

Clinical Development

CQVA149A

CQVA149ACA01 / NCT02202616

POWER: Prospective Cohort Study for the Real – Life Effectiveness Evaluation of GlycOpyrronium With IndacatERol combination in the management of COPD in Canada

RAP Module 3 – Detailed Statistical Methodology

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Document type: RAP Documentation

Document status: Amendment 1

Release date: 14-Sep-17

Number of pages: 21

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Document History – Changes compared to previous version of RAP module 3

Not applicable.

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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 CQVA149ACA01. This is a single cohort interventional study which is designed to evaluate the effectiveness of QVA149 (indacaterol 110 mcg / glycopyrronium 50 mcg) on pre-dose trough FEV₁, COPD symptoms and quality of life in COPD patients with moderate to severe airflow limitation, managed under a routine clinical care setting (i.e., treatment with either tiotropium or, fixed dose combination of fluticasone propionate/salmeterol) in Canada.

Data will be analyzed by statistical 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.

Statistical and analytical plans

Patients and treatments

1.1 Analysis sets

Intent to Treat (ITT) set will include all patients who received the study treatment and returned for at least one post-treatment follow-up visit. The ITT set will be used for summaries of patient disposition, analysis sets, listings of major protocol deviations, premature study discontinuations, demographic and baseline characteristics and all efficacy analyses including the primary analysis.

Modified intent to treat (mITT) set will include all patients from the ITT set except those who had the percent predicted FEV₁ value greater than 80% (severity of mild COPD, GOLD guidelines 2017) at screening.

Safety set (SAF) will include all patients who received at least one dose of the study treatment. The SAF will be used for all safety analyses and demographic characteristics.

Per protocol set (PPS) will include all patients without any major deviations from the protocol, i.e., who have fulfilled all the study inclusion and exclusion criteria and undergone all study visits and assessments as per the schedule mentioned in the protocol. The major protocol deviations will be defined prior to database lock. The list of major protocol deviations is available in [Appendix 16.1.9](#). The PPS will be used to assess the robustness of the results drawn for the primary and key secondary analysis using the ITT set.

1.2 Patient disposition, background and demographic characteristics

1.2.1 Patient disposition

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

The number and percentage of patients screened, included in the SAF set, included in the ITT set, attended each visit, completed and discontinued the study will be summarized. Number and percentage of patients in the ITT set will be summarized by center.

The reasons for premature discontinuation will also be summarized for patients who were discontinued from the study. Patient identification number and whether they completed or discontinued from the study (and/or treatment) will be listed, with date of last dose and primary reason for premature discontinuation.

1.2.2 Protocol deviations

The number and percentage of patients with protocol deviations will be tabulated by category and deviation for the ITT set. Protocol deviations will be listed with date and study day of occurrence, deviation code and severity for the ITT set.

The number of patients included in each analysis set will be tabulated for all screened patients. Reasons for exclusion from analysis sets will be tabulated for all screened subjects. Subject exclusion from analysis sets will be listed for all patients with reasons of exclusion (i.e., both protocol and non-protocol deviation).

1.2.3 Background and demographic characteristics

Demographics and baseline characteristics will be summarized using the SAF and ITT sets.

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

- age (in years)
- gender (Male or Female)
- predominant race (Caucasian, Black, Asian, Native American, Pacific Islander, Other)
- height (cm)
- weight (kg)
- body mass index (BMI) (kg/m²)

The following baseline disease characteristics collected at screening (Visit 1) will be summarized:

- treatment regimen (tiotropium or FDC – fluticasone propionate/salmeterol)
- smoking history (never smoked, current smoker, ex-smoker)
- number of pack-years
- alcohol consumption history
 - number of alcoholic beverages per day
- duration of COPD (years), experience of moderate and/or severe COPD exacerbations in the 12 months/6 months prior to study initiation
- use of rescue medication at baseline, type and frequency of rescue medication
- CAT score
- vital signs (sitting systolic/diastolic blood pressure (mmHg), sitting pulse rate (bpm))

In addition, the following categorizations will be done:

- Age into 40 - 64 years, 65 - 74 years, and \geq 75 years;
- BMI into \leq 30.0 kg/m² and $>$ 30.0 kg/m²;
- Duration of COPD into < 1 year, 1 - 5 years, > 5 - 10 years, > 10 - 15 years, > 15 - 20 years, and > 20 years;
- CAT scores into 0 - 10, 11 - 20, 21 - 30 and 31 - 40 representing mild, moderate, severe or, very severe clinical impact of COPD on patients.

