 years;
- Number of asthma exacerbations in the 12 months prior to the start of the study that required treatment into 0, 1, > 1
- pre-bronchodilator FEV1 into < 60%, 60 - < 70%, 70% - < 90%, and ≥ 90% of predicted FEV1 (< 60% and ≥ 90% will be included in case of protocol deviation)
- ACQ-7 into <1.5, 1.5- < 2, 2-< 2.5, ≥ 2.5 (<1.5 will be included in case of protocol deviation)

Medical history will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most recent version at the time of database lock. History/conditions will be summarized for the RAN set by primary system organ class and preferred term. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

2.4.1.1 Duration of exposure

Duration of exposure to study treatment will be calculated as the number of days starting from the first dose date up to and inclusive the last dose date. The duration of exposure will be summarized by treatment for the safety set as a continuous variable with the standard descriptive statistics. In addition, the duration of exposure will be summarized with total patient years and the number (%) of patients who were exposed to study treatment for each 1 – 29 days, 30 – 85 days and > 85 days.

The number of patients who completed the 12-week study treatment and who discontinued the study treatment prematurely will be shown including the reasons for discontinuation of study treatment.

2.4.1.2 Compliance

Compliance will be calculated by counting the days where study treatment was administered "As per protocol" according to the records on the Dosage Administration Record (DAR)

Summary eCRF. The percentage of days divided by the days of exposure will be analyzed. To be counted as a day of compliance with study treatment, two administrations, i.e., the Twisthaler and the Concept 1 inhaler in the evening, have to be taken as per protocol.

Compliance will be categorized into < 80 % and 80 % - 100 % and summarized by treatment for the safety set.

2.4.2 Prior, concomitant and post therapies

Each medication, either an asthma or non-asthma medication, will have the start and end dates recorded on the eCRF. Separate tables will be provided for medications which were started and stopped prior to the first dose of study treatment and medications which were taken concomitantly to the study treatment (regardless of whether continued or started after the first dose of study treatment).

Asthma medications will be summarized by the route of administration, the recorded prespecified drug subcategories (including types of combination) and the coded preferred terms. The summary will be repeated by showing ingredients instead of preferred terms. Non-asthma medications will be summarized by route of administration and preferred term.

Surgical and medical procedures (non-drug therapies) will be coded using MedDRA and presentations will be done by MedDRA primary system organ class and preferred term, separately for prior procedures and those after start of study treatment.

Short acting beta2 agonist (SABA) rescue medication usage (mean number of puffs) during the screening epoch will be summarized.

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

All summarizations will be by treatment group in the Safety Set.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary objective is to demonstrate the superiority of QMF149 150/80 µg to MF 200 µg in terms of trough FEV_1 after 12 weeks of treatment.

Trough FEV_1 is defined as the average of the two FEV_1 measurements taken 23 hr 15 min and 23 hr 45 min post-evening dose. Trough measurements will be done at Day 2 and Day 85 (Week 12, the primary endpoint).

For trough FEV_1, the baseline value is defined as the average of the values taken at -45 and -15 min prior to first dose of study treatment at the evening of Day 1. Checks will be performed to

ensure both values were indeed taken prior to the first dose of study treatment. If one of the -45 and -15 min values is missing (or is not confirmed to be pre-dose) then the remaining non-missing value will be taken as the baseline. If both values are missing (or not confirmed to be pre-dose), then the last out of the pre-bronchodilator measurements taken at the run-in Visits 101 and 102 or at unscheduled run-in visits will be used as the baseline. If the FEV_1, FVC or FEF_{25-75} measurements are missing both on Day 1 and at run-in visits, the respective baseline values will be set to missing. Measurements taken within 6 hours of rescue use or within 7 days of systemic corticosteroid use will be set to missing.
For all spirometry measurements, implausible values will be excluded. If a patient has implausible FEV_1 value (defined as > 7 L) at an assessment, all spirometry measurements related to that assessment will be excluded. The threshold of 7 L was chosen because according to ERS/ECCS 1993 regressions, the maximum normal predicted FEV_1 is 5.17 L, we set 7 L as the implausible cutoff to allow for some fluctuation around the maximum mean.

2.5.2 Statistical hypothesis, model, 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 (12 to 17 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 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 symmetriy covariance matrix will be used in the mixed model, if the model still does not converge the random effect will be removed, if the model converges after removing the random center effects, the original model without random center effects will be re-assessed. 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 and treatment.

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).

2.5.3 Handling of missing values/censoring/discontinuations

If any of the 23 hr. 15 min and 23 hr. 45 min values contributing to the trough FEV_1 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 window then the individual FEV_1 value will be set to missing.

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

Post-dose spirometry measurements which were actually taken pre-dose will be set to missing and not used for by time point assessments. Similarly, any pre-dose spirometry measurements which were actually taken post-dose will be set to missing and not used for by time point assessments.

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.

2.5.4 Supportive and Sensitivity analyses

As supportive analysis, the same MMRM used in the primary analysis will be also performed on the PPS to assess the treatment effect in protocol adherers.

In addition, 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 window will not be included.

As a sensitivity analysis, a so-called 'tipping point analysis' will be performed for the primary endpoint to evaluate the impact of a deviation from the MAR assumption of missing data. The delta-adjusting approach described in Ratitch et al (2013) will be used to find the tipping point, in a spectrum of conservative missing not at random (MNAR) assumptions, at which conclusions change from being favorable to QMF149 to being unfavorable. After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point. This methodology would provide a good picture of what it would take to overturn study conclusions on the basis of varying assumptions about missing data. The basic idea is to first impute the missing values using a regression based multiple imputation (MI) method based on the MAR assumption. The imputed Week 12 values for the QMF149 arms are then adjusted by a delta value. A detailed description of the analysis steps are provided in Section 6.6.

The 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 key demographic and disease related subgroups (See Section 2.2.1 for the details of subgroups).

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

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

The ACQ-7 measures asthma symptom control and consists of seven items: five on symptom assessment, one on rescue bronchodilator use and one on airway calibre (FEV_1 % predicted). Patient recall is one week. All 7 questions of the ACQ-7 are equally weighted. Items 1-5 are scored along a 7-point response scale, where 0 = good controlled and 6 = poor controlled. Item 6 is scored between 0 = no rescue medication and 6 = More than 16 puffs/inhalations most days. The 7th item will be scored by the investigator based on the FEV_1 % predicted from the masterscope at the site (i.e., Score = 0 means > 95% of predicted FEV_1, 1 = 90 95%, 2 = 80 – 89%, 3 = 70 – 79%, 4 = 60 – 69%, 5 = 50 – 59%, and Score = 6 means < 50% of predicted FEV_1). The total score is calculated as the mean of all questions. The mean will be calculated as the sum of scores divided by the number of questions that were answered, as long as there were at least 6 questions answered and the missing question is neither Question 1 ('On average, during the past week, how often were you woken by your asthma during the night?') nor Question 7. In case of one missing response (not Question 1 or Question 7), first that missing response will be imputed as per the method given in Section 2.6.3 and then the ACQ score will be calculated.

