NOVARTIS

Clinical Development

QVM149B (QMF149: Indacaterol acetate/Mometasone furoate)

CQVM149B1305 / NCT03100500

A multicenter, open-label, single arm, 52-week treatment study to assess the safety of QMF149 in Japanese patients with asthma

Statistical Analysis Plan (SAP)

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13Feb2017	Prior to FPFV	Creation of Final Version	NA
17Aug2018	Prior to DB lock for IA	Protocol amendment, consistency with protocol and pivotal studies and dry run review	• Updated defenition of categories for pre-bronchodilator FEV1 in % of predicted FEV1 at screening Visit 2 in Section2.2.1, and conducted same upadate in Section 2.3 and section 2.5.4 • Removed ATC code for summarizing concomitant medication in Section 2.4.2 • Removed list of special interest AEs in Section 2.5.2 • Updated definition of baseline in PEF in Section 2.6.2 • Added summary in PEF by 4 weekly interval and definition for post baseline in Section 2.6.2 • Added summary in ACQ-7 at week 12 in Section 2.6.2 • Removed a category, “QTc <30”, in section 2.7.3.1 • Replaced notable criterion for Sodium with one for Magnesium in section 5.3

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This document contains details of the statistical methods that will be used in the phase III clinical trial CQVM149B1305. This study is designed to provide long term safety data of QMF149 in Japanese patients with asthma for the registration of QMF149 in Japan.

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

Important information and details are given in the following sections.

1.1 Study design

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

This study is designed to obtain safety data of QMF149 in 59 Japanese asthma patients. Details of sample size are described in Section 3 in this document.

No randomization is planned in this study.

The primary objective of this study is to assess the safety/tolerability of 52 weeks of treatment with QMF149 (150/320 µg, once daily), particularly with regard to treatment emergent adverse event reporting in Japanese patients with inadequately controlled asthma.

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

An interim analysis for 6-month data will be performed for the initial New Drug Application submission in Japan. This analysis will be performed after all patients have been enrolled and completed Visit 107 (Week 26) or discontinued the study. Details of the interim analysis are described in Section 2.13 in this document.

1.2 Study objectives and endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the safety/tolerability of 52 weeks of treatment with QMF149 (150/320 µg, once daily) in Japanese patients with inadequately controlled asthma.	• The incidence and severity of treatment emergent adverse events (AEs) over 52 weeks of treatment
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the safety of QMF149 over 52 weeks of treatment	• ECG, vital sign (blood pressure, pulse rate), laboratory parameters (hematology, clinical chemistry and urinalysis), plasma cortisol over 52 weeks of treatment
• To assess the efficacy of QMF149 in terms of lung-function in Japanese patients with inadequately controlled asthma.	• Change from baseline of pre-dose FEV_1 measured after 26 and 52 weeks treatment • Change from baseline of morning and evening PEF during 52 weeks treatment

Objective(s)	Endpoint(s)
• To assess the efficacy of QMF149 in terms of asthma control.	• Change from baseline of ACQ-7 after 26 and 52 weeks treatment • Responder rate of patients achieving the minimal important difference (MID) of ACQ-7 ≥ 0.5 after 26 and 52 weeks treatment
• To assess the efficacy of QMF149 in terms of rescue medication use	• Change from baseline of rescue medication use during 52 weeks treatment

[redacted]

2 Statistical methods

2.1 Data analysis general information

All data analysis will be performed by Novartis according to the data analysis section 9 of the study protocol using the most actual version of SAS at the time of database lock.

General descriptive statistical rules to summarize quantitative or qualitative parameter are: continuous variables will be summarized using descriptive statistics (number of non-missing data, mean, median, standard deviation, 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.

The analysis will be conducted on all subject data at the time the trial ends.

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

2.1.1 General definitions

Study day is defined as the number of days since the date of first dose of study medication. The date of first dose of study medication was defined as Day 1 and the day before the first dose of study medication was 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 medication,

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

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

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

In general, baseline is defined as the last measurement before the first dose of study drug at Day 1. Refer to the baseline definitions for each analysis described in the later sections.

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

Data from unplanned or unscheduled visits or the early treatment/study discontinuation visits will be listed. For patients who do not complete the study, 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, their respective 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 but will be included in the summaries of the notable values and extreme values.

