NOVARTIS

Clinical Development

QMF149

CQMF149G2203 / NCT04589663

An open-label, two-period, single-sequence, crossover study to compare the systemic exposure of a single inhaled dose of mometasone furoate (MF) when administered alone via the MF Twisthaler® (TH) to a single inhaled dose of QMF149 indacaterol acetate/MF fixed dose combination when administered via the Concept 1 (Breezhaler®) device in ≥ 6 to <12 year old asthma patients

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
01-Jun-2021	Prior to DB Lock	Creation of final version	N/A-First version	NA
19-Apr-2022	Prior to DB Lock	Creation of Amendment1 final version	Amendment 1 - First version	Section 2.5 – Analysis of the primary objective. Added the information related to correction factors.

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List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
C1	Concept 1 Breezhaler®
CI	Confidence Interval
CRF	Case Report Form
CRS	Case Retrieval Strategy
CSR	Clinical Study Report
CV	Coefficient of Variation
DMS	Document Management System
ECG	Electrocardiogram
EXCL	Exclusion
IA	Interim Analyses
ICS	Inhaled corticosteroid
INCL	Inclusion
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MF	Mometasone furoate
PK	Pharmacokinetics
RAP	Reporting & Analysis Process
SAE	Serious Advere Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
TFLs	Tables, Figures, Listings
TH	Twisthaler®

1 Introduction

This document contains details of the statistical methods that will be used in the phase II clinical trial CQMF149G2203.

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 Appendix 5.

1.1 Study design

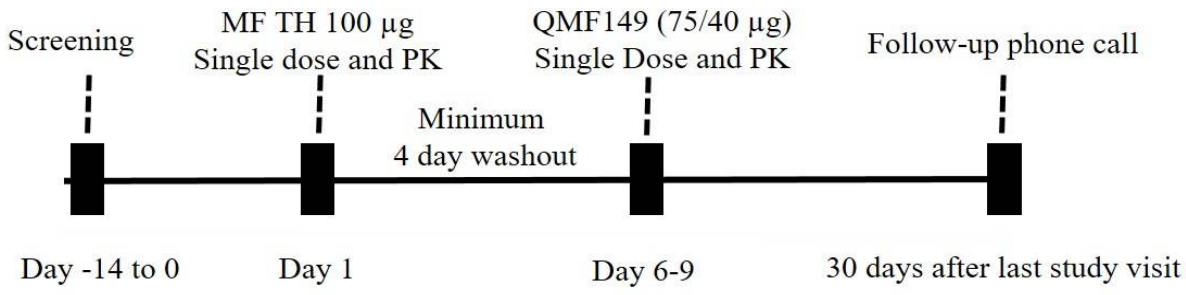
This is an open-label, two-period, single-sequence, crossover study to assess the pharmacokinetics, safety and tolerability of single inhaled doses of mometasone furoate (MF) when administered alone via MF Twisthaler® (TH) or as an indacaterol acetate/MF fixed dose combination (QMF149) via the Concept 1 (C1) device in ≥ 6 to <12 year old asthma patients. The study includes two open-label single-dose treatment visits. On the first treatment visit (Day 1) patients receive a single inhaled dose of 100 µg MF administered via the Twisthaler® device. On the second treatment visit (Day 6) patients receive a single inhaled dose of 75/40 µg indacaterol acetate/MF fixed dose combination (QMF149). Both treatments are in addition to their rescue medication and potentially SoC asthma therapy (excluding MF and indacaterol acetate).

Patients currently taking low-dose ICS asthma medications other than MF can enroll in the study. However, since the patients will be provided MF or QMF149 as part of study treatment on Day 1 and Day 6 respectively, patients should be instructed not to take low-dose ICS medication on the 2 treatment days.

