NOVARTIS

Clinical Development

QVA149

CQVA149ADE05 / NCT02442206

A randomized, double-blinded, single-center, placebo controlled, cross-over study to assess the effect of QVA149 (indacaterol maleate / glycopyrronium bromide) on cardiac function in patients with chronic obstructive pulmonary disease (COPD)

RAP Module 3 – Detailed Statistical Methodology

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Statistical methods planned in the protocol and determination of sample size

1 Introduction

This document contains details of the statistical methods which will be used in the phase IV clinical trial CQVA149ADE05. This is a randomized, double-blinded, single-center, placebo controlled, cross-over study which is designed to evaluate the effectiveness of dual bronchodilation with QVA149 (indacaterol maleate/glycopyrronium bromide) on cardiac and lung function parameters in hyperinflated COPD patients.

1.1 Statistical and analytical plans

Data will be analyzed by statistical analysis software (SAS) version 9.4 according to the data analysis section 9 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

For descriptive statistics, the following number of decimal places will be used: arithmetic mean, and median to 1 more decimal places than the raw data; minimum and maximum to the same number of decimal places as the raw data and SD to 2 more decimal places than the raw data. Percentages will be presented to 1 decimal place. Confidence interval(s) will be presented to the same decimal places as the estimate.

1.2 Subjects and treatments

1.2.1 Analysis sets

Full analysis set (FAS) will include all randomized patients who received at least one dose of randomized study treatment. Patients will be analyzed according to the treatment assigned at randomization. The FAS will be used for summaries of patient disposition, analysis sets, protocol deviations, demographic and baseline characteristics, efficacy analyses relates to lung function- and QoL- parameters.

Per protocol (PP) set will include all patients in the FAS who did not have any major protocol deviations. Major protocol deviations will be defined prior to database lock and the un-blinding of the study. The list of major protocol deviations is available in Appendix 16.1.9 of this document. The PP set will also be used for the primary analysis of cardiac function parameters, where the aim is to explore mechanistic effects rather than on an estimate of effects achievable in clinical practice. Additionally PP analyses will be used for lung function- and QoL- parameters to support the respective FAS-findings.

Safety set (SAF) will include all patients who received at least one dose of the study treatment, whether or not being randomized. Patients will be analyzed according to the treatment they received. The SAF will be used for all safety analyses.

Note that the FAS and safety set are the same except that the safety set allows the inclusion of non-randomized patients who received study drug in error. In addition, the FAS assigns randomized treatment and the safety set assigns received treatment. Unless otherwise stated, the actual and planned treatments are same.

1.3 Patient disposition and demographic characteristics

1.3.1 Patient disposition

The FAS set will be used for the summary and listing of patient disposition.

From the screening log, the overall number of patients who were screened, completed screening phase, discontinued from the screening phase with reason for not completing screening will be summarized. Only one attempt of rescreening is allowed in the study, the total patients screened will count individual patients and not attempts of screening.

Using the screened patients and end of treatment CRF the number of patients randomized, completed the treatment phase and discontinued from the treatment phase will be summarized by treatment sequences with reasons for premature discontinuation for all patients in the FAS.

Finally, using the end of study CRF, the number of patients completing and discontinuing the study, with reason for not completing the 30 day safety follow-up period will be summarized by treatment sequence for the FAS.

In addition, the number of patients in each analysis set by treatment sequence will also be summarized for all randomized patients. Patient identification number, treatment sequence and whether they completed or discontinued from the different study phases will be listed, with date of last dose and primary reason for premature discontinuation.

For patients who were rescreened at a certain visit, to avoid duplication of data in the database, all pages of previous visits were blanked, except the following pages which will be used for data summaries as appropriate:

Visit	**CRF Page**
Visit 1	Demography
Visit 1	Informed Consent
Screen fail visit	Visit date
Screen fail visit	Inclusion Exclusion Criteria (Screen Failure visit)
Screen fail visit	Screening Log (Screen Failure visit)

For patients who passed the screening, data from the last completed visit where patient qualified the study eligibility criteria would be considered as screening assessments.

1.3.2 Protocol deviations

The FAS set will be used for the summary by treatment and listing of protocol deviations.

The number and percentage of patients with protocol deviations will be tabulated by deviation category and treatment. The number of patients with protocol deviation that leads to exclusion in each analysis set will also be presented by treatment sequences. Subject exclusion from analysis sets will be listed for all patients with reasons of exclusion (i.e., both protocol and non-protocol deviation). Protocol deviations will be listed with date and study day of occurrence, deviation code and severity.

1.3.3 Patient demographics and other baseline characteristics

Demographics and baseline characteristics will be summarized by treatment sequence using the FAS. Derivations related to demographic and baseline disease characteristics are defined in Section 16.1.9.3.

