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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

QVM149

CQVM149B2209

A randomized, double-blind, repeat dose cross-over study to assess the bronchodilator effects of once daily QVM149 following morning or evening dosing for 14 days compared to placebo in patients with asthma

Statistical Analysis Plan (SAP)

Personal Data

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CQVM149B2209".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

This SAP is based on the final version of the following study documents:

- the study protocol, v00, 08 March 2017
- the SOM, v00, 08 March 2017

1.3 Study objectives

1.3.1 Primary objective(s)

Objective	Endpoint
• To investigate the potential influence of time of dosing (morning or evening) on the bronchodilator effect of once daily orally inhaled QVM149 compared to placebo	• Weighted mean forced expiratory volume in 1 second (FEV1) over 24 h (AUC_{0-24h}) following 14 days of treatment with QVM149 dosed in the morning, QVM149 dosed in the evening and placebo.

1.3.2 Secondary objective(s)

Objective	Endpoint
• To investigate the potential influence of time of dosing (morning or evening) on trough FEV1 of once daily orally inhaled QVM149 compared to placebo.	• FEV1 at approximately 24 h after the last p.m. or penultimate a.m. dose.
• To investigate the potential influence of time of dosing (morning or evening), on peak expiratory flow rate (PEF) of once daily orally inhaled QVM149 compared to placebo (all administered via the Concept1 inhalation device).	• Daily morning and evening peak expiratory flow rate from Day 2 to Day 14 during the three treatment periods

Objective	Endpoint
• To evaluate safety and tolerability of QVM149 when dosed in the morning or in the evening in patients with asthma during two weeks of treatment in each treatment period.	• Adverse events • Hematology • Blood chemistry • Urinalysis • Vital signs • ECG

1.4 Study design and treatment

This is a randomized, placebo-controlled, double-blind, six-sequence, three-period cross-over study in asthma patients. The study will consist of a 14-day screening period, followed by a 14-day run-in period, and a treatment epoch which consists of three treatment periods, with a minimum duration of 14 days each followed (for the 2 first treatment periods) by a wash-out period. The duration of each treatment period may be extended up to a duration of 18 days if needed for operational reasons. The third treatment period will be followed by a Study Completion evaluation at 1-7 days following the last dose. The treatment periods will be separated by wash-out periods of 14 to 21 days duration.

The total duration of the study is approximately 13 weeks (minimum) to 19 weeks (maximum) for each patient.

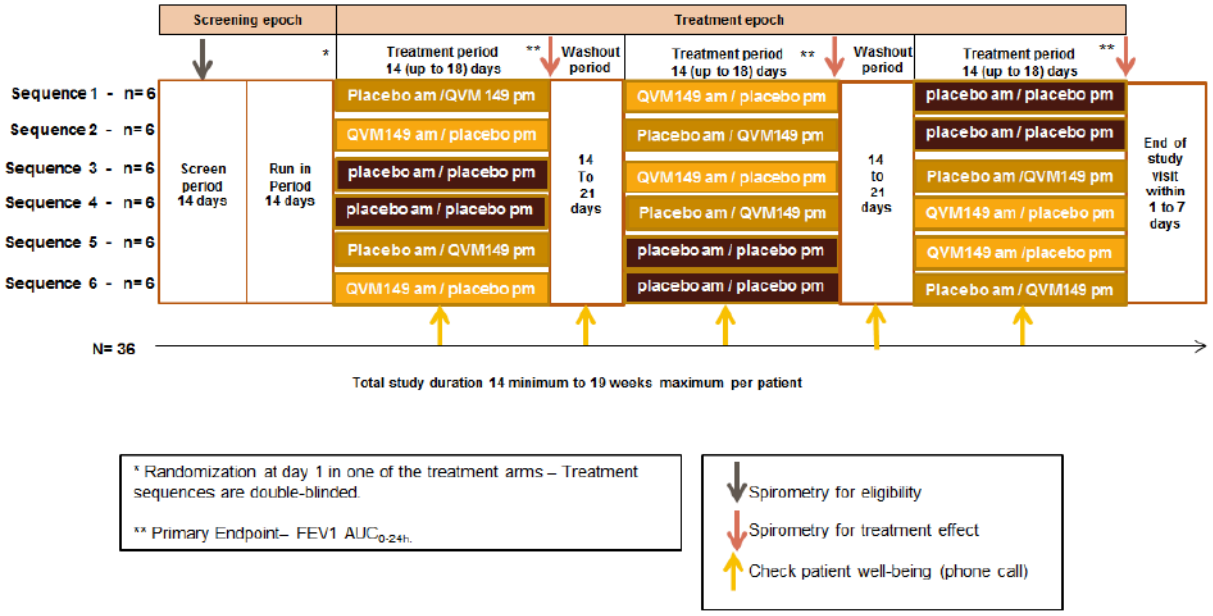
The study population will be comprised of male and female patients aged 18 and above with asthma. Approximately 36 adult patients will be randomized with the intention that at least 30 patients complete the study.