The study will include the following:

- A screening period of up to 14 days
- Two single-dose treatment periods separated by a 4-7 day washout period (4 days is minimum washout)
- A 30-day investigational drug-free follow-up period

Figure 1-1 Study design



1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To compare the systemic exposure of mometasone furoate resulting from single orally inhaled doses of QMF149 75/40 µg administered via the Concept1 unit dose dry powder inhaler versus the MF Twisthaler® 100 µg metered dose dry powder inhaler in pediatric asthma patients (≥ 6 to < 12 years of age)	• PK parameters (AUC0-6h and Cmax) of MF after single dose administration of QMF149 75/40 µg C1 and MF Twisthaler® (100 µg)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the systemic exposure of indacaterol resulting from single orally inhaled doses of QMF149 75/40 µg.	• Systemic exposure of indacaterol after single dose administration of QMF149 75/40 µg
• To evaluate the safety and tolerability of QMF149 75/40 µg after single dose administration in pediatric patients.	• Adverse Events, Serious Adverse Events and defined safety assessments

2 Statistical methods

This section and its subsections follow the CSR template structure of Section 9.7 as of the release date of this document for alignment with importing into the CSR template.

2.1 Data analysis general information

The final CSR analysis will be performed by Novartis. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

2.1.1 General definitions

Investigational and control drugs

- Treatment A: Mometasone furoate delivered via Twisthaler®inhaler, (MF 100 μ g TH)
- Treatment B: Fixed dose combination of 75 μ g indacaterol acetate and 40 μ g mometasone furoate delivered as powder in hard capsules via Concept1 Breezhaler® inhaler (QMF149 75/40 μ g C1)

A single dose of the Asmanex Twisthaler® contains 110 µg of mometasone furoate delivering 100 µg of mometasone furoate from the inhaler mouthpiece following single actuation.

Date of first administration of study drug

The date of first administration of study drug is defined as the first date when a nonzero dose of study drug is administered and recorded on the study treatment form. The date of first administration of study drug will also be referred as start of study drug.

Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a nonzero dose of study drug is administered and recorded on study treatment form. The date of last administration of study drug will also be referred as end of study drug.

Study day

Study Day 1 for all assessments is taken to be the start date of study treatment.

The study day for all assessments will be calculated as follows:

If date of assessment occurred on or after the start of study treatment, then

Study day = Date of assessment - Start of study treatment + 1.

If date of assessment occurred before the start of study treatment, then

Study day = Date of assessment - Start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Baseline

For safety evaluations, the last available assessment on or before the date and time of start of study drug is taken as ‘‘baseline” assessment. In case time of assessment and time of study drug start is captured, the last available assessment before the study drug start date/time is used for baseline.

2.2 Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment(s) received.

The Safety analysis set includes all patients who received at least one dose of study treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the assigned treatment was never received.

The PK analysis set will include all patients with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

2.2.1 Subgroup of interest

Not applicable.

2.3 Patient disposition, demographics and other baseline characteristics

The safety analysis set will be used for all baseline and demographic summaries. Listings will be presented for non-screen failed participants.

Demographics and baseline data

Demographic and other baseline data will be listed by patient. Descriptive statistics will be provided for all patients for the treatment group.

Summaries will include:

- Age (years)
- Age groups: ≥ 6 to $9 <$ year and ≥ 9 to ≤ 12 year
- Gender
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)

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

Medical history

Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Relevant medical history and current medical conditions will be listed by treatment group and participant.

2.3.1 Patient disposition

Screened participants, including those who completed screening and were treated, and reasons for not completing the study will be listed for all patients.

Treated subjects will be included in the safety analysis set will be summarized. The following summaries will be provided (with % based on the total number of safety analysis set patients):

- Number (%) of patients who were treated.
- Number (%) of patients who completed treatment and those who discontinued the study treatment phase along with the primary reason for study treatment discontinuation (based on the disposition page).

Patient disposition data will be listed by patient.

Screen failure data will not be presented.

Protocol deviations

All protocol deviations will be listed by patient.