The following demographic variables collected in the eCRF at Pre-screening (Visit 1) will be summarized:

- age (in years)
- sex (male or female)
- race (Caucasian, Black, Asian, Other)
- height (cm)
- weight (kg)
- body mass index (BMI) (kg/m^2)

Baseline characteristics (collected at Visit 1 for eCRF data, unless otherwise specified below) will be summarized:

- Duration of COPD (in years, formula specified in Section 16.1.9.3)
- History of exacerbation (number of any moderate or severe documented COPD exacerbation during the past 12 months).
- Smoking status (never smoked, current smoker, ex-smoker)
  - estimated number of pack years (for current and ex-smokers only)
  - time since termination of smoking (for ex-smokers only)
- Vital signs (sitting systolic/diastolic blood pressure (mmHg), sitting pulse rate (bpm)) at Visit 3.
- Pre- and Post- bronchodilator (salbutamol) bodyplethysmography (sReff, IC, FRC, SVC, TLC, RVol and RVol %) at Visit 3.
- Spirometry at screening including post- bronchodilator FEV_1, FVC, FEV_1/FVC, FEV_1 percentage of predicted normal value after bronchodilator and FVC percentage of predicted normal value after bronchodilator respectively at Visit 1 will be listed only.
- Spirometry at baseline Visit 3 including
  - both pre- and post- bronchodilator FEV_1 and FVC;
  - post-bronchodilator: FEV_1 percentage of predicted normal value, FVC percentage of predicted normal value, FEV_1/FVC;
  - FEV_1 reversibility result.

- mMRC results (Grade 0, 1, 2, 3, 4) at Visit 3.
- CAT total score at Visit 3.

Baseline and demographic variables: continuous variables will be summarized using descriptive statistics (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.

1.3.4 Medical history and current medical condition

The number and percentages of patients with Cardio vascular (CV) related medical history will be tabulated by terms specified in the CRF page for the FAS.

The number and percentages of patients with non-CV related medical history and current medical conditions will be summarized by primary system organ class and preferred terms. 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.

1.4 Study medication

1.4.1 Study drug administration

Duration of exposure to each treatment will be calculated as the number of days between the first dose date and the last dose date exposed to that treatment over the specified period (expressed as: Duration of exposure = Date of last known dose of study drug – Date of first dose of study drug + 1).

If by error a subject received the same in more than 1 period then the durations will be summed up. The duration of exposure (in days) will be summarized descriptively by treatment for the safety set. In addition, this duration will be summarized by categories of exposure (i.e., 1-15 days and 29-43 days) and also cumulative categories (i.e., >=1, >=15, >= 29 and >= 43 days)

For each study treatment, the period, date, time, and dose of each single administration with reasons as per the CRF will be listed for the safety set.

1.4.2 Compliance to study treatments

QVA149 110 mcg/50mcg and/or placebo of single dose dry powder inhaler per capsule with Ultibro® was prescribed to each patient once daily at two different periods.

The compliance is defined as the percentage of doses taken by the patient at each period and will be calculated using the following formula:

Compliance (%) = 100 x (total number of capsules administered / total number of capsules dispensed).

The number of capsule administered is captured in the CRF pages. The number of capsules dispensed is same as the number of days dosed as per protocol assessment schedule in each period.

Compliance will be summarized with the standard descriptive statistics and by categories (i.e., <80% and 80-100%) for the safety set.

1.5 Prior and concomitant medications

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment at Visit 4. Any medication starting on or after the day of first dose of study treatment will be a concomitant medication, including those which were started pre-baseline and continued into the study period(s).

Both COPD-related and non COPD-related medications will be coded using latest MedDRA version and summarized by ATC class and preferred term. The summaries will be provided separately for both prior and concomitant medication.

All summaries will be on the safety set.

1.6 Efficacy evaluation

Effectiveness analysis related to lung function will be performed on both FAS and PP set, whereas analysis related to cardiac function parameters will be performed only on PP set.

Summary statistics by treatment will be provided for all efficacy outcome variables.

Data within 6 hours of rescue medication use will be excluded from all efficacy analysis.

1.6.1 Primary variable

The primary variable is left ventricular end-diastolic volume (LV-EDV in mL) collected after 2 weeks of treatment at Visit 5 and Visit 7 from MRI eCRF.

1.6.1.1 Statistical model, hypothesis and method of analysis

The comparison between QVA149 (110/50) and placebo in terms of LV-EDV (mL) for the PP set will be evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a) at a two-sided 5% significance level:

H_0: There is no difference between QVA149 (110/50) compared to placebo in LV-EDV (mL)

H_a: There is a difference between QVA149 (110/50) compared to placebo in LV-EDV (mL)

The primary analysis will be performed comparing treatment means with respect to the LV-EDV (mL) using analysis of variance (ANOVA) model with period and treatment as fixed effects and patient as a random effect.

Adjusted least square means, point estimate of difference between treatment means, 95% confidence interval for treatment difference and p-value will be presented.

Additionally unadjusted descriptive statistics (raw mean, SD, range) will be provided for each treatment and for the treatment contrast.