Study treatments are defined as:

- A: Matching placebo (am); QVM149 150/50/80 µg (pm)

- B: QVM149 150/50/80 µg (am); Matching placebo (pm)
- C: Placebo (am); Placebo (pm)

Patients will be randomized to one of the following 6 treatment sequences (defined according to a Williams design for 3 treatments and 3 periods) in the ratio of 1:1:1:1:1:1.



2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

Corporate Confidential Information

3 Interim analyses

Corporate Confidential Information

4 Statistical methods: Analysis sets

For subjects for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for the analysis.

For subjects for which the actual sequence of treatments received does not match the randomized sequence of treatments, the actual sequence will be used for analysis involving a sequence component (e.g. ANOVAs with a sequence effect) if the actual sequence is one of the sequences planned in the study design. If the actual sequence is not one of the sequences planned in the study design, the randomized sequence will be used for analysis involving a sequence component but data points from periods in which the subject has not received the randomized treatment will be excluded from the analysis.

The safety analysis set will include all subjects that received any study drug.

The PD analysis set will include all subjects with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

Anyone who did not complete an informed consent will not have their data reported.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from all (safety) analysis in case of these PDs:		Exclude subject from all (safety) analysis set
INCL01	Written informed consent was not obtained prior to performing study assessment	Exclude from Safety set
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
INCL01	Written informed consent was not obtained prior to performing study assessment	Exclude from PD set

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

Not applicable.

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary objective is to investigate the potential influence of time of dosing (morning or evening) on the bronchodilator effect of once daily orally inhaled QVM149 (150 µg indacaterol / 50 µg glycopyrronium / 80 µg MF) compared to placebo (all administered via the Concept1 inhalation device).

6.1.1 Variables

The primary variable is the weighted mean forced expiratory volume in 1 second (FEV1) over 24 hours ($AUC_{0\text{-}24h}$) following 14 days of treatment with QVM149 dosed in the morning, QVM149 dosed in the evening and placebo.

The primary variable will be determined for each patient on day 14 on each treatment using the linear trapezoidal rule. FEV_1 measurements are taken 5 min before the evening dose on day 14 then, +3h, +6h, +9h, +12h, +15h, +18h, +21h and +23h55 (timing from the post-evening dose).

The weighted mean will be calculated as the $AUC_{0\text{-}24h}$ divided by the t_f-t_l hours time interval for each subject (t_f=time of the first observation, t_l is the time for the last observation).

$$\frac{1}{2}\sum_{f-l}\frac{(C_{i+1}+C_i)(t_{i+1}-t_i)}{t_f-t_l}$$

where,

C_i = the highest value at planned relative timepoint i

t_i = the actual time for planned relative timepoint i

i = the planned relative time of assessment

f =the first i

l =the last i.

6.1.2 Descriptive analyses

$AUC_{0\text{-}24h}$ FEV1 will be calculated and listed by treatment sequence and subject, and summarized by treatment.

6.1.3 Statistical model, assumptions and hypotheses

The primary variable, FEV1 weighted mean (0- 24 h) ($AUC_{0\text{-}24h}$), will be analyzed using a linear mixed model. The model will include period, treatment (QVM149 morning, QVM149 evening, placebo), and sequence as fixed effect factors. The patient effect will be assumed to be random. Restricted maximum likelihood method will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. From these analyses, point estimates and their associated 90% confidence intervals will be constructed for each treatment. The difference between adjusted means and the corresponding two-sided 90% confidence interval for morning dose versus placebo, evening dose versus placebo will be presented. In addition, difference between adjusted means and the corresponding two-sided 90% confidence interval for morning versus evening doses will be presented.

6.1.3.1 Model checking procedures

Missing values

If a patient takes rescue medication within 6 hours prior to the spirometry assessments and the visit is not rescheduled to the next day then all spirometry assessment data from this visit and the following visits in this treatment period will be set to missing. If rescue medication is taken during the 24-hour spirometry assessment then from the time of the rescue medication intake, all post-time point spirometry assessments will be considered as missing in this treatment period and AUC (0-24hr) will be considered as missing.

Sensitivity analyses

Sensitivity analyses will be performed on a subset of patients where patients having drug administered outside of the allowed time window on day 14 or 15 will be excluded. Spirometry data assessed outside of the allowed time window will also be excluded.

On Day 14 in the morning, study drug must be administered at 07:00h with a time window of ± 30 min i.e. [6.30; 7.30]. There must be 12 hours in between morning and evening doses on Days 14 and 15 with an acceptable deviation of ± 15 min.

For example:

If on Day 14, study drug is given at 7.30 am then study drug must be given between [7.15 pm; 7.45 pm] on day 14 in the evening and between [7:00am; 8:00am] on day 15 in the morning.

If on Day 14, study drug is given at 6.30 am then study drug must be given between [6.15 pm; 6.45 pm] on day 14 in the evening and between [6:00am; 7:00am] on day 15 in the morning.