Baseline and demographic variables: continuous variables will be summarized using descriptive statistics (mean, median, standard deviation, 95% confidence intervals (95% CI), minimum and maximum) and categorical variables will be summarized in terms of the number and percentage of patients in each category.

Details regarding the definition of baseline measurements are given in [Appendix 16.1.9](#).

1.2.4 Medical history and current medical condition

Medical history will be coded using the Medical Dictionary for Regulatory Activities terminology (MedDRA version 17.1 or later). History/conditions will be summarized for the SAF and ITT sets by primary system organ class and preferred term, and overall. 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.

1.3 Study medication

1.3.1 Study drug administration

Duration of exposure to the 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).

The duration of exposure (in days) will be summarized for the SAF and ITT sets as

- a continuous variable with the standard descriptive statistics, and
- a categorical variable classified into \leq 4 weeks, > 4 – 8 weeks, > 8 - 12 weeks, > 12 - 16 weeks and > 16 weeks, with number and percentage of patients in each category.

1.3.2 Compliance

As per the protocol, QVA149 inhalation powder hard capsules 110 mcg/50mcg per capsule with ULTIBRO® BREEZHALER® are to be prescribed to each patient once daily.

Compliance with treatment will be defined as the percentage of doses taken by the patient and will be calculated as follows:

Step 1: to calculate the duration (in days) for each patient in the study (treatment end date – treatment start date +1). The prescribed dose is to be taken once daily. So the number of dose prescribed is equal to the duration of exposure in days.

Step 2: Number of capsule consumed = Capsules dispensed – Capsule returned. (based on the data entered in the CRF)

Step 3: Compliance (%) = (Number of doses consumed/Number of doses prescribed) X 100%.

Compliance will be summarized by visit for the ITT set as

- a continuous variable with the standard descriptive statistics, and
- a categorical variable classified into < 80%, ≥ 80% to < 100%, ≥ 100 to < 120%, ≥ 120%, with number and percentage of patients in each category.

1.4 Prior and concomitant medication

COPD-related (COPD or COPD exacerbation) medications, including rescue medications, will be coded using the WHO Dictionary and summarized by the respective ATC level I and IV terms.

Non COPD related medications will be summarized in the same way as COPD-related medications.

Both COPD-related and non COPD-related medications will be summarized separately for prior and concomitant medications.

All summaries will be on the SAF and ITT sets.

1.5 Efficacy evaluation

All effectiveness analysis will be performed on the ITT set and selected analyses will be repeated on the PPS.

1.5.1 Primary variable

The primary variable is pre-dose trough FEV₁ (L).

The primary effectiveness variable is the absolute change in trough FEV₁ from baseline (Visit 1) to the Week 16 visit.

1.5.1.1 Statistical model, hypothesis and method of analysis

The primary objective of the study is to evaluate the effectiveness of treatment with QVA149 (110/50) in the management of patients with moderate to severe COPD. The effectiveness will be assessed by change from baseline in pre-dose trough FEV₁ (L) to Week 16. Baseline pre-dose trough FEV₁ (L) is the assessment taken prior to the start of QVA 149, which is typically the value at Visit 2. If the trough FEV₁ (L) value at Visit 2 is missing, then the baseline value will be set to missing. The primary analysis will include patients with a valid observation at baseline and Week 16.

The mean change from baseline in pre-dose trough FEV₁ (L) will be summarized using standard descriptive statistics and estimated along with the 95% confidence interval, which will be used to assess the precision of the estimate and to make inferences to the target population.

The above analysis will be repeated separately for the two subgroups of patients based on the prior COPD treatment (i.e., Tiotropium or FDC – fluticasone/salmeterol).

In addition, between subgroup comparison (Tio – Flu/Sal) for change from baseline in pre-dose trough FEV₁ (L) to Week 16, will be performed using a Student's t-test for independent samples.

All the analyses mentioned in this section will be repeated for the PPS, to support the results obtained using the ITT set.

As a sensitivity analysis, the primary analysis will also be repeated on the mITT set.