2.2 Analysis sets

The Safety Set will consist of all patients who received at least one dose of study medication during this study. The Safety Set will be used in the analysis of all safety variables.

Full Analysis Set (FAS) will consist of all patients who entered in the treatment epoch of this study and received at least one dose of study medication during this study. The efficacy analysis will be based on FAS.

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

2.2.1 Subgroup of interest

- Age (18 - < 65years, ≥ 65years)
- Sex (male, female)
- Pre-bronchodilator FEV_1 in % of predicted FEV_1 at screening Visit 2 (< 50%, 50% - < 60%, 60% - ≤ 85%, > 85%)

Refer to the Section 2.5.4 in this document.

2.3 Patient disposition, demographics and other baseline characteristics

Demographics and baseline characteristics including age, sex, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, screening spirometry parameters: (FEV1, FVC, and FEV_1/FVC), FEV_1 reversibility, percentage of predicted FEV1, baseline PEF, duration of asthma, history of asthma exacerbations, smoking history, prior concurrent medications (asthma-related and non-asthma-related), vital signs (systolic and diastolic blood

pressure, pulse rate), QTc using Fridericia's correction and baseline ACQ-7, will be summarized on safety set.

Baseline is defined as the last measurement before first dose of study drug. Missing baseline will not be imputed, unless otherwise specified.

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

- Age into 18 - 39 years, 40 - 64 years, and ≥ 65 years;
- BMI into < 25.0 kg/m^2, 25.0 - 30.0 kg/m^2, and > 30.0 kg/m^2;
- 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 medical care into 1, 2, 3, ≥ 4;
- pre-bronchodilator FEV_1 into < 50 %, 50% - < 60%, 60% - ≤ 85%, > 85% of predicted FEV_1;
- ACQ-7 into < 1.5, 1.5 - < 2, 2 - < 2.5, ≥ 2.5.

Medical history will be coded with the Medical Dictionary for Regulatory Activities terminology (MedDRA) using the most actual version at the time of database lock. History/conditions will be summarized for the Safety 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.

In addition, medical histories/current medical conditions will be summarized by their status at baseline (current medical conditions, past medical conditions) and primary system organ class. Current medical conditions are defined as those which were reported as "Ongoing" at baseline.

2.3.1 Patient disposition

For each study epoch (i.e., screening, 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.

The number of patients included in each analysis set will be tabulated, as well as the reasons for exclusions from analysis sets. Patient exclusion from analysis sets will be listed for all patients with reasons for exclusion (including both CSR-reportable and non CSR-reportable protocol deviations).

The number of patients with protocol deviations will be tabulated by category (e.g., selection criteria not met, prohibited concomitant medication, key procedures not performed as per protocol) and deviation for the Safety Set. Protocol deviations will be listed with date and study day of occurrence, deviation and analysis populations from which patients are excluded.

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

2.4.1 Study treatment / compliance

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

The duration of exposure and the number of patients who completed the study medication and who discontinued from the study medication will be summarized. 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 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 drug for each 1 - 29 days, 30 - 86 days, 87 - 183 days, 184 - 254 days, 255 - 365 days, and > 365 days. The number of patients who completed the 52-week study treatment and who discontinued prematurely will be shown including the reasons for discontinuation of study treatment.

Treatment compliance with study medication over the study period will be summarized. Compliance will be calculated by counting the days where study drug 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. Compliance will be categorized into < 80% and 80% - 100% and summarized for the Safety Set.

2.4.2 Prior, concomitant and post therapies

Medications started and stopped prior to study drug, and taken concomitantly will be summarized for the Safety Set. Prior medications are defined as drugs taken and stopped prior to first dose of study medication. Any medication given at least once between the day of first dose of study medication and last day of study visit will be a concomitant medication, including those which were started pre-baseline and continued into the treatment period.

Concomitant therapies will be recorded, listed and summarized separately for asthma related medications/non-drug therapies and other medications.

Separate tables will be provided for medications which were started and stopped prior to the first dose of study drug and medications which were taken concomitantly to the study drug (regardless of whether continued or started after the first dose of study drug).

Asthma medications will be summarized by the route of administration, the recorded pre-specified 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 the coded preferred terms.