The absolute values and change from period baseline values in LV-EDV (mL) by visits will be provided for each treatment.

Each of the above summary and analysis will be repeated for the FAS set.

A Q-Q plot will be presented to verify the normality assumption of the primary variable.

1.6.1.2 Handling of missing values/censoring/discontinuations

There will be no imputation for missing data, and the primary analysis will be based on only observed data.

1.6.1.3 Supportive analysis

- If the observations of the primary variable does not follow the normality assumptions (confirmed by the QQ plot) then additional analysis of LV-EDV using the Wilcoxon signed rank test will be performed to test the difference between treatments.

- Secondly, the primary variable, left ventricular end-diastolic volume will be affected by the patient's blood pressure. However as the blood pressures are collected after baseline, their effects might be confounded with treatment effects and cannot be truly adjusted. Hence as a supportive exploratory analysis, the treatment means will be compared using an analysis of co-variance (ANCOVA) model with period, treatment as fixed effects, patient as a random effect and mean systolic blood pressure and mean diastolic blood pressure as additional continuous covariates. Where the mean systolic/diastolic blood pressure is calculated as the average over four measurements (beginning and the end of the cardiac sequence, after oxygen perfusion and finally at the end of all MRI sequences).
  Adjusted least square means, point estimates as difference between treatment means, 95% confidence interval for treatment difference and p-value will be presented.

1.6.2 Secondary variables

1.6.2.1 Analysis of spirometry outcomes

The spirometry variables FEV_1 (L) (Forced Expiratory Volume in 1 second) and FVC (L) (Forced Vital Capacity) are collected after 2 weeks of treatment at visit 5 and 7 (75 min post-dose) in the spirometry eCRF.
Each of these two variables will be analyzed using analysis of variance (ANOVA) model with period and treatment as fixed effects and patient as a random effect.
Adjusted least square means, point estimate as difference between treatment means, 95% confidence interval for treatment difference and p-value will be presented.

The absolute values and change from period baseline values for spirometry outcomes by visits will be summarized descriptively for each treatment.

The above analysis will be performed on both PP and FAS set.

1.6.2.2 Analysis of bodyplethysmography outcomes

The bodyplethysmography variables such as

- sReff (Effective resistance),
- IC (inspiratory capacity),
- TLC (Total lung capacity),
- RVol (residual volume),
- SVC (Slow Vital Capacity) and
- FRC (functional residual capacity)

are collected after 2 weeks of treatment at visit 5 and 7 in the bodyplethysmography eCRF.

Each of the bodyplethysmography variables mentioned above will be analyzed using a similar analysis of variance (ANOVA) model with period and treatment as fixed effects and patient as a random effect.
Adjusted least square means, point estimate as difference between treatment means, 95% confidence interval for treatment difference and p-value will be presented.

The absolute values and change from period baseline values for bodyplethysmography outcomes by visits will be provided for each treatment.

The above analysis will be performed on both PP set and FAS.

1.6.2.3 Analysis of cardiac parameters

The cardiac variables right and left ventricular ejection fraction, right and left ventricular endsystolic volumes, right ventricular enddiastolic volume, and other cardiac outputs collected after 2 weeks of treatment at visit 5 and 7 from MRI in the eCRF.

The following cardiac variables will be analyzed using analysis of variance (ANOVA) model with period and treatment as fixed effects and patient as a random effect.

- right and left ventricular ejection fraction,
- right and left ventricular end-systolic volumes,
- right ventricular end-diastolic volume,
- right and left cardiac outputs

Adjusted least square means, point estimate of difference between treatment means, 95% confidence interval for treatment difference and p-value will be presented.

Additionally, absolute values and change from period baseline values will be summarized using standard descriptive statistics for all the cardiac parameters for each treatment. Listings will also be presented.

Cardiac output for both right and left ventricle is defined as CO [l/min] = (EDV-ESV [ml/beat]) * heart rate [bpm] /1000, and will also be summarized.

The above analysis of cardiac parameters will be performed on PP set only.

1.6.3 Analysis of exploratory parameters

1.6.3.1 COPD assessment test (CAT)

The CAT is a short instrument used to quantify the symptom burden of COPD and will be used to assess the health status of patients in this study. It consists of eight items, each presented as a semantic 6-point differential scale (with scores from 0 to 5), providing a total score out of 40. A higher score indicates a worse health status. The total CAT score will be obtained by summing the scores on individual items. If one or two items are missing, they will be replaced with the mean of the completed items. If three or more items are missing, the CAT total score will be missing.

Absolute values and change from period baseline values in the CAT total score by treatment period will be summarized using standard descriptive statistics.

The absolute values and change from baseline in CAT total score at visit 5 and 7 will be analyzed using a similar analysis of variance (ANOVA) model as used for the primary analysis; with period and treatment as fixed effects and patient as a random effect. Adjusted least square means, point estimate of difference between treatment means, 95% confidence interval for treatment difference and p-value will be presented.

