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QVM149

CQVM149B2203

A randomized, double-blind, placebo-controlled, three-period cross-over study to assess the pharmacodynamics, safety, tolerability, and pharmacokinetics of two orally inhaled indacaterol salts (maleate and acetate) delivered via the Concept1 inhalation device 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 **"*CQVM149B2203"*.**

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

1.2   Study reference documentation

Final study protocol is finalized at the time of the finalization of Statistical Analysis Plan.

This SAP Amendment 1 is based on the final version of the

- Study protocol, v00, 28 Feb 2017

1.3   Study objectives

1.3.1   Primary objectives

- To assess the bronchodilator effect of orally inhaled indacaterol salts (maleate and acetate) in subjects with asthma compared to placebo as measured by trough FEV1 after 14 days of treatment

1.3.2   Secondary objective(s)

- To assess the steady state pharmacokinetics of indacaterol after 14 days of treatment of orally inhaled indacaterol salts (maleate and acetate) in subjects with asthma.
- To assess the bronchodilator effect of orally inhaled indacaterol salts (maleate and acetate) in subjects with asthma compared to placebo as measured by:
    - Time to peak FEV1 on Day 14
    - FEV1, FEV1 (% predicted), FVC, FVC (% predicted), FEV1/FVC, and FEF25-75% at each post-dose time point after 14 days of treatment
    - Standardized FEV1 AUC from pre-dose to 4 h post-dose on Day 14 of treatment
- To assess the bronchodilator effect of indacaterol acetate, indacaterol maleate, and placebo by comparing the pre-medication (morning (pre-dose) and evening) peak expiratory flow (PEF) rate collected between days 8 and 14 of each treatment.
- To assess rescue medication usage for indacaterol salts (maleate and acetate) in comparison to placebo.
- To assess the safety and tolerability of indacaterol salts (maleate and acetate) in comparison to placebo of 14 days of treatment in each treatment period.

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1.4   Study design and treatment

Figure 1-1   Study design
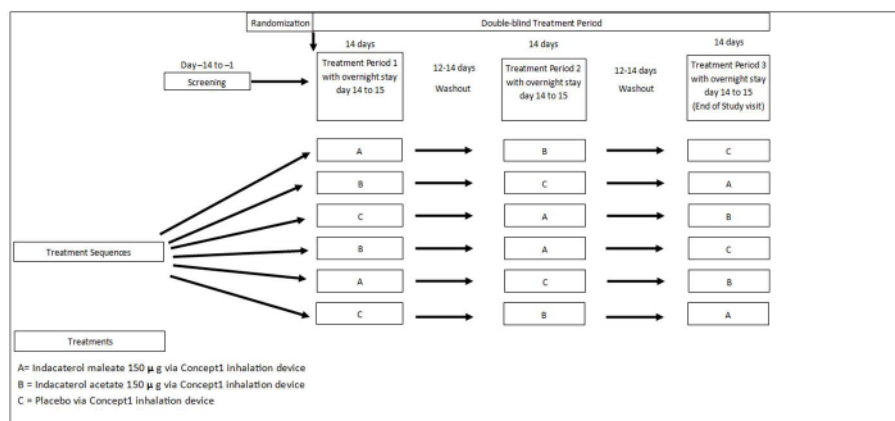
This is a confirmatory, randomized, double blind, placebo-controlled, three-period complete block, crossover study in patients with asthma.

Subjects who meet all of the eligibility criteria will be randomized to one of six treatment sequences as described in Figure 3-1. They will receive their first dose on the morning of Day 1. Subjects will be dosed between 06:00 a.m. and 10:00 a.m. under the guidance and supervision of the investigator or designee after an additional training for correct use of the Concept1 inhalation device. Dosing of investigational product and background ICS medication should occur at approximately the same time of the day throughout the study. PEF measurements (if not already performed at home on the morning of Day 1 or Day 14) should be taken prior to pre-dose spirometry and safety assessments.

On Day 1, subjects will leave the clinic after the completion of the required assessments and will dose at home once daily in the morning on Days 2 to 13. During days 2 -13, subjects will record drug administration, PEF measurements, mouth rinsing, and rescue medication use in their diary. Subjects will be domiciled at the clinic on the morning of Day 14, for drug administration and Day 14 visit assessments. Subjects will be discharged on Day 15 following the final PK and safety blood sample draw and completion of Day 15 assessments.

A washout period of 7 - 14 days will separate each treatment period.