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 drug.

Short acting beta2 agonist (SABA) rescue medication 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.

2.5 Analysis of the primary objective

The primary objective of this study is to assess the safety/tolerability of 52 weeks of treatment with QMF149 (150/320 µg, once daily), particularly with regard to treatment emergent adverse event reporting in Japanese patients with inadequately controlled asthma.

2.5.1 Primary endpoint

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

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

2.5.2 Statistical hypothesis, model, and method of analysis

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

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

- All adverse events
- All adverse events by time at onset (≤ 12 weeks, > 12 - ≤ 26 weeks, > 26 weeks)
- Serious adverse events
- Adverse events by maximum severity
- Adverse events suspected to be related to study drug
- Adverse events leading to permanent study drug discontinuation
- Adverse events of special interest

All adverse events including asthma exacerbations, coded with MedDRA using the most actual version at the time of database lock, will be listed.

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. 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.

For AEs by maximum severity, missing severity will be assumed to be severe in the summary table.

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 treatment epoch 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.

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.

2.5.3 Handling of missing values/censoring/discontinuations

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

2.5.4 Supportive analyses

Adverse events of special interest will also be analyzed for the following selected subgroups:

- Age (18 - < 65years, ≥ 65years)
- Sex (male, female)
- Pre-bronchodilator FEV_1 in % of predicted FEV_1 at screening Visit 2 (< 50%, 50% - < 60%, 60% - ≤85%, > 85%)

2.6 Analysis of secondary efficacy objective(s)

2.6.1 Secondary endpoints

The secondary efficacy measurements (Spirometry, PEF, Rescue medication and ACQ-7) during the study will be summarized for the FAS.

Baseline is defined as the last measurement before first dose of the study drug, unless otherwise specified.

Measurements made after patients discontinue study treatment (off-treatment measures) will not be used for any efficacy evaluation.

2.6.2 Statistical hypothesis, model, and method of analysis

Spirometry

For FEV_1 and FVC, the baseline is defined as the mean of the values taken in the clinic at 45 and 15 min prior to first dose at Visit 101. 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 screening Visits 2 or at unscheduled screening visits will be used as the baseline. If the FEV_1, FVC measurements are missing both on Day 1 and at screening visits, the respective baseline values will be set to missing.

The pre-dose FEV_1 is defined as the mean of the pre-dose 45 and 15 min FEV_1 values. The pre-dose FVC is defined as for the pre-dose FEV_1. If any of the pre-dose 45 and 15 min values contributing to the pre-dose value are collected within 7 days of systemic corticosteroid use, 6 hours of rescue medication use, or actual measurement times are post-dose 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 pre-dose value. If both values are missing, then pre-dose value will be missing.

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

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

Peak Expiratory Flow Rate (PEF)

PEF(liters/min) will be analysed separately for morning and evening values.

The baseline values are defined as the average from all non-missing records taken in the screening period for 14 days before Day 1 administration (in case they were measured before the first intake of study drug as scheduled in the study protocol). When calculating the baseline value there is no limitation to the 14 days immediately prior to Day 1 administration. If a patient has less than 7 days with non-missing data, then the respective baseline value will be set to missing.
The post-baseline measurements start with the morning recordings at Day 2 and end with the evening recordings at the day of last dose. Similar calculations as for baseline data will be done. For the first 26 weeks and the whole 52 weeks, 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 in the period of interest. For 4-week intervals (defined as 28 days), summary values will only be calculated if a patient has at least 50% of their diary days (i.e. 14 days) of non-missing data. 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 interval. The mean morning/evening PEF and the mean change from baseline will be summarized for the first 26 weeks (defined as up to Visit 107), and for the whole 52 weeks of treatment period (defined as up to Visit 111), and will be summarized by 4 weekly interval.

Rescue medication

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

The baseline and post-baseline valuses are defined in the same way as for the PEF.

The mean daily number of puffs of rescue medication use will be calculated for each patient over the first 26 weeks of treatment period, over the whole 52 weeks of treatment peroid and over the screening period (which will be used as the baseline value) as described for the PEF. This will be done separately for morning (night-time), evening (daytime), and daily (night-time plus daytime) rescue medication use. 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. Where the number of puffs of rescue medication is missing but the rest of the e-diary has non-missing data, the number of puffs will be assumed to be zero.