The above analysis will be performed on FAS set only.

1.6.3.2 Baseline Dyspnea Index –Transitional Dyspnea Index (BDI-TDI)

Dyspnea is measured at baseline, Visit 4 and Visit 6 using the baseline dyspnea index (BDI) for Period I and Period II respectively and at Week 5 and Week 7 using the transition dyspnea index (TDI), which captures changes from baseline by period.

The BDI and TDI grades will be summarized by treatment using number and percentage of each category.

The TDI focal scores defined as the sum of scores of three domains (i.e., Functional impairment ranging from -3 to 3; Magnitude of task ranging from -3 to 3; Magnitude of effort ranging from -3 to 3), focal ranging between -9 to 9, will be analyzed using analysis of variance (ANOVA) model with period and treatment as fixed effects and patient as a random effect. Adjusted least square means, point estimate of difference between treatment means, 95% confidence interval for treatment difference and p-value will be presented.

The above summary will be presented on FAS set only.

1.6.3.3 Biventricular cardiac mass measures

Absolute values and change from period baseline values in the right and left ventricular cardiac mass to end of each treatment period will be summarized using standard descriptive statistics.

Each of the biventricular cardiac mass parameters will be analyzed using analysis of variance (ANOVA) model with period and treatment as fixed effects and patient as a random effect. Adjusted least square means, point estimate of difference between treatment means, 95% confidence interval for treatment difference and p-value will be presented.

The above summary will be presented on PP set only.

1.6.3.4 Pulmonary parenchymal blood flow measures

Absolute values and change from period baseline values in the parameters related to pulmonary artery blood flow (room air) and pulmonary artery blood flow (100% oxygen) listed in Appendix 1 will be summarized using standard descriptive statistics to end of each treatment period.

The above descriptive statistics will be presented on PP set only.

1.6.3.5 Echocardiography assessments

Absolute values and change from period baseline values in the parameters of left and right ventricular of diastolic function, left and right ventricular of systolic function and pulmonary arterial pressures will be summarized using standard descriptive statistics to end of each treatment period.

The above descriptive statistics will be presented on PP set only.

1.6.3.6 Impulse oscillometry

Absolute values and change from period baseline values in the Resistance (R5, R20 and R5-20), Reactance (X5) and Area of reactance (AX) will be summarized using standard descriptive statistics to end of each treatment period.

The above descriptive statistics will be presented on FAS set only.

1.6.3.7 Regional lung ventilation, 19F washout time, perfusion measures and oxygen MRI

Absolute values and change from period baseline values in the parameters related to lung ventilation, 19F washout time perfusion measures and oxygen MRI in Appendix 1 will be summarized using standard descriptive statistics to end of each treatment period.

The above summary will be presented on FAS set only.

1.6.3.8 Rescue medication use

Rescue medication (salbutamol) used during the study will be captured in dispense and administration of beta-2 agonist CRF page. The number of puffs of rescue medication use will be summarized descriptively by treatment on FAS set.

1.6.3.9 Activity with Actibelt

Absolute value and change from baseline in the parameters related to the physical activity performed with Actibelt device will be summarized using standard descriptive statistics to end of each treatment period. The parameters collected using actibelt are:

- Average time belt worn
- Maximum coherent walking distance

- Mean velocity while walking/real world gait speed
- Ratio of steps within sequences of 50 or more steps
- Steps running
- Steps walking
- Total distance travelled
- Total running time
- Total walking time
- Walking step frequency
- Activity temperature raw
- Activity temperature adherence
- Walking step length

The above descriptive summary statistics will be presented on FAS set only.

1.7 Safety evaluation

All safety evaluations as a part of secondary objectives will be based on the safety set.

1.7.1 Adverse events (AE)

All adverse events (including COPD exacerbations) will be coded with MedDRA version and included in tables and listings by treatment last administered.
All AEs occurring prior to start of study treatment after signing of informed consent will be listed only. The following summaries of AEs will be presented.

- **AEs by primary system organ class and preferred term**

  The number and percentage of patients who reported adverse events will be summarized by primary system organ class and preferred term. Primary system organ classes will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending frequency within the QVA149 (110/50) treatment arm.

  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.

- **AEs by severity**

  All adverse events will be summarized by primary system organ class, preferred term and severity. If a patient reported more than one adverse event with the same preferred term, the highest (maximum) severity will be presented. If an adverse event occurs

more than once within the same patient in one treatment period will be counted once by maximum severity and treatment. A missing severity data will be considered as severe.

- **AEs suspected to be related to study drug**

  All adverse events suspected to be related to study drug (according to the investigators) will be summarized by primary system organ class and preferred term. Relationship to study drug is considered as suspected for those events where "Relationship to study drug" is answered by the investigator as "Suspected".