1.5.1.2 Handling of missing values/censoring/discontinuations

There will be no imputation for missing data at Week 16, and the primary analysis will be based on only observed data.

1.5.1.3 Subgroup analysis

The primary variable, change from baseline in pre-dose trough FEV₁ (L) to Week 16 will also be summarized for the subgroups of interest defined below. The mean change from baseline in pre-dose trough FEV₁ (L) will be summarized by subgroups using standard descriptive statistics and estimated along with the 95% confidence interval.

- gender (male/female)
- age (\leq 65 years, $>$ 65 years)
- smoking status (never smoked, current smoker, ex-smoker)
- severity of airflow limitation (GOLD guidelines 2017) as
 - ❖ GOLD 1: Mild ($FEV_1 \geq 80\%$ predicted),
 - ❖ GOLD 2: Moderate ($50\% \leq FEV_1 < 80\%$ predicted),
 - ❖ GOLD 3 and GOLD 4 : Severe and Very severe ($FEV_1 < 50\%$ predicted)
- exacerbation history in the previous year (0 exacerbation/1 exacerbation)
- treatment regimen (tiotropium or FDC – fluticasone propionate/salmeterol)

1.5.2 Analysis of secondary variable

All endpoints mentioned below will be listed. These analysis will be performed on the ITT set.

1.5.2.1 Change from baseline in pre-dose trough FEV₁ (L) to Week 4

The change from baseline in pre-dose trough FEV₁ (L) to Week 4 will be analyzed in a similar manner as the primary variable, i.e.

- The mean change from baseline in pre-dose trough FEV₁ to Week 4 will be summarized using standard descriptive statistics and estimated along with the 95% confidence interval.

- The above analysis will be repeated separately for the two subgroups of patients based on the prior COPD treatment (i.e., Tio or, Flu/Sal).
- In addition, between subgroup comparison (Tio – Flu/Sal) for change from baseline in pre-dose trough FEV1 (L) to Week 4, will be performed using a Student's t-test for independent samples.

1.5.2.2 Change from baseline in COPD Assessment Test (CAT) score to Week 4 and Week 16

The change from baseline in CAT score to Week 4 and Week 16 will be analyzed similar to the primary variable. Baseline is the CAT score obtained prior to the start of QVA 149, which is typically the score at Visit 2. If the score at Visit 2 is missing, then the baseline value will be set to missing. This analysis will include patients with a valid CAT score at baseline and Week 4 and/or Week 16.

- The mean change from baseline to Week 4 and Week16 will be summarized using standard descriptive statistics and estimated along with the 95% confidence interval.
- This analysis will be repeated separately for the two subgroups of patients based on the prior COPD treatment (i.e., Tio or, Flu/Sal).
- In addition, between subgroup comparison (Tio – Flu/Sal) for change from baseline in CAT score to Week 4 and Week 16 will be performed separately using a Student's t-test for independent samples.

1.5.2.3 Baseline Dyspnea Index –Transitional Dyspnea Index (BDI-TDI) at baseline, 4 and 16

Dyspnea is measured at baseline Visit 2 using the baseline dyspnea index (BDI) and at Week 4 and Week 16 using the transition dyspnea index (TDI), which captures changes from baseline.

The BDI grades and TDI scores at Week 4 and Week 16 will be summarized using number and percentages and standard descriptive statistics, respectively. The TDI scores at Week 4 and Week 16 will be analyzed similar to the primary variable.

- The estimated mean change from baseline and corresponding 95% confidence intervals will be displayed for each visit.
- This analysis will be repeated separately for the two subgroups of patients based on the prior COPD treatment (i.e., Tio or, Flu/Sal).
- In addition, between subgroup comparison (Tio – Flu/Sal) of TDI scores to Week 4 and Week 16 will be performed separately using a Student's t-test for independent samples.

1.5.3 Analysis of exploratory variables

All endpoints mentioned below will be listed. These analysis will be performed on the ITT set.

1.5.3.1 Change from baseline in the Medical Outcomes Study Short Form 36 (SF-36) to Week 16

Change from baseline in the SF-36 (overall and physical health only) to Week 16 will be summarized using standard descriptive statistics and analyzed using the same analysis used for the primary variable.