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

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

Asthma Control Questionnaire 7 (ACQ-7)

The baseline value is defined as the score obtained at Day 1. If the value is missing, the last measurements from screening visit 2 or unscheduled screening visits will be used.

ACQ-7 and the change from baseline at 12, 26 and 52 weeks of the study treatment will be summarized.

The proportion of patients who achieve an improvement of at least 0.5 in ACQ-7 (i.e., a decrease of ACQ-7 score of at least 0.5 from baseline) at 26 and 52 weeks visits will be summarized.

2.6.3 Handling of missing values/censoring/discontinuations

No imputation will be done for missing data.

2.7 Safety analyses

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

Baseline is defined as the last measurement before first dose of the study drug, unless otherwise specified.

No imputation will be done for post-baseline missing data.

Post-baseline measurements comprise recordings up to the last dose of study drug + 7 days for laboratory, ECG, vital signs, non-serious AE and up to the last dose of study drug + 30 days for SAEs and death.

2.7.1 Adverse events (AEs)

Refer to the AEs analyses described in Section 2.5 in this document.

2.7.1.1 Adverse events of special interest / grouping of AEs

Refer to the AEs analyses described in Section 2.5 in this document.

Deaths

A summary of deaths according to the affected primary system organ class and preferred term for the investigator-reported principal cause of death and for the adjudicated cause of death will be separately presented regardless of study drug relationship.

All the deaths in the clinical database will be listed with both the investigator-reported principal cause and the adjudicated cause presented side by side, but only those between the first treatment and (the last dose + 30 days) will be included in summary tables.

See Section 2.5 in this document as well.

2.7.2 Laboratory data

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

All laboratory data will be listed with abnormal values flagged.

Baseline laboratory data is defined as the assessment taken 30 minutes pre-dose at Day 1. If this assessment is missing or not confirmed to be pre-dose, the last value taken at the screening Visit 2 or at an unscheduled visit before the first administration of study drug will be used for baseline. Otherwise, the baseline laboratory data will be set to missing.

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

The following analyses will be performed:

- absolute values and change from baseline summarized with standard descriptive statistics for continuous laboratory parameters by visit and time point
- frequency table of results for categorical laboratory parameters by visit and time point
- shift tables relative to the normal reference ranges summarizing the change from baseline to post-baseline by visit and time point for each continuous laboratory parameter
- shift tables from baseline to post-baseline by visit and time point for categorical laboratory parameters
- the number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria (see Section 5.3 in this document 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 by-visit/time point summaries will include the worst case post-baseline values (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 5.3. 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.

Furthermore, the number and percentage of patients with newly occurring or worsening abnormalities in liver function tests (LFT) at any time post-baseline will be summarized based on the following criteria:

- **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.

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 all patients with notable laboratory values and also with clinically notable LFT values will be provided.

2.7.3 Other safety data

2.7.3.1 ECG and cardiac imaging data

Data from the ECG (including ventricular rate, QT interval, RR interval, PR interval, QRS duration , Fridericia's QTc and Bazett's QTc) will be summarized at 30 min pre-dose, and at 30 min post-dose (at selected visits only).

Furthermore, an overall interpretation of the central cardiologist will be provided as well as a specification of abnormal findings. For qualitative assessments, if multiple ECG values were taken, the worst case will be chosen for all summaries.

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

Baseline ECG is defined as ECG measured 30 minutes prior to the first dose of study drug on Day 1. If it is missing (or not confirmed to be pre-dose), then the last assessment taken at the screening Visit 2 or at an unscheduled visit before the first administration of study drug will be used. Otherwise, the ECG baseline will be set to missing without imputation.

QTc will be calculated from the QT interval and RR (in seconds) by two methods:

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

The following analyses will be performed:

- 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 /QTcB values (see bellow 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 and with shift tables from baseline to the worst interpretation during treatment
- 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/QTcB 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 QTcF/QTcB value and a worsening notable QTcF/QTcB value.

A listing of all patients with notable QTcF/QTcB values and changes will be provided.

The following table shows the clinical notable criteria for QTcF/QTcB.

