NOVARTIS

Clinical Development

QVA149/ indacaterol maleate/glycopyrronium bromide

CQVA149AKR01/ NCT02566031

A randomized, multicenter, open-label, parallel-group, 12-week study to assess the efficacy and safety of switching from tiotropium to QVA149 (indacaterol maleate/glycopyrronium bromide) in symptomatic mild to moderate COPD patients

Statistical Analysis Plan (SAP)

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Date	Reason for update	Section and title impacted (Current)
20-Nov-2018	Rule of exclusion criteria OTH06, OTH07, OTH08 were added.	Section 5.5

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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ATC	Anatomical Therapeutic Classification
ANCOVA	Analysis of Covariance
AST	Asprtate aminotransferase
ATS	American Thoracic Society
BDI	Baseline Dyspnea Index
BTPS	Normal body temperature (37°C), ambient pressure, saturated with water vapor
CAT	COPD Assessment Test
CCV	Cardio-cerebrovascular Event
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical Study report
ECG	Electrocardiogram
ERS	European Respiratory Society
FAS	Full Analysis Set
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
eCRF	Electronic Case Report Form
GOLD	Global Initiative for Chronic Obstructive Lung Disease
hCG	Human Chorionic Gonadotropin
ICS	Inhaled Corticosteroid
IRT	Interactive Randomized Technology
IUD	Intrauterine Device
IUS	Intrauterine System
LABA	Long Acting Beta-2 Agonist
LAMA	Long Acting Muscarinic Antagonist
LOCF	Last Observation Carried Forward
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mMRC	Modified Medical Research Council
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PSW	Premature Study Withdrawal
qd	Once Daily
QoL	Quality of Life
QT	Time between start of Q wave and end of T wave in heart’s electrical cycle
QTc	Corrected QT
QTcF	Fridericia corrected QT formula
RAP	Report and Analysis Process
SABA	Short Acting Beta-2 Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SDDPI	Single Dose Dry Powder Inhaler
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
SUSARs	Suspected Unexpected Serious Adverse Reactions
TDI	Transitional Dyspnea Index
TFLs	Tables, Figures, Listings
TURP	Transurethral Resection of Prostate
WHO	World Health Organization

1 Introduction

This document describes the planned statistical methods for all safety and efficacy analyses which will be used in the phase IV clinical trial QVA149AKR01.

The main purpose of this document is to provide summary of the statistical methodology that will be used for this clinical study; this includes a detailed description of data summaries. Analyses plan in this document refers to the related statistical analysis sections in clinical study report.

Data will be analyzed by Novartis using 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. That statistical methodology is described below and any deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section 16.1.9 of CSR.

Please refer to the following document:

Clinical Protocol QVA149AKR01

1.1 Study design

This is a randomized, multicenter, open-label, parallel-group, 12-week study to assess the efficacy and safety of QVA149 (indacaterol maleate/glycopyrronium bromide) versus tiotropium in symptomatic mild to moderate COPD patients.

The schematic of study design is is given in Figure 1.1 below.

Planned number of patients and randomization

It is intended that total of 404 patients will be recruited to compensate dropouts and protocol violaters.

Patient eligibility will be assessed during a 3-weeks (21 days) Screening period. At Baseline visit (Visit 1/ Day 1), eligible patients will be randomized to one of the following treatment groups and treated for 12 weeks:

- QVA149 (110/50 μg once daily)
- tiotropium 18 μg once daily.