- The mean change from baseline to Week 16 will be estimated along with the 95% confidence interval.
- This analysis will be repeated separately for the two subgroups of patients based on the prior COPD treatment.
- In addition, between subgroup comparison of this change to Week 4 and Week 16 will be performed separately using a Student's t-test for independent samples.

1.5.3.2 Change from baseline in the Dimension Health Status Questionnaire (EQ-5D) to Week 4 and Week 16

Change from baseline in the EQ-5D summary score using the UK weights to Week 4 and Week 16 will be summarized using standard descriptive statistics and analyzed using the same analysis used for the primary variable.

- The mean change from baseline to Week 16 will be estimated along with the 95% confidence interval.
- This analysis will be repeated separately for the two subgroups of patients based on the prior COPD treatment.
- In addition, between subgroup comparison of this change to Week 4 and Week 16 will be performed separately using a Student's t-test for independent samples.

1.5.3.3 Patient and Physician Global Satisfaction with COPD Treatment between at 4, 12 and 16 weeks of treatment

- The patient's and physician's global satisfaction responses with QVA149 at Weeks 4, 12 and 16 will be summarized with absolute and percentage of patients in each of the response categories specified in the study CRF (i.e., Very dissatisfied, Dissatisfied, Neither satisfied or dissatisfied, Satisfied and Very satisfied).
- Further to assess the dependency of the global satisfaction level on prior COPD treatment, the McNemar's test will be performed.

1.6 Pharmacokinetic evaluations (change / add PD, PK/PD, Biomarkers, as needed)

Not applicable.

1.7 Safety evaluation

All safety evaluations 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 17.1 (or later) and listed. Adverse events starting on or after the time of the first inhalation of study drug but not later than 7 days (30 days in the case of a SAE) after the date of last dose of study drug taken will be classified as a treatment emergent adverse event and will be included in all summaries.

1.7.1.1 Common Adverse events

AEs by primary system organ class and preferred term

The number and percentage of patients who reported treatment emergent 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 order of frequency.

If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once at the system organ class level.

AEs by severity

All treatment emergent adverse events will also be summarized by maximum severity, primary system organ class and preferred term. If a patient reports more than one adverse event within the same primary system organ class, only one adverse event will be counted for that patient at the highest severity level in the total row for each primary system organ class. If a patient reported more than one adverse event with the same preferred term, the highest (maximum) severity will be presented. Missing severity will be assumed to be severe in the summary table.

AEs suspected to be related to study drug

The treatment emergent 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

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

AEs requiring dose adjustment or interruption

Treatment emergent adverse events requiring dose adjustment or temporary interruption, regardless of study drug relationship, will be summarized by primary system organ class and preferred term.

AEs requiring significant additional medication or therapy

Treatment emergent adverse events requiring significant additional therapy (concomitant medication, non- drug therapy), regardless of study drug relationship, will be summarized by primary system organ class and preferred term.

AEs requiring hospitalization or prolonged hospitalization

Treatment emergent adverse events requiring hospitalization or prolonged hospitalization will be summarized by primary system organ class and preferred term. The number and percentages of the most frequent treatment emergent AEs will be summarized separately by primary system organ class and preferred term.

1.7.1.2 Serious adverse events (SAE)

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

Additionally separate tables will be provided for SAEs occurring more than 30 days after the last dose administration for patients who discontinued the study treatment but remained in the study for more than 30 days and for SAEs which happened between Visit 1 (screening) and the time of first dose for all patients in the safety set.

1.7.1.3 Adverse events of special interest

Number and percentage of patients with the following adverse events of special interest will be identified from the aforementioned summary tables:

- Atrial fibrillation
- Cardiac arrhythmias (Brady-Tachy arrhythmias)
- Cardiac Failure
- Cerebrovascular events
- Hyperglycemia
- Intubation, hospitalization and death due to asthma related events in asthma (off label use)
- Ischemic Heart disease
- Myocardial Infarction
- Narrow-angle glaucoma
- QTc prolongation

These events will be determined by pre-defined MedDRA version 17.1 search terms.

1.7.2 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 until 30 days after the date of last treatment will be summarized with numbers and percentages by visits.

1.8 Interim analyses

An interim analysis will be performed when 300 patients will have completed their Visit 3.

1.9 Other topics

No other topics were studied.