Epoch Completion assessments must be conducted for subjects who complete all three treatment periods or at any time a subject early terminates from the trial. . The last visit (Day 65) of Treatment period 3 will also be the end of study visit. Subjects should be discharged from the site after the completion of Day 15 assessments for all 3 periods.

2   First interpretable results (FIR)

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

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4   Statistical methods: Analysis sets

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

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

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

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.

The PD analysis set will include all subjects with available PD parameter data who received any study drug and experienced no major protocol deviations with relevant impact on PD data. Any PD data for the primary endpoint obtained within 6 hours after rescue medication use or within 7 days of systemic corticosteroid will be set to missing.

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 Safety analysis in case of these PDs:		Exclude subject from Safety analysis set
INCL01	Deviation from inclusion criteria: In the unlikely event that a subject was included without written informed consent, then their data will not be used	Yes
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
INCL01	Deviation from inclusion criteria: In the unlikely event that a subject was included without written informed consent, then their data will not be used	Yes
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis sets
INCL01	Deviation from inclusion criteria: In the unlikely event that a subject was included without written informed consent, then their data will not be used	Yes

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

5.1 Variables

The concentrations of indacaterol in plasma will be determined by a validated LC-MS/MS method;
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Other pharmacokinetic parameters may be determined as appropriate.

5.2 Descriptive analyses

Indacaterol plasma concentrations will be listed by treatment sequence, subject, profile day, and sampling time point. Descriptive summary statistics will be provided by treatment, profile day, and sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

Concentrations below LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be listed by treatment sequence, profile day, and subject. Descriptive summary statistics will be provided by treatment and profile day. 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.

5.3 Statistical model, assumptions and hypotheses

The log transformed pharmacokinetic parameters AUC0-24h,ss and Cmax,ss on day 14 will be compared for indacaterol acetate (test) relative to indacaterol maleate (reference) using a mixed effects model with sequence, treatment and period as fixed effects and subject nested within sequence as random effect. Body weight assessed in period 1 will be included as a continuous covariate and applied as a fixed effect in the model. The estimates of the treatment differences (indacaterol acetate (test) vs. maleate (reference); Frel) along with their 90% confidence intervals will be obtained. The estimates and confidence intervals will be transformed back to the original scale to provide ratios of the geometric means together with their corresponding 90% confidence intervals.

Tmax,ss will be analyzed using non-parametric methods. The median difference and the 90% confidence interval of the median difference in Tmax,ss will be estimated using Hodges-Lehmann estimation procedure.

5.3.1 Model checking procedures

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

Subjects with missing PK parameters (e.g. Cmax,ss, and AUC0-24h,ss) in some but not all periods will be included in a mixed model analysis.

5.3.2 Graphical presentation of results

Individual concentration-time profiles and mean profiles with SD bars will be presented for Day 14 PK data.

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary objective is to assess the bronchodilator effect of orally inhaled indacaterol salts (maleate and acetate) in subjects with asthma compared with placebo as measured by trough FEV1 after 14 days of treatment.

6.1.1 Variables

The primary variable is trough FEV1 after 14 days of treatment. Trough FEV1 is defined as the average of the FEV1 measurements at 23 h 15 min and 23 h 45 min post dose.

6.1.2 Descriptive analyses

Trough FEV1 will be listed by treatment sequence, subject and visit/time and descriptive summary statistics will be provided by treatment and visit/time. Summary statistics will include arithmetic mean, SD, CV (arithmetic), median, minimum and maximum.

6.1.3 Statistical model, assumptions and hypotheses

The following hypothesis will be tested for each of indacaterol salts (acetate and maleate) versus placebo separately:

H0 (Null Hypothesis): There is no difference in terms of the trough FEV1 after 14 days of treatment between:
>   Indacaterol acetate and placebo
>   OR
>   Indacaterol maleate and placebo

H1 (Alternative Hypothesis): There is a difference in terms of the trough FEV1 after 14 days of treatment between:
>   Indacaterol acetate and placebo
>   AND
>   Indacaterol maleate and placebo

No adjustments will be made for multiplicity because the objective is to prove that both formulations must be statistically significantly different from placebo each at 2-sided 5% level of significance.

The trough FEV1 after 14 days of treatment will be analyzed using an analysis of variance (ANOVA) with treatment, period and sequence as fixed effects and subject nested within sequence will be included as a random effect. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The final model estimates will include the LS mean for each treatment (indacaterol acetate, maleate and placebo) together with standard error (SE), the adjusted mean difference between indacaterol salts (acetate and maleate) and placebo, and corresponding two-sided 95% confidence intervals and P-value for the differences (acetate vs placebo and maleate vs placebo) using placebo as reference treatment.