ACQ-7 measurements are scheduled for Days -21, 1, 30 and 84.

For the ACQ-7 score, the baseline value is defined as the score obtained at Day 1 prior to first dose of study treatment. If the value is missing, the last measurements from run-in visit 101 or unscheduled run-in visits will be used.

2.6.2 Statistical hypothesis, model, and method of analysis

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.

2.6.3 Handling of missing values/censoring/discontinuations

For a missing individual item while on-treatment, the interpolation method using either previous or subsequent completions of the questionnaire (ACQ User Guide, 2004) will be used. For instance,

Item	Visit 1	Visit 2
1	4	6
2	3	5
3	0	0
4	4	4

5	0	0
6	2	Missing
7	5	6

Total visit 1 score for items answered on both visits is 4+3+0+4+0+5=16 (A)

Total visit 2 score for items answered on both visits is 6+5+0+4+0+6=21 (B)

Item 6 score at visit 1=2

Item 6 score at visit 2= B/A * 2=21/16*2=2.63

The ACQ score for visit 1 is (4+3+0+4+0+2+5)/7=2.57

The ACQ score for visit 2 is (6+5+0+4+0+2.63+6)/7=3.38

For post-baseline visits, missing items will be imputed by using data from subsequent visit first, if these are not available, data from previous visit will be used for imputation of the missing item. For baseline, missing item at Day 1 will be imputed by using Day -21 data or data from any unscheduled run-in visit, whichever is later. To clarify, for imputation of the first post-baseline value, if the second post-baseline assessment is not available, the value of the baseline assessment will be used. If there are two assessments from the same day, the first will be used only and the second ignored even for imputation.

If more than one individual item is missing, then ACQ-7 score will set to be missing. The MMRM which is used for analysis of ACQ-7 score, is based on missing at random mechanism for the missing values and assesses the treatment effects of ACQ-7 without explicit imputation.

2.6.4 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.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Spirometry data other than the primary endpoint

Pre-dose trough is defined as the average of the two measurements taken 45 min and 15 min pre-evening dose. FEF_{25-75} is defined as forced expiratory flow between 25% and 75% of Forced Vital Capacity (FVC).

For all FEV_1, FVC, and FEF_{25-75} endpoints, the baseline value is defined in a similar way as defined for trough FEV_1 (See Section 2.5.1).

For FEV_1, FVC and FEF_{25-75} measurements, missing values will be handeled similarly as mentioned for trough FEV_1 (See Section 2.5.3). Additionally for pre-dose trough, pre-dose measurements will be set to missing when they are actually taken post-dose. However, the post-

evening dose time window of 22 – 25 hours can not be applied here since the time of evening dose of the previous day will not be recorded. If one of the -45 and -15 min values is missing (or is not confirmed to be pre-dose) then the remaining non-missing value will be used as average pre-dose value.

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-squares 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 at days 30 and 84.

Post-dose FEV_1 (Day 1, Day 30 and Day 84) measurements will be analyzed separately by visit using the same MMRM as trough FEV_1 with time point as repeat variable (i.e. in statistical model visit will be replaced by timepoint).

Pre- and post-dose FVC and FEF_{25-75} will be analyzed similar to FEV_1 with respective baseline values (See Section 2.1.1.2).

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

For additional details of statistical models, please refer to Section 5.6.

2.7.2 Asthma control questionnaire (ACQ)

Results for ACQ-7 at day 30, obtained from MMRM for the key secondary endpoint ACQ-7 at day 84, will be displayed.

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

The proportion of patients who achieve an improvement of at least 0.5 in ACQ-7 (i.e. decrease of ACQ-7 score of at least 0.5 from Baseline) at post-baseline visits will be analyzed using a logistic regression model. First missing ACQ-7 values will be imputed using a regression based Multiple Imputation (MI) method under missing at random (MAR) assumption, based on continuous ACQ values. Then continuous ACQ values will be converted into binomial responses and generalized estimating equation (GEE) method will be used to analyze the datasets and then the results from GEE method will be combined for the inference. The GEE model will include terms for treatment, age (12 to 17 or ≥ 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.

Additionally, the number of patients will be summarized by response relative to baseline ACQ-7 with the following categories: Response (decrease of >= 0.5 units in ACQ-7), No change (-0.5 < change in ACQ-7 < 0.5), Worsening (increase of >= 0.5 units in ACQ-7), Net response (response – worsening) and Total.

In addition to ACQ-7, average of first 5 questions in ACQ (ACQ-5) will be calculated and all the analyses described for ACQ-7 will be repeated for ACQ-5.

2.7.3 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 e-Diary. For rescue medication use, the baseline values are defined as the average from all non-missing records taken over the last 21 days in the run-in period between run-in Visit 101 and up to one day before first dose of study treatment Missing diary data will not be imputed.

If for the value over the whole day (24 hours) the number of puffs is missing for part of the day (either day-time or night-time) then a half day will be used in the denominator to calculate the average value. Any values > 30 for the number of puffs of rescue medication in a 12 hour period will be set to missing. These high numbers are not realistic and could impact the analyses. If a patient has less than 7 days with non-missing data, then the baseline value will be set to missing.

Post-baseline measurements start with the morning recordings at Day 2 and end with the evening recordings one day after the last evening dose. Summary data (i.e., mean values and percentage of days with) will be calculated for 4-weekly intervals (defined as 28 days), and for Weeks 1 – 12 (defined as the whole treatment period up to Visit 204, Day 85). Similar calculations as for baseline diary data will be done. If there will be less than 14 days with data in a 4-week period, then the data should collapse with the previous 4-week period. For Weeks 1 – 12, summary values will only be calculated if a patient has at least 30% of their diary days and at least 20 diary days with evaluable data for that variable.

The mean daily number of puffs of rescue medication use over the 12 weeks of treatment will be summarized by treatment. The change from Baseline in the mean daily number of puffs of rescue medication use will be analyzed using an ANCOVA model. The model will contain treatment, age (12 to 17, or ≥ 18), region as fixed effect factors with center nested within region as a random effect and baseline rescue medication use, FEV_1 prior to inhalation and FEV_1 within 15 to 30 min post inhalation of salbutamol/albuterol (components of SABA reversibility) as covariates. No imputation will be done for missing data. The adjusted mean (LS mean) treatment 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 during daytime and nighttime) will be summarized by treatment and analyzed the same way as described for the number of puffs of

the rescue medication use with baseline percentage of ‘rescue medication free days’ as a covariate instead of baseline rescue medication use.