- **AEs leading to permanent study drug discontinuation**

  All adverse events leading to permanent study drug discontinuation, regardless of study drug relationship, will be summarized by primary system organ class and preferred term.

In addition, adverse events resulting in dose adjustment or temporary interruption, use of concomitant medication, non-drug therapy, hospitalization or prolonged hospitalization will be summarized by treatment last administered.

1.7.2 Serious adverse events (SAE)

Number and percentage of patients with serious adverse events by treatment last administered, regardless of study drug relationship, will be presented by primary system organ class and preferred term.

1.7.3 Deaths

All the deaths in the clinical database will be listed with the investigator-reported principal cause. Deaths occurring after the first dose of study treatment will be summarized by treatment last administered.

1.7.4 Vital signs

Summary statistics for absolute and change from baseline will be provided of vital signs (pulse rate and systolic and diastolic blood pressure) at baseline, start and end of Period I and start and end of Period II will be provided and all vital signs will be listed.

The number (%) of patients with pulse rate of <40 and >130 bpm; systolic blood pressure of <75 and >200 mmHg; diastolic blood pressure of <40 and >115 mmHg will be summarized by treatment group.

Notable values for vital signs and change from baseline will be summarized. A notable value is defined as follows:

- Systolic blood pressure

“Low” criterion: <75 mmHg, or ≤90 mmHg and decrease from baseline ≥20 mmHg

“High” criterion: >200 mmHg, or ≥180 mmHg and increase from baseline ≥20 mmHg

- Diastolic blood pressure

"Low" criterion: <40 mmHg, or ≤50 mmHg and decrease from baseline ≥15 mmHg

"High" criterion: >115 mmHg, or ≥105 mmHg and increase from baseline ≥15 mmHg

- Pulse rate

"Low" criterion: <40 bpm, or ≤50 bpm and decrease from baseline ≥15 bpm

"High" criterion: >130 bpm, or ≥120 bpm and increase from baseline ≥15 bpm

An additional listing will be provided for patients with notably abnormal vital signs.

1.7.5 Weight

Summary statistics for weight at pre-screening, baseline and end of Period-II assessments will be provided. Listing will be provided for weight and height (pre-screening only).

1.7.6 Laboratory data

1.7.6.1 Hematology

Laboratory assessments related to hematology are scheduled at baseline, end of Period I and end of Period II.

Summary statistics for absolute and change from baseline will be provided and all laboratory data (including any unscheduled assessments) will be listed with abnormal values flagged. The listing will include the last treatment received before assessment (if any) and the number of days since last treatment. Any value considered as significantly notable will be reported by the investigator as an adverse event.

1.7.6.2 Clinical chemistry

Laboratory assessments related to hematology are scheduled at baseline, start and end of Period I and start and end of Period II.

Summary statistics for absolute and change from baseline will be provided and all laboratory data (including any unscheduled assessments) will be listed with abnormal values provided by central laboratory being flagged. The listing will include the last treatment received before assessment (if any) and the number of days since last treatment. Any value considered as significantly notable will be reported by the investigator as an adverse event.

1.7.7 Electrocardiogram (ECG)

ECG assessments are scheduled at baseline, start of period I and start period II. Summary statistics of ECG parameters by sequence will be presented.

The number and percentages of patients with clinically notable QTcF values will be summarized by treatment sequence and visits.

Where QTc will be calculated from the QT interval and RR (in seconds) using Fridericia's formula as $QTcF = QT / 3\sqrt{RR}$, where $3\sqrt{}$ denotes the cube root.

ECG results will be listed by patients.

Clinical notable criteria for QTcF (Fridericia's formula)

ECG parameter (unit)	Clinically notable range
QTc (ms)	> 450 for males
QTc (ms)	> 470 for females

1.8 Determination of sample size

A QVA149-placebo treatment difference in left ventricular enddiastolic volume (primary endpoint) of 4 ml is considered a sufficient magnitude of effect to reveal mechanistic aspects relevant for COPD patients. The effect size of 4 ml is estimated based on different publications comparing COPD patients with non-COPD patients or with patients of different percentage emphysema, demonstrating differences in LVEDV between 4 – 25 ml [7, 8, 17, 18].

The intraindividual standard deviation of 10 ml is based on Bellenger et al, who describes the interstudy variability within 7 days with an SD of 7.4 ml [19]. As the reproducibility of the method itself (2 measurements with a minimal time interval) is given with a SD of 6.7 ml, an overall SD for this trial is assumed to be 10 ml [20].

With a (within-patient-) standard deviation of 10 ml, 62 patients will be randomized initially with the intention that 52 patients complete the study with valid MRI-measurements. This samples size will provide 80% power to detect the difference as statistically significant at the 5% significance level (2 sided).

1.9 Changes in the conduct of the study or planned analysis

The terms center and patient within center is dropped from the primary analysis model due to the fact that there is only one center in the study. Patient is included in the model as a random effect.