1.10 Determination of sample size

The primary effectiveness outcome measure of the study will be the change from baseline to 16 weeks in trough FEV₁ measurements in patients treated with QVA149. Therefore, the study must have sufficient sample size to produce a precise estimate of these changes in FEV₁. Precision is assessed by the width of the 95% confidence interval.

In the SPARK study the mean difference between QVA149 (indacaterol 110 mcg + glycopyrronium) and tiotropium with respect to trough FEV₁ was between 0.060 L – 0.080 L during 64 weeks of treatment. In the SHINE study the difference between tiotropium and QVA149 at 26 weeks was 0.08 L. In the ILLUMINATE study the difference between QVA149 and fixed dose combination LABA/ICS with respect to FEV₁ at 12 weeks was 0.092 L. Using the 95% CI and SEM estimates from these studies the calculated SD for the change in FEV₁ at 16 weeks is approximately 0.220 L.

Sample size calculations for the current study are based on the primary objective which is to describe the change in FEV₁ at 16 weeks after the initiation of treatment on indacaterol + glycopyrronium. The precision of the estimated mean change in FEV₁ at 16 weeks, as assessed by the 95% confidence interval, is the parameter driving the sample size.

For the current study we can assume a mean change in FEV₁ at 16 weeks of 0.080 L for the patients previously treated with tiotropium monotherapy and approximately 0.092 L for the patients previously treated fixed dose combination with LABA / ICS.

The sample size requirements of the study have been determined on the basis of the above parameters and in order to achieve a 95% confidence interval of the mean change in FEV₁ at 16 weeks with a width ($\omega/2$) of $\pm 30\%$ of the point estimate. This value is comparable with the results reported in the above clinical trials and provides reasonable precision of the estimated FEV₁ change at 16 weeks. Assuming a 0.080 L mean change in FEV₁ for the patients previously treated with tiotropium the 95% confidence interval for this cohort will be between 0.056 L – 0.104 L; for the patients previously treated with fixed dose combination LABA/ICS assuming a mean change in FEV₁ of 0.092 L the 95% confidence interval will be between 0.064 L and 0.120 L. For purposes of sample size calculations, for both cohorts the SD of the mean change in FEV₁ between baseline and 16 weeks will be assumed to be 0.220 L.

Based on the above criteria and assumptions, for the cohort of patients previously treated with tiotropium the sample size requirement is 323 patients. For the patients previously treated with fixed dose combination LABA/ICS the sample size requirement is 245 patients. The total sample size of the study will be 568. Assuming a 20% attrition rate, the total number of patients recruited will be **710** (404 previously treated with tiotropium and 306 previously treated with fixed dose combination LABA/ICS).

Patient enrolment will be designed to enroll at a 3:2 ratio of patients previously treated with tiotropium to those previously treated with fixed dose combination LABA/ICS per individual site and at the study level. Once study-wise recruitment has been completed for one of the strata, the each site will be instructed to pursue recruitment onto the other stratum only.

1.11 Changes in the conduct of the study or planned analysis

- The mITT set is introduced in the analysis plan in addition to protocol defined analysis set based on the discussion with Clinical Trial Team. This set is identical to ITT set except it excludes patients who had a percent predicted FEV₁ value of greater than or equal to 80% at screening.

The primary analysis involving the ITT set will be include all patients. As a sensitivity analysis the primary analysis will also be repeated on the mITT set.

- Based on the strong positive results for primary and secondary objectives observed in the planned interim analysis, the study team in consultation with respective medical and statistical experts confirmed that there were no anticipated additional statistical benefits in reaching the initially planned sample size of 710 enrolled subjects (assuming 20% attrition rate, whereas the actual attrition rate observed in the study was much less than 20%).

After conducting proper scientific and methodological due diligences, the recruitment was closed on the 31st of January 2017. As a result of this decision, the sample size in the final CSR analysis is reduced to 401.

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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 (or higher).