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 the change from baseline in mean number of puffs of rescue medication will be 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. In case of non-convergence or evidence of highly skewed data, non-parametric tests such as Wilcoxon Rank Sum Test will be explored.

2.7.4 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.

Baseline values are defined similarly as rescue medication in Section 2.7.3

For post-baseline measurements, similar procedure will be followed, as mentioned for rescue medication use.

Mean morning/evening PEF over 12 weeks of treatment phase 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 the change from baseline in mean morning/evening PEF will be analysed using a similar MMRM as specified for the primary analysis with baseline FEV_1 value replaced with the appropriate baseline PEF.

2.7.5 Asthma symptoms based on e-Diary

The night-time symptom score consists of one question 'How did you sleep last night?' which has to be answered with scores from 0 = 'I did not wake up because of any breathing problems.' up to 4 = 'I had difficulty sleeping because of my breathing problems even though I used my rescue medication.' The morning score consists of the question 'Did you have asthma symptoms upon awakening in the morning?' which has to be answered with scores from 0 = 'None' up to 4 = 'Very Severe'. There are 5 questions including the today's severity of shortness of breath,

wheeze, cough, and chest tightness during the past 12 hours, and 'Did your respiratory symptoms stop you from performing your usual daily activities?' which are part of the daytime symptom score. All have to be answered with a score from 0 = 'None / Not at all' up to 4 = 'Very Severe / Completely'.

Daily e-Diary recordings will be used to derive:

- the mean daytime asthma symptom score i.e., the mean score over the 5 evening questions with respect to shortness of breath, wheeze, cough, chest tightness, and 'Did your respiratory symptoms stop you from performing your usual daily activities?', each with scores from 0 (no problems) to 4 (very severe problems)
- the total daily symptom score, defined as the sum of the nighttime score ('How did you sleep last night?' with scores from 0 - 4), the morning awakening score ('Did you have asthma symptoms upon awakening in the morning?' with scores from 0 - 4) and the mean daytime asthma symptom score. The sum will be in the range of 0 – 12.
- day with no daytime symptoms, i.e., all 5 evening questions must have a score = 0.
- night with no night-time awakenings, i.e., the question 'How did you sleep last night?' must be answered with 'I did not wake up because of any breathing problems'.
- morning with no symptoms on awakening, i.e., the question 'Did you have asthma symptoms upon awakening in the morning?' to be answered with 'None'.
- asthma symptoms free days, i.e., days with no daytime symptoms and no night-time awakenings and no symptoms on awakening.

Baseline values are defined similarly as rescue medication in Section 2.7.3. Additionally, the baseline total daily symptom score will be obtained in the first step by adding the nighttime symptom score, the morning score, and the mean daytime symptom score for each single day. In the second step, these daily symptom scores will be averaged over the days of the run-in period with non-missing data. The score is in the range from 0 to 12. For the derivation of the total daily symptom score, all 3 scores have to be available at that day. Otherwise a total daily symptom score will not be calculated for that day. If a patient has less than 7 days with non-missing data, then the baseline value will be set to missing.

For post-baseline measurements, similar procedure will be followed, as mentioned for rescue medication use.

Daily scores will be averaged for each patient over the days of the run-in period (which will be used as the baseline value), 12 weeks double-blind period, and over 4 weekly intervals (from Weeks 1-4 up to Weeks 9-12). Days with no daytime symptoms, nights with no night time awakenings, mornings with no symptoms on awakening and days with no asthma symptoms will be expressed in percentage of days with data during the respective periods. The same periods as for average scores will be analyzed for percentage of days. In case of non-convergence or evidence of highly skewed data, non-parametric tests such as Wilcoxon Rank Sum Test will be explored.For post baseline periods only the days on double-blind treatment will be considered. ANCOVA and MMRM will be performed on changes from baseline similar to the analysis of PEF with the appropriate baseline symptom score value as a covariate.

2.7.6 Asthma Exacerbations

All analyses will base on data as reported on the "Asthma Exacerbation Episodes" eCRF. The following asthma exacerbation-related parameters will be summarized considering the whole 12 weeks of double-blind treatment. The analysis will be performed by exacerbation category wherever specified. The exacerbation categories are: All (mild, moderate, severe) , and the combination of moderate or severe. The data for categories mild, moderate and severe will be collected as a part of Asthma Exacerbation Episode CRF and an additional category moderate or severe will be added for analysis.

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

In patients with multiple exacerbations, if the start date of an exacerbation was 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. The worst severity of these episodes will be taken as the severity of the collapsed exacerbation. Collapsing of exacerbation episodes will only be done for efficacy analyses but not for safety analyses of adverse events which includes asthma exacerbations.

Asthma exacerbations starting after the first dose and not later than one day after the date of last dose will be included in the analyses of efficacy.

Time-to-event variables will be analyzed using a Cox regression model stratified by age (12 to 17 or ≥ 18). The model will include treatment, region and history of asthma exacerbation in the 12 months prior to screening (Yes, No) as fixed-effect factors, and FEV_1 prior to inhalation and FEV_1 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. Patients without any asthma exacerbation will be censored at the earliest date of (last dose of study treatment + 1, death, last visit).

The annual rate of asthma exacerbations will be analyzed using a generalized linear model assuming the negative binomial distribution including treatment, age (12 to 17 or ≥ 18), and region and history of asthma exacerbation in the 12 months prior to screening (Yes, No) as fixed-effect factors, and FEV_1 prior to inhalation and FEV_1 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.
study treatment

2.7.7 Quality of life as assessed by Asthma Quality of Life Questionnaire (AQLQ-S+12)

AQLQ is a 32-item disease specific questionnaire designed to measure functional impairments that are most important to patients with asthma, with a recall time of two weeks and each question to be answered on a 7-point scale (1-totally limited/problems all the time, 7-not at all limited/no problems). It consists of 4 domains:

- Symptoms = Mean of Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30 (12 items)
- Activity limitation = Mean of Items 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32 (11 items)
- Emotional function = Mean of Items 7, 13, 15, 21, 27 (5 items)
- Environmental stimuli = Mean of Items 9, 17, 23, 26 (4 items)
- Overall Score = Mean of Items 1 to 32 (32 items)

Dr. Juniper, developer of AQLQ questionnaire suggests no more than 10% of missing data. This means that for a questionnaire of 32 items, no more than 3 items should be missing. Further, for the activity and symptom domains, the recommendation is no more than 1 missing value per domain, and for the emotional function and environmental stimuli domains, no missing responses at all. Missing individual items will be imputed similarly to missing items for ACQ-7.