Supportive analysis

Repeated measures of FEV1 will be analyzed using a mixed model for repeated measures (MMRM) with period, sequence, visit and treatment as factors having fixed effects and period specific baseline FEV1 as covariate. The modeling will assume an unstructured variance covariance matrix to account for the correlations between assessments over time points. Average treatment effect on the overall FEV1 profile over 0-24hr will be estimated in terms of adjusted mean difference between morning dose vs. placebo and evening dose vs. placebo with corresponding 2-sided 90% CIs. The inference is valid under 'Missing at Random (MAR)' assumption on missingness mechanism and provides evidence on robustness of the primary analysis results to the missing value handling techniques

Subgroup analysis

The primary analysis will be performed by subgroup of patients based on their compliance of study medication within the 7 days before the spirometry assessment: if spirometry assessment is done on the evening of day 14, then compliance will be calculated between day 8 and day 14 on a total number of 14 doses.

This analysis will be provided per compliance of study medication within the 7 days before spirometry assessment defined as follows:

- <80% Compliance of study medication within the 7 days before spirometry assessment (less than a total number of 12 doses)
- 80-100% Compliance of study medication within the 7 days before spirometry assessment (more or equal a total number of 12 doses)

6.1.3.2 Graphical presentation of results

Plot of treatment differences with 90% CI for $AUC_{0\text{-}24h}$ FEV1, and plot by treatment and additionally by period and sequence of the mean of FEV1 and 90% CI over the 24h after the evening dose given on day 14 will be displayed.

6.2 Secondary objectives

6.2.1 Variables

The secondary endpoints are:

- Trough FEV1 at approximately 24 h after the last p.m. or penultimate a.m. dose.
- Daily morning and evening peak expiratory flow (PEF) rate from Day 2 to Day 14 during the three treatment periods

6.2.2 Descriptive analyses

The a.m. trough FEV1 is defined for each subject as the FEV1 measurement at day 15, +12h (timing from the post-evening dose on day 14) (before Day 15 am dose).

The p.m. trough FEV1 is defined as the FEV1 measurement at day 15, +23h55 (timing from the post-evening dose on day 14).

The morning/evening PEF (L/min) will be averaged between days 2 to 14 of each treatment period for each patient.

Summary statistics of a.m. and p.m. trough FEV1 and average morning/evening PEF score between days 2 to 14 will be presented by treatment.

6.2.3 Statistical model, assumptions and hypotheses

The a.m. and p.m. trough FEV1 (mL) will be analyzed by fitting the same model as described for the primary endpoint above.

PEF (L/min) will be analyzed separately for morning and evening values. The morning/evening PEF (L/min) will be averaged between days 2 to 14 of each treatment period for each patient. The average morning/evening PEF score between days 2 to 14 in each period will be analyzed using the same model as for the primary endpoint.

6.2.3.1 Model checking procedures

Missing values

If a patient takes rescue medication within 6 hours prior to the spirometry assessments and the visit is not rescheduled to the next day then a.m. and p.m. trough FEV1 for this treatment period will be set to missing. If rescue medication is taken during the 24-hour spirometry assessment then from the time of the rescue medication intake, all post-timepoint spirometry assessments will be considered as missing in this treatment period.

6.2.3.2 Graphical presentation of results

Plot of mean morning/evening PEF and 90% CI over time between day 2 to 14 by treatment, and plot of treatment differences with 90% CI for mean morning/evening PEF and treatment differences with 90% CI for a.m. and p.m. trough FEV1 will be displayed.

7 Statistical methods for safety and tolerability data

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

The last daily dose of inhaled corticosteroids taken before being enrolled into the study will be categorized into three categories: Low, medium and high defined based on 2017 GINA report. http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/

Box 3-6. Low, medium and high daily doses of inhaled corticosteroids

Adults and adolescents (12 years and older)			
Drug	**Daily dose (mcg)**		
	Low	Medium	High
Beclometasone dipropionate (CFC)*	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate(DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment sequence and subject.

Subject disposition

A disposition summary will be presented for all subjects. This table will present the number and percentage of subjects who completed each study epoch and discontinued early for each epoch, along with the reasons for early discontinuation.

The number and percentage of subjects in each analysis set will be summarized for all subjects. All analysis set results will be presented in listings by treatment sequence and subject. A separate listing of all subjects excluded from any analysis set and the reasons for their exclusion will be provided.

All study epoch completion data will be listed by treatment sequence and subject.

Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment sequence and subject.

Vital signs

All vital signs data will be listed by treatment sequence, subject, 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.

ECG evaluations

All ECG data will be listed by treatment sequence, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment sequence, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time.

Adverse events

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

The number and percentage of subjects with treatment emergent adverse events will be tabulated by body system and preferred term with a breakdown by treatment. Adverse events starting on or after the time of the first inhalation of study drug will be classified as a treatment emergent adverse event. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A subject with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

Any adverse event occurring during the washout period is counted under the current treatment epoch. For example, if AE occurs during the washout period just after treatment period 1 will be counted under treatment epoch 1.

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 5% 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.

Protocol Deviations

Protocol deviations will be listed by treatment sequence and subject.

Liver events

Liver event data may be reported in listings and summaries if data is collected during the study.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.