16.1.9.1 Protocol deviations and other exclusion criteria

Deviation code	Text description	Severity codes	Exclude from analysis set	Additional notes
I01A	No diagnosis of COPD according to GOLD guidelines	1	Exclude from PPS	
I01B	No diagnosis of COPD according to GOLD guidelines	1	Exclude from PPS	Exclude from mITT
I04	Smoking History of < or = 10 pack years	1	Exclude from PPS	
C03	Compliance with treatment < 80% or > 120% during any treatment/dispensing period	49	Include in all analysis	
I06	Treatment with QVA149 is indicated not as per product monograph or inappropriate for the patient	1	Exclude from PPS	
I07	Signed informed consent not obtained	8	Exclude from all analysis	
C09	Prohibited Medication taken	1	Exclude from PPS	
E04	Patient had > or = 2 moderate to severe exacerbations in past year	1	Exclude from PPS	
I03	Age < or = 40 years	1	Exclude from PPS	
E06	Patient requires ICS treatment with QVA149	1	Exclude from PPS	
E07	Patient with chronic respiratory conditions excluding lung cancer	1	Exclude from PPS	
I05	No persistent symptom as CAT score < or = 10	1	Exclude from PPS	Exclude from mITT
E08	Patient has cancer or other conditions	1	Exclude from PPS	
E09	Patients participating in an investigational drug trial.	1	Exclude from PPS	

E10	Hypersensitivity to indacaterol maleate, glycopyrronium bromide or similar component or excipient	1	Exclude from PPS	
E11	Use of other investigational drugs within 30 days of enrollment	1	Exclude from PPS	
E02	Patient on triple therapy for COPD	1	Exclude from PPS	
E13	Patient pregnant or nursing anytime during the study	1	Exclude from PPS	
E14	Effective contraceptive methods not followed by WCBP	1	Exclude from PPS	
E03	Patient has asthma or a history of asthma	1	Exclude from PPS	
E05	Patient had > or = 1 exacerbations in past 6 weeks	1	Exclude from PPS	
S13	Patient took study drug not as per protocol	49	Include in all analysis	
E072	Medical History- Lung Cancer	1	Exclude from PPS	
C07	Other GCP deviation	49	Include in all analysis	
C08	Major GCP deviation	1	Exclude from PPS	
C01	Treatment interruption instructions not followed	49	Include in all analysis	
S06	Time of study drug is before pre-dose FEV1 at BL	0	Exclude from all efficacy analysis (ITT, mITT and PPS)	Exclude from mITT
S07	Spirometry date is same as the Last study treatment date, and Dosing time is prior to the Spirometry time.	0	Exclude from all efficacy analysis (ITT, mITT and PPS)	Exclude from mITT
C05	Patient was administered screening TDI questionnaire by unqualified study personnel.	1	Exclude from PPS	

16.1.9.2 Patient classification

Protocol deviations severity codes defined in VAP Module 3 leading to patient classification into the analysis sets are as follows:

Severity codes	Actions
0	Exclude from all efficacy analyses (ITT set, PPS)
1	Exclude from Per-Protocol analysis only (PPS)
5*	Exclude from all safety analyses (SAF)
8	Exclude from all analyses (ITT set, PPS, SAF)
9	Included in all efficacy analyses
49	Report relevant PD, include in all analyses

Patient classification based on severity codes

Analysis set	PD severity codes that cause a subject to be excluded	Criteria that cause a subject to be excluded
ITT	0, (5*), 8	Enrolled but no study drug received. Not having a follow-up assessment.
Safety	5, 8	Enrolled but no study drug received
Per Protocol	0, 1, (5*), 8	

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

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

16.1.9.3 Assessment windows, baseline and post-baseline definitions, missing data handling

Data pooling and assessment windows

Data from unplanned or unscheduled visits or the early treatment/study discontinuation visits will be listed. For subjects who do not complete the study, the treatment discontinuation visit will be an unscheduled visit.

All efficacy data from unscheduled or premature discontinuation visits will not be used for missing data imputation.

For values with missing date/time, scheduled visit date and time will be used. This rule will be applied to data from scheduled visits only.

Study day

Study day is defined as the number of days since the date of first dose of study medication (QVA149 110/50). The date of first dose of study medication is defined as Day 1 and the day before the first dose of study medication is defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the first date of study medication,
Study day = Assessment date – Date of first dose of study medication + 1;
- for dates prior to the first date of study medication,
Study day = Assessment date – Date of first dose of study medication.

Baseline measurements

In general, baseline is defined as the last measurement before the first dose of study drug at Visit 2 or Day 1.