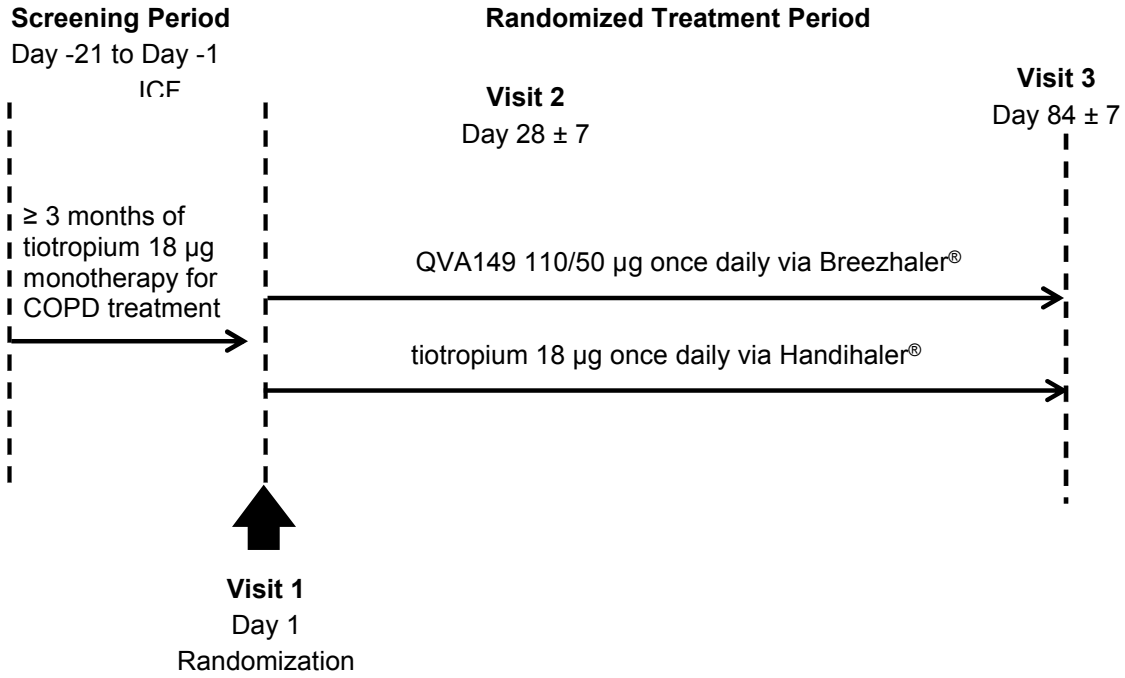
Primary analysis time point

The primary analyses will be performed at Week 12.

Interim analyses

No interim analysis is planned for this study.

Figure 1.1: Study Design



1.2 Study objectives and endpoints

Table 1.2-1 Objectives and related endpoints

Objective	Endpoint
Primary objective	
To demonstrate the superiority of QVA 110/50 µg once daily to tiotropium 18 µg once daily of trough forced expiratory volume in 1 second (FEV_1) at Week 12	Mean of pre-dose trough FEV_1 (L) at Week 12
Secondary objective	
To evaluate the effect of QVA149 (110/50 µg) as compared to tiotropium 18µg of Pre-dose trough FEV_1 at Week 4	Mean of pre-dose trough FEV_1 (L) at Week 4
To evaluate the effect of QVA149 (110/50 µg) as compared to tiotropium 18µg of Transitional dyspnea index (TDI) focal score at Week 12	Mean Transitional dyspnea index (TDI) focal score at Week 12
	Proportion of patients with a clinically important improvement of TDI focal score at Week 12
To evaluate the effect of QVA149 (110/50 µg) as compared to tiotropium 18µg of symptom control by total CAT score at Week	Mean of CAT score at Week 12

12	
To evaluate the effect QVA149 (110/50 µg) as compared to tiotropium 18µg of rescue medication used reported by the patients at Week 12	Mean daily number of puffs (rescue medication) at Week 12
	Mean percentage of days with no rescue medication
To evaluate the safety and tolerability of QVA149 (110/50 µg) as compared to tiotropium 18µg	Overall safety, as measured by frequency and severity of adverse events and changes in laboratory, vital signs and ECG values from baseline

[redacted]

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis and/or by the designated CRO. It is planned that the data from all centers that participate in this protocol will be used for analysis. Analysis datasets and statistical outputs will be produced using the most recent SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment (GPS).

Summary statistics for continuous variables will include N, mean, standard deviation, median, minimum and maximum. Summary statistics for discrete variables will be presented in the number and percent of patients in each category.

For descriptive statistics, the following number of decimal places will 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.

The analysis will be conducted on all patients data at Week 12. Data will be presented by treatment group, Unless otherwise stated.

2.1.1 General definitions

Study treatment: Study treatment refers to:

QVA149 (110/50 µg once daily) or tiotropium 18 µg once daily.

Study treatment start and end date: Study treatment start date is defined as the first date of study drug is administered and recorded on the Drug Administration Record (DAR) CRF page. Similarly, study drug end date is defined as the last date of study drug is administered and recorded on the study phase completion CRF page.

Study day: Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g.visit, lab samples, AEs). For events prior to study drug start date (e.g., time of diagnosis), study day will be negative and calculated as (event date – study drug start date).

Baseline and post baseline: In general, a *baseline* value refers to the last measurement made prior to administration of the first dose of study treatment or the average values taken prior to administration of the first dose of study treatment. A post-baseline value refers to a measurement taken after the first dose of study treatment.

2.2 Analysis sets

The following analysis sets will be used in this trial:

The Randomized set (RAN) comprises all randomized patients regardless of whether or not they actually received study treatment.

The Full analysis set (FAS) will include all randomized patients who received at least one dose of study treatment and have at least one evaluable post-baseline assessment. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned at randomization. The FAS will be used for all efficacy analyses.

The Per-protocol set (PPS) 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. Patients will be analyzed according to the treatment they were assigned to at randomization. The PPS will be used to assess the robustness of the results drawn from the primary analysis using FAS set.