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. an increase of AQLQ score of at least 0.5 from baseline) will be analyzed using a logistic regression model via GEE on the FAS as specified for ACQ-7 analysis except that the GEE model will include terms for treatment, age (12 to 17 or $\geq$ 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. The handling of missing data will also be the same as for ACQ-7, i.e., first missing continuous AQLQ values will be imputed using a MI method under MAR assumption. Then continuous AQLQ values will be converted into binomial responses and GEE method will be used to analyze the datasets and then the results from GEE method will be combined for the inference.

2.8 Safety analyses

All safety evaluation will be based on the safety set.

The study will be reviewed for safety issues by an independent, external data safety monitoring board (DMC), as described in Section 2.11 Interim analysis.

For **safety data**, post-baseline measurements comprise recordings up to the last dose of study treatment + 7 days for laboratory, ECG, vital signs. ECG, vital signs and laboratory values

which have complete date and time values are assigned to pre or post-dose assessment based on the actual date/time. However, values with missing date/time are assigned to their respective scheduled visit date and time given the visit number and time point are non-missing. If a measurement scheduled as pre-dose is actually performed post-dose, or vice versa, the data will not be used for by time point assessments but will be included in the summaries of the notable values and extreme values.

2.8.1 Serious asthma outcome

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 treatment 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.

2.8.2 Adverse events (AEs)

All adverse events including asthma exacerbations, coded with MedDRA using the most actual version at the time of database lock, will be listed. In general, summaries will include treatment-emergent adverse events only, i.e., those starting on or after the time of the first administration of study treatment but not later than 7 days (30 days in the case of a SAE) after the last administration. Any AEs that started during the study before the time of the first inhalation of study treatment will be classified as a prior AE.

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

- all adverse events
- all adverse events by maximum severity
- adverse events suspected to be related to study treatment
- adverse events leading to permanent study treatment discontinuation
- all adverse events by standardized MedDRA query (SMQ) level
- serious adverse events
- fatal adverse events

Unless otherwise specified, primary system organ classes will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending order of frequency in the QMF149 150/80 µg treatment group. If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once at the system organ class level.

In addition, the most frequent adverse events will be presented by preferred term in descending order of frequency in the QMF149 150/80 µg treatment group.

2.8.2.1 AE reporting for CT.gov and EudraCT

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 2% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2.2 Adverse events of special interest

The number and percentage of patients who reported treatment-emergent adverse events of special interest will be summarized by risk name, preferred term and treatment groups..

Risk names will be sorted alphabetically and, within each risk name, the preferred terms will be sorted in descending order of frequency in the QMF149 150/80 µg treatment group. If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once. If a patient reported more than one adverse event within the same risk, the patient will be counted only once at that risk.

The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify events of special interest. The most recent list of adverse events of special interest at the time of database lock will be used.

Adverse events of special interest will also be analyzed for the following selected subgroups:
- Age group (12 to 17 years, $\geq$ 18 years)

2.8.3 Deaths

A summary of deaths will be presented by primary system organ class, preferred term, and treatment groups regardless of study treatment relationship. In addition, deaths will be summarized by adjudicated primary cause and treatment group.

All the deaths in the clinical database will be listed with both the investigator-reported principal cause and the adjudicated primary cause presented side by side. If adverse events (including asthma exacerbations) leading to death start between the first study treatment and (the last dose + 30 days), then those deaths will be included in summary tables..

2.8.4 Laboratory data

All laboratory samples will be processed through the central laboratory. Laboratory data consist of hematology, biochemistry and urinalysis measurements, including plasma cortisol. All data will be listed with abnormal values flagged.

Baseline laboratory data is defined as the assessment taken 20 minutes pre-dose at Day 1. Checks will be performed to ensure the assessments were indeed taken prior to the first dose of study treatment on Day 1. If this assessment is missing or not confirmed to be pre-dose, the last value taken at the run-in Visit 101 (applicable for hematology, biochemistry and urinalysis) or at an unscheduled visit before the first administration of study treatment will be used for baseline. Otherwise, the baseline laboratory data will be set to missing without imputation.

Laboratory data measured more than 7 days after last inhalation of study treatment are regarded as post-treatment data and will not be summarized, only listed. All data will be included in the analyses regardless of rescue medication use.

The following analyses will be performed by treatment:

- absolute values and change from baseline summarized for continuous laboratory parameters by visit and time point, including the minimum/maximum post-baseline value
- frequency table of results for categorical laboratory parameters by visit and time point, including the worst post-baseline value
- shift tables relative to the normal reference ranges summarizing the change from baseline to the most extreme post-baseline value for each continuous laboratory parameter (except urinalysis parameters)
- shift tables from baseline to the worst post-baseline value for categorical laboratory parameters (except urinalysis parameters)
- the number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria (see Section 6.4 for definition of notable values) 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.

The worst case post-baseline values and the most extreme post baseline values will be determined from all post-baseline data even if from unscheduled and premature discontinuation visits, if not measured more than 7 days after last dose. To determine the worst case, the direction of interest (maximum and/or minimum value) is tabulated for hematology and biochemistry parameters in Section 6.4. For continuous urinalysis parameters the direction of interest is always "High" (maximum value).

For a patient to meet the criterion of a newly occurring clinically notable value, the patient needs to have a baseline value that is not clinically notable for that parameter. For a patient to meet the criterion of a worsening clinically notable value, the patient needs to have a baseline value that is clinically notable and also have a worse post-baseline value. For patients with missing baseline value, any post-baseline notable value will be considered as newly occurring. A listing of all patients with notable laboratory values will be provided.

Maximum change from baseline laboratory result for liver parameters will be summarized. Furthermore, the number and percentage of patients with newly occurring or worsening abnormalities in liver function tests (LFT) will be summarized by treatment and 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 visit (if not measured more than 7 days after last dose) based on the criteria mentioned in the section 5.4.

When a criterion contains multiple laboratory parameters, the criterion will only be considered to have been met when all conditions occur at the same time (i.e., within the same sample). A case where all criteria are met at a post-baseline time point will be considered as newly occurring if the criteria are not met at baseline and will be considered as worsening if the criteria are met at baseline and at least one component is worsening from baseline irrespective of whether the other(s) are better.

Listings of patients with clinically notable LFT values will be provided.