Baseline pre-dose trough FEV₁ (L) is defined as the value taken prior to the first dose of study drug (QVA 110/50) typically on Day 1 i.e., Visit 2. If FEV₁ value on Visit 2 is missing, then baseline will be set to missing.

Baseline dyspnea scale (BDI), baseline CAT, SF-36 and EQ-5D scores are the values obtained prior to the first dose of study treatment on Day 1 i.e. Visit 2.

Post-baseline assessments

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

For efficacy, pre-dose trough FEV₁ (L), TDI, CAT, SF-36 and EQ-5D assessments taken at any of the post-baseline visits will be considered for the analysis. Missing values will not be imputed. Post-baseline study visits are Visit 3, 4 and 5 (End of study).

For safety data, all AEs starting on or after the first dose of study treatment until 7 days (30 days for SAEs and death) after the date of last treatment will be considered as post-baseline observations.

Deaths (if any) that happened to occur after the clinical database lock will be manually described in the CSR main text, but not in the post-text table that will be done by programming.

When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available: **Change from baseline = post-baseline value – baseline value.**

Derivation of demographics and baseline characteristics

Baseline values are as described in “Baseline measurements” section above.

1. Airflow limitation is classified based on % of predicted FEV₁ and FEV₁/FVC post bronchodilation as per GOLD guidelines:

Mild (GOLD 1): FEV₁/FVC < 70 % and % of predicted FEV₁ ≥ 80 %

Moderate (GOLD 2): FEV₁/FVC < 70 % and 50% ≤ % of predicted FEV₁ < 80 %

Severe (GOLD 3): FEV₁/FVC < 70 % and 30% ≤ % of predicted FEV₁ < 50 %

Very Severe (GOLD 4): FEV₁/FVC < 70 % and % of predicted FEV₁ < 30 %

According to the study inclusion criteria 1, patients diagnosed and treated for moderate to severe COPD according to GOLD guideline are enrolled in the study. Thus, **it can be**

assumed that all enrolled patients with an exception of some who have protocol deviations (not meeting the inclusion criteria 1) **will have FEV₁/FVC < 70 %** (as FVC is not databased, this ratio cannot be verified). Further, the statistical programming will categorize patients to moderate or severe based on the following criteria ($50\% \leq \% \text{ of predicted FEV}_1 < 80\%$ %) or, ($30\% \leq \% \text{ of predicted FEV}_1 < 50\%$ %), respectively.

2. Duration of COPD is calculated from the date of COPD first diagnosed as recorded on the CRF 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.
3. The estimated number of pack years is defined as the total years of smoking multiplied by cigarette packs smoked per day (e.g. 10 pack years = 1 pack /day x 10 yrs., or $\frac{1}{2}$ pack/day x 20 yrs.). The number of pack years will be analyzed as recorded on the CRF.
4. Years since subject stopped smoking is calculated using the formula: Years since subject stopped smoking = (Date of visit 1 – date stopped smoking)/365.25. If the date stopped smoking is missing in day and/or month, it will be imputed in the same way as described above for the date of COPD diagnosis.
5. Percent of predicted FEV₁ is obtained as a percentage of FEV₁ relative to the predicted normal value of FEV₁.
6. For subjects greater than 18 years of age, this study will utilize the spirometric prediction equation standards for the European Community for Coal and Steel (Quanjer et al. 1993) or NHANES (Hankinson et al. 1999). The equation of Quanjer et al. (1993) will be used by third party vendors to calculate predicted FEV₁ (L):

Male: (4.30 x Height in meters) – (0.029 x Age in years) – 2.49

Female: (3.95 x Height in meters) – (0.025 x Age in years) – 2.60

If Race = Black or Ethnicity = Indian then the predicted normal given by the formulae above was multiplied by 0.9.

16.1.9.4 Statistical methodology and assumptions

Students t-test for change from baseline in pre-dose trough FEV₁ (L) to Week 16

```
proc ttest data=<.....>;  
  class trt;  
  var chg;  
  run;
```

where trt = prior COPD treatment,

chg = change from baseline in pre-dose trough FEV₁ (L) to Week 16.

Chi-square test to assess the relationship between prior COPD treatment and patient's/physician's global satisfaction:

```
proc freq data = <.....>;  
tables trt*satis / chisq;  
run;
```

where trt = prior COPD treatment,
satis = global satisfaction response.