Analysis sets

The number of patients included in each analysis set (defined in Section 2.2) will be tabulated, as well as the reasons for exclusions from analysis set will be listed.

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

2.4.1 Study treatment / compliance

Dose administration data will be listed by patient.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient.

2.5 Analysis of the primary objective

The primary objective of this study is to compare the systemic exposure of mometasone furoate resulting from single orally inhaled doses of QMF149 75/40 administered via the Concept 1 versus the MF Twisthaler® (100 µg) in pediatric asthma patients (≥ 6 to < 12 years of age).

All patients evaluated for pharmacokinetic (PK) parameters data will be included in the pharmacokinetic data analysis.

2.5.1 Primary endpoint

The primary PK parameters of interest are Cmax, and AUC0-6h of MF after single dose administration of QMF149 75/40 µg C1 and MF TH 100 µg.

2.5.2 Statistical hypothesis, model, and method of analysis

Log-transformed PK parameters Cmax and AUC(0-6h) will be analyzed for mometasone furoate by linear fixed effects model with treatment and patient as fixed effect. The estimated mean and 90% confidence interval of treatment difference of test vs reference (QMF149 vs MF) will be back transformed to obtain the geometric mean and 90% confidence intervals (CI) of the ratio.

Indacaterol and mometasone furoate plasma concentration data will be listed by treatment, patient, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), Coefficient of Variation (CV) (arithmetic and geometric), median, minimum, and maximum.

Indacaterol and mometasone furoate pharmacokinetic parameters will be listed by treatment and patient. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented. PK parameters AUC0-6h and Cmax will be used for comparison of MF exposure after the two treatments.

Arithmetic mean (+/- SD) and overlaying individual plots for plasma concentration data will be presented by treatment and also by age group.

For comparison purpose of MF delivered in QMF149 through C1 Breezhaler® and MF delivered by Twisthaler® the blood exposure values (e.g., Cmax, AUC0-6h) obtained with C1 Breezhaler® will be multiplied with the factor FPMprimed (MF) / FPMunprimed (MF) to assess equivalent MF component doses.

For MF Twisthaler, the correction factor is 1.26, for MF Concept 1 device the correction factor is 1.62 and for Indacaterol Concept 1 device the correction factor is 2.0.

Similar analysis as mentioned above will be performed using a correction factor for plasma PK concentration and PK parameters.

The following pharmacokinetic parameters (Table 2-1) will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8.0 or higher):

Table 2-1 Non-compartmental pharmacokinetic parameters

AUC0-6h	The AUC from time zero to the last sampling time point 6h (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUClast	The AUC from dosing to the time of the last measured concentration.
Cmax	The maximum (peak) observed plasma drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, or other body fluid drug concentration after single dose administration (time)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time-1) may also be used for terminal elimination rate constant (time-1)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL/F	The total body clearance of drug from the plasma (volume x time-1)
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) volume.

2.5.3 Handling of missing values/censoring/discontinuations

All drug concentrations below the lower limit of quantification (LLOQ) will be reported as "zero" and will be treated as zero for the calculation of PK parameters.

Patients with missing PK parameters (e.g. Cmax, AUClast, AUCinf) in one period will be excluded from the primary analysis.

In case a certain PK time point is not collected and missing in data, PK parameters may not be calculated from this treatment.

2.5.4 Supportive analyses

Not applicable.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary objective(s)

The secondary objectives of this study are:

- To evaluate the systemic exposure of indacaterol resulting from single orally inhaled doses of QMF149 75/40 µg.
- To evaluate the safety and tolerability of QMF149 75/40 µg after single dose administration in pediatric patients.

2.7.1 Secondary endpoints

Pharmacokinetics:

Systemic exposure of indacaterol after single dose administration of QMF149 75/40 µg

Safety parameters: All safety data, including adverse events, laboratory measurements, vital signs, 12 Lead ECG

2.8 Safety analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group. Screen failure data will not be presented in the listings.