Additionally as a secondary consideration, an estimate of the differences in trough FEV1 between indacaterol acetate (test) and indacaterol maleate (reference) will be calculated together with the corresponding two sided 95% confidence intervals.

6.1.3.1 Model checking procedures

Subjects withdrawn for any reasons other than safety and tolerability may be replaced on a case by case basis.

If one of the 23h 15 min and 23h 45 min values are missing (or set to missing) then the remaining non-missing value will be taken as trough FEV1. If both values are missing, or if the subject withdrew from the study, regardless of the reason for discontinuation, then trough FEV1 will be regarded as missing.

If any of the values used in the trough FEV1 are collected within six hours of rescue medication or 7 days of systemic corticosteroid then the individual FEV1 within 6 hours after rescue medication use or within 7 days of systemic corticosteroid will be set to missing. If rescue medication is taken during the 24 hour spirometry assessments then from the time of the rescue medication intake, all post-time point spirometry assessments will be considered as missing in this treatment period.

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 during day 14, then compliance will be calculated between day 8 and day 14 on a total number of 7 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 5 doses)

- 80-100% Compliance of study medication within the 7 days before spirometry assessment (more or equal a total number of 5 doses)

6.1.3.2   Graphical presentation of results

Individual time profiles and the results of statistical analysis will also be presented in a graphical representation called forest plot showing the estimated mean differences indacaterol salts (acetate and maleate) to placebo and estimated difference between acetate and maleate salts and their confidence intervals per time point for each comparison.

6.2   Secondary objectives

6.2.1   Variables

Forced Expiratory Volume in 1 second (FEV1), 3 seconds (FEV3), 6 seconds (FEV6), FEV1% predicted, Forced Vital Capacity (FVC), FVC% predicted and Forced Expiratory Flow 25-75% (FEF25-75%) will be measured at screening, pre-dose, and specific time points for approximately 24 hours post dose (on Days 14 and 15) in each treatment period. Additional lung function parameters will be derived mathematically from the listed measurements (e.g. FEV1/FVC, FEV1/FEV6, FEV3/FVC, FEV3/FEV6, 1-FEV3/FVC, 1-FEV6/FVC).

For each patient, the spirometric measurements must be taken at approximately the same corresponding time of day in each treatment period as closely as practically possible.

Pre-bronchodilator FEV1, FEV3, FEV6, FVC, and FEF25‑75 assessments will be conducted at screening.

Spirometry timepoints following the last dose of study medication in each treatment period are as follows:

- Day 14 predose: - 45 min and -15 min
- Day 14/15 post-dose: 5 min, 15 min, 30 min,1 h, 2 h, 3h, 4 h, 8 h, 12 h, 23 h 15 min, 23 h 45 min

Time to peak FEV1 (maximum FEV1 post treatment) on Day 14 will be derived from the spirometry timepoints following the last dose of the study medication in each treatment period.

Standardized FEV1 AUC (0-4hr) (i.e. Area Under Curve between 5 min (=time 0h) and 4h post dose) on Day 14 of treatment. Area under curve for FEV1 from Spirometry data and will be calculated by trapezoidal rule as follows:

$$AUC_{0-T} = \frac{\sum_{i=1}^{n}(t_i - t_{i-1})*(c_i + c_{i-1})}{2}, \quad with\ t_0 = 0\ and\ t_n = T$$

Where 't' is time-point and 'c' is FEV1 at time-point t.

T0 is initial time-point, Tn is the last time point of interest.

Peak FEV1 defined as the highest bronchodilatory effect on FEV1 during a period of 5 min to 4h on Day 14 of treatment. FEV1 measurements to consider defining peak FEV1 are on day 14 +5 min, +15 min, +30 min, +1h, +2 h, +3h, +4h.

PEF will be recorded twice daily using a Peak Flow Meter device, once in the morning and once approximately 12 h later in the evening. The morning/evening and overall (average of both morning and evening) PEF measurements will be averaged separately between days 8 to 14 of each treatment period and each subject.

The number of puffs of rescue medication taken is recorded twice (morning/evening) by subjects in the eDiary. The morning/evening and overall (both morning and evening) number of puffs of rescue medication will be averaged separately between days 8 to 14 of each treatment period and each subject.

Below is an example for averaging the rescue medication for each treatment period and subject.