All statistical analyses models similar to primary analysis were modified similarly.

Clinical Study Report –

Appendix 16.1.9 Documentation of statistical methods

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

16.1.9.1 Major protocol deviations and other exclusion criteria

Deviation code	Text description	Severity code
I01	Written informed consent was not obtained before performing any assessment.	5
I02	Subject age is less than 40 or Subject age is missing	age < 37 : 1 Age >=37 : 49
I03	COPD is not stable according to the current GOLD guidelines (GOLD2014) and the subject was continuing in the study	1
I04	"FEV1 of normal predicted value after inhalation of salbutamol" is greater than or equal to 80% of the predicted normal value at Visit 3 or Visit 3a	1
I04a	Post-bronchodilator FEV1/FVC is greater than or equal to 0.7 at Visit 3 or V3a	1
I05	Subject is Current or ex-smokers and Estimated number of pack years is less than 10 pack years	1
I05a	Smoking history is Never smoked at visit 1 or 1a	1
I06	RVol is less than or equal to 135% at Visit 3, before taking salbutamol.	1
E01	Subject with conditions contraindicated for treatment with, or having a history of reactions/hypersensitivity to any of the anticholinergics or long and short acting beta-2 agonists or sympathomimetic amines or lactose or any of the other excipients inhaled drugs, drugs of a similar class and the subject was continuing in the study.	1
E02	QTcF measured at Visit 3 or Visit 3a is greater than or equal to 450 ms for males	1
E02a	QTcF measured at Visit 3 or Visit 3a is greater than or equal to 470 ms for females	1
E02b	Subject with history of long QT syndrome at Visit 3 and the subject was continuing in the study	1
E03	Clinically significant abnormality reported on the ECG at Visit 3 would be at potential risk for patients by the Judgement of the investigator and the subject was continuing in the study.	1
E04	Subject with clinically significant cardiovascular abnormalities, cardiac arrhythmias, heart failure with left ventricular ejection fraction equal to or less than 40% by MRI scan at Visit 4, unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, history of myocardial infarction 6 months prior to Visit 2 and the subject was continuing in the study	1

E05	Subject with History or current atrial fibrillation confirmed by ECG at Visit 3 and the subject was continuing in the study	1
E06	Subject having pacemaker or bypass and the subject was continuing in the study	1
E07	Mean sitting systolic blood pressure is greater than160 mmHg and/or Mean sitting diastolic blood pressure is greater than 90 mmHg at Visit 3 or Visit 3a	1
E08	Past or present disease may affect the outcome of this study as judged by the investigator	1
E09	History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases and the subject was continuing in the study	49
E10	Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or severe renal impairment (GFR equal to or less than 30 mL/min/1.73 m2) including those with end-stage renal disease requiring dialysis or urinary retention and the subject was continuing in the study	49
E11	Subject reported with Type I Diabetes mellitus	49
E11a	Subject is with uncontrolled Type II diabetes and the subject was continuing in the study	49
E12	Patients with active/ clinical history of asthma and the subject was continuing in the study	1
E13	Subject with claustrophobia or presence of any metal objects within the patient and unable to undergo MRI scan and the subject was continuing in the study	49
E14	History of lower respiratory tract infection within four weeks prior to Visit 2 and between Visit 2 and Visit 4 and the subject was continuing in the study	1
E15	History of one COPD exacerbation that required treatment with antibiotics and/or systemic steroids (oral or intravenous) and/or hospitalization within 3 months prior to Visit 2 or Visit 2a and the subject was continuing in the study	1
E16	More than one COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalization within 6 months prior Visit 2 and the subject was continuing in the study	1
E17	Subject reported with COPD exacerbation between Visit 2 or Visit 2a and Visit 4 or visit 4a and the subject was continuing in the study	1
E18	Subject requiring long term oxygen therapy on a daily basis for chronic hypoxemia and the subject was continuing in the study	1
E19	Patient with active pulmonary tuberculosis, unless confirmed by imaging in the last year to be no longer active and the subject was continuing in the study	1
E20	Patient with pulmonary lobectomy or lung volume reduction surgery or lung transplantation and the subject was continuing in the study	1