2.8.5 Other safety data

2.8.5.1 ECG

ECG measurements include ventricular rate, QT interval, RR interval, PR interval, QRS duration, and Fridericia's QTc (calculated as $QTcF = QT / 3\sqrt{RR}$(in seconds), where $3\sqrt{}$ denotes the cube root). Furthermore, an overall interpretation of the central cardiologist will be provided as well as a specification of abnormal findings.

Baseline ECG is defined as ECG measured 35 minutes prior to the first dose of study treatment on Day 1. Checks will be performed to ensure the ECG was indeed assessed prior to the first dose of study treatment. If it is missing (or not confirmed to be pre-dose), then the last assessment taken at the run-in Visit 101 or at an unscheduled visit before the first administration of study treatment will be used. Otherwise, the ECG baseline will be set to missing without imputation.

ECG data measured more than 7 days after last inhalation of study treatment are regarded as post treatment data and will not be summarized, only listed. All data will be included in the analyses regardless of rescue medication use.

The following analyses will be performed by treatment:

- absolute values and change from baseline summarized by parameter, visit and time point
- the number and percentage of patients with newly occurring or worsening notable QTcF values (see Section 6.5 for definition of notable values) summarized by 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
- frequency table of results for overall ECG interpretation (normal, abnormal) by visit and time point
- the number and percentage of patients with ECG abnormalities summarized by evaluation type, abnormality finding, visit and time point. In addition, the number and percentage of patients with newly occurring or persistent/recurrent ECG abnormalities at any time point over the treatment period (considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits) will be summarized by evaluation type and abnormality finding

The by-visit/time point summaries will include the maximum QTcF and maximum ventricular rate (even if from post-baseline unscheduled and premature discontinuation visits, if not measured more than 7 days after last dose).

The same approach as for notable laboratory values will be used to define a newly occurring notable QTc value and a worsening notable QTc value.

A listing of all patients with notable QTc values and changes will be provided.

2.8.5.2 Vital signs

Vital signs measurements include systolic and diastolic blood pressure (SBP and DBP), pulse rate, height (for adolescents only) and body weight (at selected visits only).

Baseline vital signs (systolic and diastolic blood pressure (SBP and DBP), pulse rate) are defined as the assessment taken 25 minutes pre-dose at Day 1. Checks will be performed to ensure the assessments were indeed taken prior to the first dose of study treatment on Day 1. If this assessment is missing or not confirmed to be pre-dose, the last value taken at the run-in Visit 101 or at an unscheduled visit before the first administration of study treatment will be used for baseline. Baseline height and weight are defined as the measurements taken at the run-in Visit 101. Missing baseline values will not be imputed.

Vital signs data measured more than 7 days after last inhalation of study treatment are regarded as post-treatment data and will not be summarized, only listed. All data will be included in the analyses regardless of rescue medication use.

The following analyses will be performed by treatment:

- absolute values and change from baseline summarized by parameter, visit and time point
- the number and percentage of patients by parameter, visit and time point with
  - pulse rate < 40 bpm, 40 – 90 bpm, and > 90 bpm
  - SBP < 90 mm Hg, 90 – 140 mm Hg, and > 140 mm Hg
  - DBP < 50 mm Hg, 50 – 90 mm Hg, and > 90 mm Hg
- the number and percentage of patients with newly occurring or worsening notable vital signs values (see Section 6.5 for definition of notable values) summarized by parameter (except height), 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

The by-visit/time point summaries will include the maximum and minimum post-baseline SBP, DBP, and pulse rate values (even if from post-baseline unscheduled and premature discontinuation visits, if not measured more than 7 days after last dose).

The same approach as for notable laboratory values will be used to define a newly occurring notable vital sign value and a worsening notable vital sign value.

A listing of all patients with notable vital sign values and changes will be provided.

2.8.5.3 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.

Number of hospitalizations, number of unscheduled health care provider visits (office and home visit combined), number of visits in emergency room <=24 hours and number of other type of facility will be summarized for asthma related reason. Here “asthma related” reason will combine both asthma related and asthma exacerbation related reason.

Data of the adjudicated hospitalization reports will be used to derive the number of hospitalizations. Asthma – Healthcare Resource Utilization – Outpatient Visits CRF data will be used for summarization of all other type of facilities.

2.11 Interim analysis

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

No interim analysis for efficacy is planned. It is planned that the independent DMC will review semi-blinded (i.e., treatment group named as T01 and T02) safety data. The details of the information flow, confidentiality and specific analyses required for the safety monitoring analysis will be documented in the DMC Charter. The Charter will be finalized prior to semi-blinding the data for the safety monitoring analysis. Since the purpose of the DMC is not based on efficacy for stopping rule, there will be no alpha spent for the safety monitoring analysis. All analyses will be considered exploratory.

3 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.

1. 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 (ie 375/arm) will provide approximately 93% power for item 1 and 77% power for item 2 with multiplicity adjustment.

The sample size calculation was performed in PASS software.

4 Change to protocol specified analyses

Section 2.7.2 Asthma control questionnaire (ACQ) : All the analyses described for ACQ-7 has been included for ACQ-5.

5 Analyses to be reported outside of CSR

5.1 Subgroup analyses

Subgroup analyses for Japanese patients will be performed for the FAS to explore the treatment effect in this sub population. These analyses will only include patients of the respective country.

The following endpoints will be summarized and/or analyzed using similar methods as described in previous sections, if not marked with special symbol.

- Patient disposition
- Protocol deviations
- Analysis sets
- Demographics
- Disease characteristics
- Spirometry at run-in visits and at baseline
- Trough FEV1
- ACQ-7
- Pre-dose trough FEV_1
- Trough FVC
- Pre-dose trough FVC
- Mean morning/evening PEF
- Asthma symptom based on e-diary

- Rescue medication
- Asthma exacerbations
- Asthma Quality of Life Questionnaire (AQLQ-S+12)*
- [redacted]
- Exposure
- Concomitant asthma medications
- Laboratory data
- Vital signs
- ECG
- Adverse events

The specific outputs for the sub population under each endpoint will be specified in the TFLs.

6 Appendix

This appendix gives details about statistical methods in addition to the report text. All analyses will be performed by using SAS Version 9.4.

6.1 Imputation rules

6.1.1 Study treatment

Missing/partial start date or end date of study treatment will not be imputed.

6.1.2 AE date imputation

Rules for imputing AE end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

6.1.3 Concomitant medication date imputation

Rules for imputing the CM end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

6.2 AEs coding/grading

The MedDRA version which will be available at the time of database lock, will be used for the coding purpose of the adverse events.