Subject	Day	Rescue Medication		
		Morning	Evening	Overall
5101	8	7	5	12
5101	9	6	8	14
5101	10	5	6	11
5101	11	6	7	13
5101	12	4	8	12
5101	13	9	6	15
5101	14	4	4	8

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6.2.2   Descriptive analyses

All the above secondary variables will be listed by treatment sequence, subject and visit/time and descriptive summary statistics will be provided by treatment and visit/time. Summary statistics will include arithmetic mean, SD, CV (arithmetic), median, minimum and maximum.

The mean morning/evening and overall number of puffs of rescue medication use will be listed by treatment sequence and subject and summary statistics by treatment. The number and percentage of subjects with rescue medications, together with the number of puffs, will be tabulated by treatment.

The average morning/evening and the overall PEF (L/min) will be listed by treatment sequence and subject and summary statistics by treatment.

6.2.3   Statistical model, assumptions and hypotheses

All the above secondary variables (Section 6.2.1) for spirometry (excluding Time to peak FEV1, Standardized FEV1 AUC (0-4hr), Peak FEV1, Average rescue medication for morning/evening and Average PEF measurements for morning/evening) after 14 days of treatment will be analyzed using repeated measures of ANOVA including treatment, period, sequence, time, treatment by time as fixed effects and subject nested within sequence will be included as a random effect. Time will be repeated within each subject*period interaction term. An unstructured variance unstructured covariance matrix will be applied.

Standardized FEV1 AUC (0-4hr) between baseline (pre dose) and 4h post dose and peak FEV1 on Day 14 of treatment will be analyzed using the same model (ANOVA) as for the primary analysis.

Averaged morning/evening and overall number of puffs of rescue medication and average morning/evening and overall number of PEF measurements will be analyzed using the same model (ANOVA) as for primary analysis.

Time to peak FEV1 on Day 14 will be analyzed using non-parametric methods. The median difference and the two-sided 95% confidence interval of the median difference in time to peak FEV1 will be estimated using Hodges-Lehmann estimation procedure.

6.2.3.1   Model checking procedures

For the FEV1 AUC (0-4hr) if an observation is missing between two non-missing observations, the AUC will be linearly interpolated between the two non-missing values i.e. the subject's profile will be assumed to be linear between the two available values. Multiple occurrences of such missing values (an observation missing between adjacent non-missing observations) will be handled in a similar manner. But in case of missing consecutive assessments, then the patient profile will be excluded from analysis. No imputation will be made if either the first or the last observation is missing and AUC (0-4hr) is calculated from the available part of the profile ignoring the first and last time points.

For all secondary end points, if a patient takes rescue medication within 6h prior to the spirometry assessments and the visit is not rescheduled to the next day then all spirometry assessments 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 assessments 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 (0-4hr) will be considered as missing.

6.2.3.2   Graphical presentation of results

Individual time profiles and Mean (SD) plots for all secondary parameters will be presented by treatment group and time.

The results of statistical analysis will also be presented in a graphical representation called forest plot showing the estimated mean differences indacaterol salts (acetate and maleate) to placebo and estimated difference between acetate and maleate salts and their confidence intervals per time point for each comparison including studentized residual plots.

6.3   Exploratory objectives

6.3.1   Variables

Not Applicable

6.3.2   Descriptive analyses

Not Applicable

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.

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. Summary table for percentage and number of subjects with abnormal values <40 /40-90 />90 bpm in heart rate and summary table for percentage and number of subjects with notable values increase >30 / increase >60 / >450 />480/>500 msec in QTcF interval will be provided.

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.

Summary table for percentage and number of subjects with notable values for serum potassium (<3 /3-<3.5 />5.5 mmol/L) and plasma glucose (>10-15 />15 mmol/L) will be provided.

Adverse events

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

All treatment emergent adverse events will be summarized. Adverse events starting on or after the time of the first inhalation of study drug will be classified as a treatment emergent adverse event. Any adverse events that started during a washout period will be assigned to the treatment period just prior to that washout period. Any adverse events that started during the study before the time of the first inhalation of study drug of the first period will be classified as a prior adverse event and will not be summarized.

The number and percentage of subjects with treatment emergent adverse event will be summarized by treatment, overall by system organ class and preferred term, overall by system organ class, preferred term and maximum severity, suspected drug-related adverse events by system organ class and preferred term, serious adverse events by system organ class and preferred term, and adverse events leading to permanent discontinuation of study drug by system organ class and preferred term with a breakdown by treatment. 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.

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 analysis 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.