2.8.1 Adverse events (AEs)

All information obtained on adverse events will be displayed by treatment sequence and patient.

All treatment emergent AEs will be summarized and listed.

AEs starting on or after the time of the first inhalation of study drug and until 30 days after the last inhalation will be classified as a treatment emergent AE. Any AEs that started during the study after signing informed consent and before the time of the first inhalation of study drug will be classified as a prior AE and will not be included in tabulations of the treatment emergent AEs.

The following treatment emergent AE summaries will be produced:

- by treatment, system organ class and preferred term,
- by treatment, system organ class, preferred term, and maximum severity

suspected drug-related AEs by system organ class and preferred term, SAEs by system organ class and preferred term, and AEs leading to discontinuation of study-drug by system organ class and preferred term.

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

2.8.1.1 Adverse events of special interest

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.

2.8.2 Deaths

All deaths will be listed by patients.

2.8.3 Laboratory data

All laboratory data will be listed by treatment sequence, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

2.8.4 Other safety data

2.8.4.1 ECG data

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted centrally. All ECG data will be listed by treatment sequence, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

2.8.4.2 Vital signs

All vital signs data will be listed by treatment sequence, patient, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

2.9 Pharmacokinetic endpoints

Refer to Section 2.5 and Section 2.7 for primary and secondary objectives related to PK endpoints.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Not applicable.

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

Not applicable.

2.14 Interim analysis

An iterim analysis is planned to be performed when 12 patients complete both study traetment and there are at least 3 completers in each of the two age groups ≥ 6 to 9 < year olds and ≥ 9 to ≤ 12 year olds. The interim analysis will be based on preliminary PK and safety data. An estimate of the systemic exposure as measured by the PK parameter ratios (QMF149 Concept 1 Breezhaler® vs MF Twisthaler®) together with corresponding 90% confidence intervals will be calculated in order to enable early decision making (e.g., study termination due to having achieved the primary objectives). Rationale for study continuation may include measures such as a review of training procedure for inhaler use by patients or sample size re-estimation.

3 Sample size calculation

Approximately 32 patients will be recruited in order to obtain 24 completers in this study considering 25% of drop out rate. The sample size of 24 complete patients is considered to yield satisfactory precision in the estimation of the systematic exposure, as measured by the ratio of the PK parameter Cmax, AUC(0-6h) of QMF149 Concept 1 Breezhaler® vs MF Twisthaler®. With 24 complete patients, the 90% confidence intervals of the PK parameter (AUC (0-6h) and Cmax) ratios (QMF149 Concept 1 Breezhaler® vs MF Twisthaler®) are expected to be within 72% to 138% with 90% coverage probability. The calculation was based on an assumed 2-fold increase in variability in pediatric population compared to adults who showed intra-patient CV of 30% in the CQMF149E2101 study.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

The sections below contain additional details on statistical methodology that will be included in Appendix 16.1.9 (Documentation of Statistical Methods) of the CSR as well as details on programming rules that will be followed to implement the analyses described in Section 2.

5.1 Imputation rules

5.1.1 Study drug

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

5.1.2 AE date imputation

Partial AE start and end dates will be imputed. If there is uncertainty whether an AE occurred on-treatment or not, imputation will be performed, such that AE will be considered as on-treatment. Rules for imputing AE end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.1.3 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.

5.2 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.

5.3 Laboratory parameters derivations

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

5.4 Statistical models

5.4.1 Primary analysis

Refer to Section 2.5.

5.4.2 Key secondary analysis

Refer to Section 2.7.

5.5 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	
INCL02	Informed consent was not obtained before any assessment.
EXCL11	Parent or guardian has a history of psychiatric disease, intellectual deficiency, or substance abuse

6 Reference

- Clinical Study Protocol, CQMF149G2203 v01 dated 19-Mar-2021.