6.3 Data pooling and assessment windows

Data from unplanned or unscheduled visits or the early treatment/study discontinuation visits will be listed. For patients who do not complete the study treatment, the treatment discontinuation visit will be an unscheduled visit.

Clinical laboratory measurements, vital signs and ECG data from unplanned or unscheduled visits will only be included in the summaries of the notable values and extreme values. All efficacy data (including spirometry data) from these visits will not be used for missing data imputation unless specified otherwise.

Laboratory, vital signs, and ECG values that have complete data and time values will be slotted into pre- or post-dose assessment based on the actual date/time. For values with missing date/time, scheduled visit date and time will be used. This rule will be applied to data from scheduled visits only. If a measurement scheduled as pre-dose is actually performed post-dose, or vice versa, the data will not be used for by time point assessments.

6.4 Laboratory parameters – direction of interest and definition of clinically notable values

The following table shows the direction of interest when analyzing worst case values in form of maximum and/or minimum post-baseline values. If the direction of interest is given as "High" the maximum value will be calculated and used as worst value, if the direction is given as "Low" the minimum value will be taken, and if it is given as "Low and high", both the minimum value and the maximum value will be calculated and presented in summary tables.

Direction of interest for worst case value for laboratory parameters

Laboratory Parameter	Direction of interest for worst case value
A. Hematology	
Hemoglobin	Low
Hematocrit	Low
Erythrocytes	Low
WBC	Low and high
Basophils	High
Eosinophils	High
Lymphocytes	Low and high
Monocytes	High
Neutrophils	Low and high
Platelets	Low and high
B. Chemistry	
Albumin	Low
Alkaline Phosphatase	High
ALT/SGPT	High
AST/SGOT	High
Bilirubin Total	High
Blood Urea Nitrogen (BUN)	High
Creatinine	High
Glucose	Low and high
Gamma GT	High
Potassium	Low and high
Magnesium	Low and high
Uric acid	High
Plasma cortisol	Low and high

The following table shows the criteria for clinically notable laboratory values. Not all parameters have notable criteria defined.

Laboratory parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Hematology		
Hematocrit (v/v)		
Male	*0.37*	
Female	*0.32*	
Hemoglobin (g/L)		
Male	*115*	
Female	*95*	
Platelets (x10E^9/L)	*75*	*700*
WBC (x10^9/L)	*2.8*	*16.0*
Chemistry		
Albumin (g/L)	*25*	-
Alkaline Phosphatase (U/L)	-	*3xULN*
ALT/SGPT (U/L)	-	*3xULN*
AST/SGOT (U/L)	-	*3xULN*
Bilirubin Total (mcmol/L)	-	*34.2*
BUN (mmol/L)	-	*9.99*
Creatinine (mcmol/L)	-	*176.8*
Glucose (mmol/L)	*2.78*	*9.99*
Gamma GT (U/L)	-	*3 x ULN*
Potassium (mmol/L)	*3*	*6*
Magnesium (mmol/L)	*0.51*	*1.07*

v = volume, ULN = upper limit of normal

Notable liver function test values

Criterion
ALT > 3 x the upper limit of normal range (ULN) ALT > 5 x ULN ALT > 8 x ULN ALT > 10 x ULN ALT > 20 x ULN
ALT or AST > 3 x ULN ALT or AST > 5 x ULN ALT or AST > 8 x ULN ALT or AST > 10 x ULN ALT or AST > 20 x ULN
Total bilirubin > 1 x ULN Total bilirubin > 1.5 x ULN Total bilirubin > 2 x ULN Total bilirubin > 3 x ULN
ALP > 1.5 x ULN ALP > 2 x ULN ALP > 3 x ULN ALP > 5 x ULN
ALT or AST > 3 x ULN and total bilirubin > 1.5 x ULN ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 5 x ULN and total bilirubin > 2 x ULN ALT or AST > 8 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN and total bilirubin > 2 x ULN ALT or AST > 20 x ULN and total bilirubin > 2 x ULN
ALP > 3 x ULN and total bilirubin > 2 x ULN ALP > 5 x ULN and total bilirubin > 2 x ULN
ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN and ALP < 2 x ULN (Hy's law)
ALT or AST > 3 x ULN and (nausea or vomiting or fatigue or general malaise or abdominal pain or (rash and eosinophilia))*

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase
* Based on the signs/symptoms information as recorded on the liver events eCRF, not the adverse events eCRF.

6.5 Vital signs and ECG – definition of clinically notable values

The following table shows the clinical notable criteria for vital signs.

Vital sign parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Notable value considering newly occurring or worsening cases		
Systolic blood pressure (mmHg)	< 75	> 200
Diastolic blood pressure (mmHg)	< 40	> 115
Pulse rate (bpm)	< 40	> 130
Notable change from baseline		
Systolic blood pressure (mmHg)	≤ 90 and decrease from baseline by ≥ 20	≥ 180 and increase from baseline by ≥ 20
Diastolic blood pressure (mmHg)	≤ 50 and decrease from baseline by ≥ 15	≥ 105 and increase from baseline by ≥ 15
Pulse rate (bpm)	≤ 50 and decrease from baseline by ≥ 15	≥ 120 and increase from baseline by ≥ 15

The following table shows the clinical notable criteria for QTcF.

Clinical notable criteria for QTcF (Fridericia's formula)

ECG parameter (unit)	Clinically notable range
Notable value considering newly occurring or worsening cases	
QTc (msec)	> 450 (male)
QTc (msec)	> 460 (female)
QTc (msec)	> 500 (both)
Notable change from baseline	
QTc	30 – 60
QTc	> 60
Combined criterion	
QTc (msec)	> 500 & increase from baseline > 60

6.6 Statistical methodology and assumptions

SAS codes for all statistical methodology described in this section will be included as programming note in TFL Shells.

- **Mixed Model Repeated Measures (MMRM)**

The following MMRM ANCOVA will be used for trough FEV_1, ACQ-7, and other data:

Dependent variable = intercept + treatment + age group + region + baseline value + FEV_1 prior to inhalation + FEV_1 within 15 to 30 min post inhalation + visit + treatment*visit + baseline value*visit + random effect of center nested within region + error.

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).

For the final analysis, if the model does not converge with unstructured covariance matrix, the compound symmetry covariance structure will be used, if the model still does not converge the random effect will be removed, if the model converges after removing the random center effects, the original model without random center effects will be re-assessed

The SAS procedure PROC MIXED will be used for analysis. Results will be presented with least squares mean (LSM) and standard error (SE) for treatment effects and LSM, SE, associated two-sided 95% confidence interval, and two-sided p-value for the treatment contrast.

In the analysis of laboratory data [redacted], the covariates FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation will not be included in the MMRM.