E21	Patients with a diagnosis of alpha 1 anti-trypsin deficiency and the subject was continuing in the study	1
E22	Body mass index (BMI) is greater than 40 kg/m2 at visit 3 or V3a	1
E23	Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study and the subject was continuing in the study	1
E24	Patients are known to be unreliable or non-compliant as judged by the investigator and the subject was continuing in the study	1
E25	Relevant history of drug or alcohol abuse as judged by the investigator and the subject was continuing in the study and the subject was continuing in the study	49
E26	Suspected inability to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study and the subject was continuing in the study	1
E27	Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever is longer and the subject was continuing in the study	1
E28	Patients receiving any prohibited medications as per protocol and the subject was continuing in the study	1
E30	Subject was pregnant or breast feeding (pregnancy defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG test (less than 5mIU/ml)) and the subject was continuing in the study	49
E31	Subject of child-bearing potential or capable of becoming pregnant, not using effective methods of contraception during dosing of study treatment and the subject was continuing in the study	49
S02	An alternative inhalation device was used for the administration of the Study drug or placebo capsules during the study and the subject was continuing in the study	1
S03	Patient taking Nebulized salbutamol and or other rescue treatment other than salbutamol and the subject was continuing in the study.	1
S04	Subject received at least one pack of incorrect study drug at dispensing visit and the subject was continuing in the study	1
S15	Written informed consent of 19F MRI Informed consent was not obtained before performing 19F MRI assessment.	49
D01	Abnormal test procedure results indicating risk for the patient on continued inhalation of the study drug and the subject was continuing in the study	49
D02	Codes broken accidentally	1
OTH01	Premature discontinuation of study	50
OTH02	Premature discontinuation of study drug	50
OTH03	Compliance to study drug < 80% in any study period	50

16.1.9.2 Patient classification

Protocol deviations severity codes leading to patient classification into the analysis sets are as follows:

Severity codes	Actions
0	Exclude from all efficacy analysis (FAS, PP)
1	Exclude from Per-Protocol analysis (PP)
5	Exclude from all safety analyses (SAF)
8	Exclude from all analysis (FAS, PP, SAF)
9	Included in all efficacy analysis
49	Report relevant PD, include in all analysis
50	No PD, but affects data availability/validity, exclude from Per-Protocol analysis (PP)

Patient classification based on severity codes

Analysis set	PD severity codes that cause a subject to be excluded
FAS	0, (5*), 8
SAF	5, 8
PP	0, 1, (5*), 8, 50

* Note: given that the PP is nested within the FAS set, which is itself nested within the SAF, severity code 5 implies exclusion from all three of these analysis sets (i.e. SAF, FAS and PP).

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

16.1.9.3 Derivations, Baseline and post-baseline definitions

- Data from unplanned or unscheduled visits or the early treatment/study discontinuation visits will be listed.
- Duration of COPD is calculated from the date of COPD first diagnosed as recorded on the eCRF until the date of Visit 1. If the date is missing in day and/or month, it will be imputed as follows. If the year is before Visit 1, the missing days will be imputed as the first of the month and the missing months will be imputed as July. If the year is the current year of Visit 1, the missing days will be imputed as the first of the month and the missing months will be imputed as January.
- **BMI (kg/m^2)** = weight (kg) / [height (m)]^2
- Time since termination of smoking is calculated from the date of smoking termination as recorded on the eCRF until the date of Visit 1.
- When change from baseline is of interest then it will be calculated at each period using following formula, where baseline and post-baseline values are both available:

  Change from baseline at period x = post-baseline value at period x– baseline value at period x.

Study day

Study day is defined as the number of days since the date of first dose of study medication. It is defined by statistical programming and reported in the CSR listings.

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.

Baseline measurements

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

Period baseline value is defined as value taken prior to first dose of study treatment at visit 4 and visit 6 for period I and period II respectively.

If the value is missing at visit, then the baseline value will be imputed by the non-missing last available pre-dose value.

Post-baseline assessments

Post-baseline values are defined as assessment taken after first dose of study treatment at each period.

For safety data, all AEs starting on or after the first dose of study treatment will be summarized as post-baseline observations.

16.1.9.4 Statistical methodology and assumptions

SAS codes to perform ANOVA

The SAS procedure PROC MIXED will be used with the following SAS code:

```
PROC MIXED DATA = ....  ORDER =internal;
 CLASS usubjid aperiod trtpn;
 MODEL aval = aperiod trtpn / DDFM=kr;
 RANDOM usubjid;
  LSMEANS trtpn;
 ESTIMATE "QVA149 - Placebo" 1 -1/ CL ALPHA=0.05;
RUN;
```

where aval = dependent variable, e.g. left ventricular enddiastolic volume
trtpn = Treatment within period as randomized
aperiod = Period
usubjid = Patient identifier

Model fit will be identified by a QQ plot of residuals.

SAS code to perform ANCOVA

The SAS procedure PROC MIXED will be used with the following SAS code:

```
PROC MIXED DATA = ....  ORDER =internal;
 CLASS usubjid aperiod trtpn;
 MODEL aval = aperiod trtpn msystolic mdiastolic/ DDFM=kr;
 RANDOM usubjid;
 LSMEANS trtpn;
 ESTIMATE "QVA149 - Placebo" 1 -1/CL ALPHA=0.05;
RUN;
```

where aval = dependent variable, e.g. left ventricular enddiastolic volume
trtpn = Treatment within period as randomized
aperiod = Period
usubjid = Patient identifier
msystolic = Mean systolic BP
mdiastolic = Mean diastolic BP