Clinical notable criteria for QTcF and QTcB

ECG parameter (unit)	Clinically notable range
Notable value considering newly occurring or worsening cases	
QTc (ms)	> 450 (male)
QTc (ms)	> 460 (female)
QTc (ms)	> 500
Categories used for the change from baseline	
QTc	30 – 60
QTc	> 60

2.7.3.2 Vital signs

Vital signs measurements include systolic and diastolic blood pressure (SBP and DBP), and pulse rate.

Vital signs data measured more than 7 days after last inhalation of study drug 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.

Baseline vital signs are defined as the assessment taken 30 minutes pre-dose at Day 1. If this assessment is missing or not confirmed to be pre-dose, the last value taken at the screening Visit 2 or at an unscheduled visit before the first administration of study drug will be used for baseline.

The following analyses will be performed:

- 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 mmHg, 90 – 140 mmHg, and > 140 mmHg
  - DBP < 50 mmHg, 50 – 90 mmHg, and > 90 mmHg
- the number and percentage of patients with newly occurring or worsening notable vital signs values (see bellow for definition of notable values) summarized by 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 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.

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

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

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

Not applicable.

2.11 Biomarkers

Not applicable.

[redacted]

2.13 Interim analysis

[redacted]

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

3 Sample size calculation

Since asthma is a chronic disease, and QMF149 is expected to be administered over a long period, safety in long-term treatment needs to be confirmed. “Regarding sample size and treatment period required to assess safety at the clinical study stage of a new drug anticipated to be administered for a non-fatal disease over a long period” (Notification No. 592 of the Pharmaceuticals and Cosmetics Division, Pharmaceutical Affairs Bureau, MHLW, dated 24-May 24, 1995), this notification requires to collect safety data of at least 100 patients who receive the drug over one year. CQVM149B2301 and 2302 study were planned to collect

efficacy and safety data of about 41 Japanese Asthma patients exposed to QMF149. Therefore this study, CQVM149B1305, is designed to obtain safety data of approximately 59 Japanese asthma patients exposed to QMF149. Since a 25% screening failure rate and a 10% dropout rate are expected, approximately 88 patients will need to be screened in order to collect approximately 66 patients who enter the treatment epoch and to collect a total of approximately 59 completed patients.

4 Change to protocol specified analyses

No change from protocol specified analysis is made.

5 Appendix

5.1 Imputation rules

No imputation is planed in this study.

5.2 AEs coding/grading

Refer to the AEs analyses described in Section 2.5 in this document.

5.3 Laboratory parameters derivations

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
Leukocytes	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
Sodium	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.

Clinical notable criteria for selected laboratory tests

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
Leukocytes (x10^9/L)	2.8	16.0
Chemistry		
Albumin (g/L)	25	-
Alkaline Phosphatase (U/L)	-	3 x ULN
ALT/SGPT (U/L)	-	3 x ULN
AST/SGOT (U/L)	-	3 x ULN
Bilirubin Total (µmol/L)	-	34.2
BUN (mmol/L)	-	9.99
Creatinine (µmol/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

5.4 Statistical models

5.4.1 Primary analysis

Not applicable.

5.4.2 Key secondary analysis

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

The following protocol deviations will be considered as major and will lead to exclusion of patients from the FAS or the Safety Set:

- Patient received study drug but not intended to enter in the treatment epoch of this study (excludes from FAS)

Note: The list will be completed when the major PDs are defined and will be updated shortly before database lock.

Protocol deviations will lead to patient classification into the analysis sets as follows:

Analysis set exclusions based on population codes

Analysis set	Population codes that cause a subject to be excluded
SAF	2, 3
FAS	1, 3

Population code text

Population Code	Population code - text
0	INCLUDE IN EVERYTHING
1	EXCLUDE FROM FULL ANALYSIS SET (FAS)
2	EXCLUDE FROM SAFETY
3	EXCLUDE FROM FAS AND SAFETY

Note that the population codes will be derived in the analysis datasets and are not part of the source data.

Unless otherwise stated, summary tables, figures and listings will be on all subjects included in the analysis set under consideration.

Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
TRT01	Patient was entered treatment epoch but no study drug was taken	Excluded form FAS and Safety Set analysis
TRT02	Patient received wrong treatment or expired drug	Excluded form FAS analysis

6 Reference

Not applicable.