- **Tipping point analysis for trough FEV1 at Week 12**

As a sensitivity analysis to evaluate the impact of missing data, a tipping point analysis will be performed for the primary endpoint trough FEV_1 at Week 12. The delta-adjusting approach described in Ratitch et al (2013) will be used to find the tipping point, in a spectrum of conservative missing not at random (MNAR) assumptions, at which conclusions change from being favorable to QMF149 to being unfavorable. The basic idea is to impute the missing values using a regression based multiple imputation (MI) method based on the MAR assumption. The imputed Week 12 values for the QMF149 arms are then adjusted by a delta value.

The endpoint is assumed to have a normal distribution at Day 2 and Week 12. The primary analysis is performed on the delta-adjusted datasets to see if the conclusions change. If not, a larger delta is chosen and the process is repeated until the conclusion is overturned. The tipping point is the delta value which will cause the QMF149 vs. MF comparison on the primary endpoint to be no longer statistically significant. A series of analyses on a range of delta values will be performed to find the tipping point. For each delta value, the following steps will be performed.

1. Impute missing covariates (baseline FEV_1, FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation value) and missing values at Day 2 and/or Week 12 using the MI approach based on the fully conditional specification (FCS) method for 100 times and obtain 100 imputed datasets. Missing baseline FEV_1, FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation value will be imputed separately for each treatment group using a model with age group, geographic region, and the respective other covariates (baseline FEV_1, FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation value) as predictors. Missing Day 2 values will be imputed separately for each treatment group using a model with the imputed values of age group, geographic region, baseline FEV_1, FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation value as predictors. Missing Week 12 values will be imputed separately for each treatment group using a model with the imputed values of age group, geographic region, baseline FEV_1, FEV_1 prior to inhalation, FEV_1 15 to 30 min post inhalation, and Day 2 value as predictors.

2. After the imputation obtained in above step, for subjects in the QMF149 treatment arms only, make the imputed value at Week 12 worse by a value of delta (i.e., subtract delta from the imputed value at Week 12). Note: delta = 0 represents the standard missing at random (MAR) based MI.

3. The final multiply-imputed dataset where all missing values are filled will be analyzed (by imputed dataset) using a linear mixed model with treatment, age group, geographic region, baseline FEV_1, FEV_1 prior to inhalation, and FEV_1 within 15 to 30 min post inhalation as predictors.

4. The results for the treatment effect from the 100 datasets will then be combined using Rubin's rule. If the combined results does not change the conclusion (i.e., the QMF149 treatment effect is still statistically significantly superior to MF), a larger delta will be chosen and Steps 1-4 will be repeated using the datasets from Step 2 until the tipping point is found (when $p > 0.05$).

- **Logistic regression analysis**

The analysis of 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 performed using the following steps:

1. Impute missing covariates (baseline ACQ-7, FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation value) and missing continuous ACQ-7 values at Day 30 and/or Week 12 using the MI approach based on the fully conditional specification (FCS) method for 100 times and obtain 100 imputed datasets. Missing baseline ACQ-7, FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation value will be imputed separately for each treatment group using a model with age group, geographic region, and the respective other covariates (baseline ACQ-7, FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation value) as predictors. Missing Day 30 values will be imputed separately for each treatment group using a model with the imputed values of age group, geographic region, baseline ACQ-7, FEV_1 prior to inhalation and FEV_1 15 to 30 min

post inhalation value as predictors. Missing Week 12 values will be imputed separately for each treatment group using a model with the imputed values of age group, geographic region, baseline FEV_1, FEV_1 prior to inhalation, FEV_1 15 to 30 min post inhalation, and Day 30 value as predictors.

The SAS procedure PROC MI will be used and this will result in 100 copies of the original dataset.

2. Then continuous ACQ values will be converted into binomial responses (1= an improvement of at least 0.5, 0= no improvement) and generalized estimating equation (GEE) method will be used to analyze the dataset. The GEE model will include terms for treatment, age (12 to 17 or ≥ 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 SAS procedure PROC GENMOD will be used.

Combining results from X copies of original dataset:

3. In the next step, results from each copy, obtained from GEE method will be combined for the inference using Rubin's rule. The SAS procedure PROC MIANALYZE will be used for combining the results considering the linear scale and then we will take exponential of combined result to obtain the odds ratio.

The estimated adjusted odds ratio will be displayed along with the associated 95% confidence interval and p-value (two-sided).

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 the same procedure as mentioned above for ACQ-7, with the following changes:

Replace ACQ-7 in all steps by AQLQ. Change step 1 as follows.

1. In Step 1, Impute missing covariates (baseline AQLQ, FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation value) and missing continuous AQLQ values at Week 12 using the MI approach based on the fully conditional specification (FCS) method for 100 times and obtain 100 imputed datasets. Missing baseline AQLQ, FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation value will be imputed separately for each treatment group using a model with age group, geographic region, and the respective other covariates (baseline AQLQ, FEV_1 prior to inhalation and FEV_1 15 to 30 min post inhalation value) as predictors. Missing Week 12 values will be imputed separately for each treatment group using a model with the imputed values of age group, geographic region, baseline AQLQ, FEV_1 prior to inhalation, FEV_1 15 to 30 min post inhalation.

- **Linear Mixed Model Analysis of Covariance (ANCOVA)**

The following linear mixed ANCOVA model will be used for diary data summarized over 12 weeks:

Dependent variable = intercept + treatment + age group + region + baseline value + FEV_1 prior to inhalation + FEV_1 within 15 to 30 min post inhalation + random effect of center nested within region + error.

The SAS procedure PROC MIXED will be used for analysis. Results will be presented with LSM and SE for treatment effects and LSM, SE, associated two-sided 95% confidence interval, and two-sided p-value for the treatment contrast.

- **Cox regression analysis**

A Cox proportional hazards regression model stratified by age (12 to 17, ≥ 18 years) will be applied in time-to-event analyses to test the null-hypothesis H_0: $\lambda_{QMF}(t) / \lambda_{Control}(t) = 1$, where $\lambda(t)$ is the hazard function for the failure time of patients treated with QMF and the control group, respectively.

The SAS procedure PHREG will be used for analysis. Results will be presented with adjusted hazard ratio for the treatment group comparison and associated 95% confidence interval and two-sided p-value. P-value will be obtained from the Wald chi-squared statistic testing the null-hypothesis that the parameter estimate for the respective treatment effect is 0 (then the hazard ratio is exp(0) = 1).

No check for the validity of proportional hazards assumptions will be done.

- **Generalized linear model assuming a negative binomial distribution**

The annual rate of asthma exacerbations (by exacerbation category) will be analyzed using a generalized linear model assuming a negative binomial distribution.