SAS code to perform Wilcoxon signed rank test

```
PROC NPAR1WAY DATA = … WILCOXON hl alpha=.05;
        CLASS trtpn;
        VAR aval;
        EXACT hl;
RUN;
```

where aval = dependent variable, e.g. left ventricular enddiastolic volume
trtpn = Treatment within period as randomized

16.1.9.5 Appendices

Appendix 1: List of MRI Parameters

Heart function	
Heart frequency (SA cine):	

Blood Pressure during MRI	systolic		diastolic	
Prior to heart sequence:		/		mmHg
Prior to oxygen:		/		mmHg
During to oxygen:		/		mmHg
End of MRI:		/		mmHg

Left ventricle	Value		Index	
LV-EDV:		ml		ml/m²
LV-ESV:		ml		ml/m²
LV-SV:		ml		ml/m²
LV-EF:		%		
LV-mass:		g		g/m²
E/Ea:				

LV significant focal wall motion abnormalities:

Right ventricle	Value		Index	
RV-EDV:		ml		ml/m²
RV-ESV:		ml		ml/m²
RV-SV:		ml		ml/m²
RV-EF:		%		
RV-mass:		g		g/m²

RV significant focal wall motion abnormalities:

Pulmonary arterial blood flow (room air):	
Forward volume:	ml/beat
Regurgitant volume :	ml/beat
Maximal flow velocity:	cm/s
Mean systolic flow velocity:	cm/s
Mean flow velocity (total cardiac cycle):	cm/s
Acceleration volume:	ml
Acceleration time:	ms
Duration of systole:	ms
Heart frequency:	/min
Diameter of pulmonary artery:	cm
Area of pulmonary artery (syst):	mm^2
Area of pulmonary artery (diast):	mm^2

Pulmonary arterial blood flow (100% oxygen):	
Forward volume:	ml/beat
Regurgitant volume :	ml/beat
Maximal flow velocity:	cm/s
Mean systolic flow velocity:	cm/s
Mean flow velocity (total cardiac cycle):	cm/s
Acceleration volume:	ml
Acceleration time:	ms
Duration of systole:	ms
Heart frequency:	/min
Diameter of pulmonary artery:	cm
Area of pulmonary artery (syst):	mm^2
Area of pulmonary artery (diast):	mm^2

Lung perfusion	
PBF mean total:	ml/min/100 ml lung volume
Variation coefficient PBF total:	ml/min/100 ml lung volume
Coronary flow (trachea):	ml/min/100 ml lung volume
Right lung PBF (mean)	
total:	ml/min/100 ml lung volume
upper lobe:	ml/min/100 ml lung volume
middle lobe:	ml/min/100 ml lung volume
lower lobe:	ml/min/100 ml lung volume
Left lung PBF (mean)	
total:	ml/min/100 ml lung volume
upper lobe:	ml/min/100 ml lung volume
lower lobe:	ml/min/100 ml lung volume
anterior/posterior PBF fraction :	
PTT:	s

Oxygen MRI:	
O_2 wash-out time:	s
room air	
T1	ms
variation coefficient	
100% oxygen	
T1	ms
variation coefficient	
OTF:	10^{-4} s^{-1} $\%O_2^{-1}$

Ventilation MRI:	
Fractional ventilation total (coronal)	
Fractional ventilation :	
Fractional ventilation total normalized:	
variation coefficient:	
% area under cutoff:	
Fractional ventilation saggital right	
Fractional ventilation :	
Fractional ventilation total normalized:	
variation coefficient:	
% area under cutoff:	
Fractional ventilation saggital left:	
Fractional ventilation :	
Fractional ventilation total normalized:	
variation coefficient:	
% area under cutoff:	

19 F washout time	
Mean:	s
Variation coefficient of washout time:	
Mean number of breaths:	
Variation coefficient of number of breaths:	

Appendix 2: GOLD guidelines

Classification of severity of airflow limitation in COPD based on post-bronchodilator FEV_1	
	In patients with $FEV_1/FVC < 0.7$
GOLD 1	• $FEV_1 \geq 80\%$ predicted
GOLD 2	• $50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	• $30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	• $FEV_1 < 30\%$ predicted

Appendix 3: GOLD guidelines (2014)

- Patient Group A – Low Risk, Less Symptoms
  Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation); and/or 0-1 exacerbation per year and not hospitalization for exacerbation; and CAT score <10 or mMRC grade 0-1.
- Patient Group B – Low Risk, More Symptoms
  Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation); and/or 0-1 exacerbation per year and no hospitalization for exacerbation; and CAT score ≥10 or mMRC grade ≥2.
- Patient Group C – High Risk, Less Symptoms
  Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation); and/or ≥2 exacerbations per year or ≥1 with hospitalization for exacerbation; and CAT score <10 or mMRC grade 0-1.
- Patient Group D – High Risk, More Symptoms
  Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation); and/or ≥2 exacerbations per year or ≥1 with hospitalization for exacerbation; and CAT score ≥10 or mMRC grade ≥2.