The time at risk for a patient is defined as the duration of exposure in days + 1 day and the log(time at risk in years) will be used as the offset variable in the model.

The SAS procedure GENMOD will be used for analysis. Treatment group ratio of exacerbation rate will be presented together with 95% confidence interval and two-sided p-value.

6.7 Rule of exclusion criteria of analysis sets

The following table provides the protocol deviations (PD) and other criteria leading to partial or complete exclusion from analyses sets

Deviation ID	Description of Deviation
Deviations leading to exclusion from all analyses sets	
INCL01A	Informed consent not obtained
EXCL22A	Patient with custodial sentence. Do not have permanent residence or detained under local mental health legislation/regulation
Deviations leading to exclusion from RAN, FAS, PPS [redacted] analysis set	
OTH05A	Patient received study drug but was not randomized
Deviations leading to exclusion from FAS, PPS, Safety [redacted] analysis set	
OTH04A	Patient randomized but did not receive study drug
Deviations leading to exclusion from FAS and PPS	
OTH03A	Patient Randomized more than once in this study or randomized in another study
Deviations leading to exclusion from PPS	
INCL02A	Age < 12 years or > 75 years or missing
INCL03A	No documented diagnosis of Asthma for at least 3 months prior to Visit 1
INCL04A	Patients who are not treated with low dose ICS, with or without controller (ie, LABA, Leukotriene Receptor Antagonist (LTRA) at stable dose for at least 1 month (=30 days) prior to Visit 1
INCL05A	Adult patients with ACQ-7 score < 1.5 at visit 101 and/or visit 102
INCL06A	Adolescent patient on ICS only (without LABA), have ACQ -7 < 1.5 at visit 101 and/or visit 102
INCL06B	Adolescent patient on ICS+LABA have ACQ-7 score < 1 or >= 1.5 at visit 101
INCL06C	Adolescent patient on ICS+LABA have ACQ-7 score < 1.5 at visit 102
INCL07A	Pre Bronchodilator FEV1 < 60% or >= 90% of predicted normal after withholding bronchodilator both at visit 101 and 102
INCL08A	Patients for whom increase in FEV1 < 12% and/or < 200 ml within 30 minutes after administration of 400 microgram salbutamol/360 microgram albuterol (or equivalent dose) at Visit 101
INCL08B	Patient has not achieved an acceptable spirometry result does not have historical reversibility
INCL08C	Patient has not achieved assessments according to ATS/ERS criteria
EXCL01A	Patients who have smoked or inhaled tobacco products (including electronic ciggarettes) within 6 months prior to visit 1
EXCL01B	Patient has a smoking history of >= 10 pack years or missing
EXCL02A	Adults: who had an asthma attack or exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 weeks of visit 1
EXCL02B	Adults: who had an asthma attack or exacerbation requiring systemic steroids or hospitalization or emergency room visit between visit 1 and 102

Deviation ID	Description of Deviation
EXCL02C	Adolescents: who had an asthma attack or exacerbation requiring systemic steroids or hospitalization or emergency room visit within 6 months prior to visit 1
EXCL02D	Adolescents: who had an asthma attack or exacerbation requiring systemic steroids or hospitalization or emergency room visit within: between Visit 1 and 102
EXCL03A	History of Intubation for severe asthma attack or exacerbation
EXCL05A	Patients with respiratory tract infection or asthma worsening between Visit 1 and Visit 102
EXCL05B	Patients with respiratory tract infection or asthma worsening within: 4 weeks prior to visit 1
EXCL06A	Clinically significant oropharyngeal candidiasis at Visit 102 or earlier, with or without treatment.
EXCL07A	Patient with chronic condition affecting upper respiratory tract (eg. chronic sinusitis)
EXCL08A	Patient have a medical history of chronic lung diseases other than asthma
EXCL11A	Other investigational drugs used within 30 days of visit 1 or 5 half lives or untill return of baseline pharmacodynamic effect whichever is longer.
EXCL21A	Patient on Maintenance Immunotherapy (desensitization) for allergies less than 3 months prior to Visit 101
EXCL21B	Patient on Maintenance Immunotherapy for allergies more than 3 months prior to Visit 101 but expected to change therapy throughout the study
EXCL21C	Monoclonal antibodies: IgE inhibitors and other asthma related biologics (e.g. omalizomab) IL-5 inhibitors (e.g. mepolizomab) taken within 4 months prio to run-in 101.
EXCL23A	Patient associated with any member of study team
EXCL24A	Patient unable to use the dry powder inhalers
EXCL25A	Patient has history of alcohol or other substance abuse since last 10 years
EXCL34A	LAMA taken less than 3 months prior to Visit 101
COMD09A	Parenteral or oral corticosteroids taken within 4 weeks prior to run in 101
COMD10A	Intra-muscular depot corticosteroids taken within 3 months prior to Run in 101
COMD12A	Xanthines taken within 7 days prior to Run In 101
COMD13A	Systemic mast cell stabilizers taken within7 days prior to Run in visit 101
OTH01A	Patient not having correct run in medication (i.e. 100mcg accuhaler or 125 mcg via MDI inhaler) or dose eqivalent
OTH07A	Patient took study treatment not as per protocol (i.e not inhaled the study medication)
OTH12A	Compliance failure of the patient influencing the safety and efficacy data as per investigator judgement
OTH14A	Patient receiving investigational drug other than study drug during the course of the study
COMD02A	SAMA taken less than 8 hours prior to visit 101
COMD03A	Fixed combinations of β2-agonists and inhaled corticosteroids taken within 48 hours prior to Visit 101

Deviation ID	Description of Deviation
COMD04A	Fixed combinations of short-acting β2-agonist and short-acting anticholinergic taken within 8 hours prior to Visit 101
COMD05A	Leukotriene Receptor Antagonist (LTRA) and leukotriene synthesis inhibitors taken within 7 days prior to Run-in (Visit 101)
COMD06A	LABA b.i.d taken within 48 hours prior to visit 101
COMD07A	LABA o.d continuing at visit 1
COMD08A	Short Acting B2 Agonist, other than rescue medication is continuing after visit 1
WTH01A	Patient still on study treatment even after having 1 severe asthma exacerbation requiring treatment with systemic corticosteroids or hospitalizations
WTH06A	Blind broken and study treatment not permanently discontinued
COMD16A	Banned asthma related concomitant Medications used during the study*
Deviations leading to exclusion of data collected after occurence of that event, from all analyses set	
WTH07A	Study procedures performed after withdrawing of informed consent

[redacted]

7 Reference

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