The Safety set (SAF) will include all patients who received at least one dose of study treatment. 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 treatment in error. In addition, the FAS assigns randomized treatment and the Safety set assigns received treatment.

2.2.1 Subgroup of interest

There is no planned subgroup of interest.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

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

The number of patients who were screened, randomized, completed the study and discontinued from the study will be summarized by treatments with reasons for premature discontinuation for randomized set. In addition, number of screen failures with reasons will be presented for all screened patients. Patient identification number and whether they completed or discontinued from the study will be listed, with date of last dose and primary reason for premature discontinuation.

2.3.2 Protocol deviation

The number and percentage of patients with protocol deviations will be tabulated by category and deviation for randomized set. Patients with protocol deviations will be listed with date and study day of occurrence, deviation and severity codes for randomized set.

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

2.3.3 Demographic characteristics

Demographics and baseline characteristics will be summarized using the randomized set.

The following demographic variables collected in the CRF at screening (Visit 0) will be summarized:

- age (in years)
- sex (Male or Female)
- race (Caucasian, Black, Asian, Native American, Pacific Islander, Unknown, Other)
- ethnicity (Hispanic or Latino, East Asian, Southeast Asian, South Asian, West Asian, Russian, Mixed Ethnicity, Not Reported, Unknown, Other)
- height (cm)
- weight (kg)
- body mass index (BMI) (kg/m^2)

The following baseline disease characteristics collected at screening (Visit 0) will be summarized:

- Duration of COPD (in years, formula specified in Section 16.1.9.3)
- Spirometry at baseline Visit 0 including
  - both pre- and post- bronchodilator FEV_1 percentage of predicted normal value, FEV_1 and FVC;
  - post-bronchodilator: FEV_1/FVC, FEV_1 percentage of increase;

– pre- bronchodilatory: FEV_1 predicted normal value;

- severity of airflow limitation at baseline Visit 0 (COPD severity: mild and moderate)
- smoking history
  – number of pack-years
- smoking status (current smoker and ex-smoker)
  – number of packs per year (for current and ex-smokers only)
- Vital signs (sitting systolic/diastolic blood pressure (mmHg), sitting pulse rate (bpm)) at Visit 0.
- ECG at Visit 0.

In addition, the following categorizations will be done:

- Age into 40 - < 65 years, 65 - < 75 years, and ≥ 75 years;
- BMI into ≤ 30.0 kg/m^2 and > 30.0 kg/m^2;
- Duration of COPD into < 1 year, > 1 - 5 years, > 5 - 10 years, > 10 - 15 years, > 15 – 20 years, and > 20 years;

2.3.4 Medical history/ current medical condition

Medical history will be coded using the Medical Dictionary for Regulatory Activities terminology (MedDRA). History/conditions will be summarized for the randomized set 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.

2.3.4.1 Cardiovascular risk factors

Number and percentage of patients with specific cardiovascular risk factors will be summarized. In addition, the number and percentage of patients with 0, 1, 2, 3, 4 or more cardiovascular risk factors will be summarized. Cardiovascular risk factors are defined as the following 7 medical histories/conditions:

- CCV history/condition
- Hypertension
- Hyperlipidemia
- Diabetes mellitus of either type
- Obesity at baseline (i.e. BMI > 30 kg/m2)
- Age ≥ 65 years
- Current smoker at baseline.

The algorithms to identify the presence of the cardiovascular risk factors CCV history/condition, hypertension, hyperlipidemia, and diabetes mellitus is described in Appendix 5.1.1.

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

2.4.1 Study treatment / compliance

Duration of exposure

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 safety set as

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

Compliance

QVA149 110/50µg of blister strips of capsules with single dose dry powder inhaler device and /or Tiotropium 18 µg of blister strips of capsules with HandiHaler® device was prescribed to each patient once daily.

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

Compliance (%) = 100 x number of doses taken / duration of exposure.

Compliance will be summarized with the standard descriptive statistics and by categories (i.e., <80 %, >= 80 % - < 100 %, >= 100% - < 120% and >= 120 %) for the safety set.

2.4.2 Prior, concomitant and post therapies

Each medication has the start and end dates recorded. Prior medications are defined as those medications which were taken and stopped prior to first dose of study treatment. Concomitant medications are defined as those medications which were taken on or after the first dose of study drug but not prior to the first dose of study treatment, also includes those which were taken prior to and continued after the first dose of the study treatment. All prior/concomitant medications will be summarized as concomitant medications, and will not be included in prior medication outputs.

All prior and concomitant medication will be coded using WHO drug dictionary with most updated version. COPD-related medications will be summarized by pre-specified drug categories, route of administration, and preferred term, as recorded on the eCRF. The summary will be repeated by showing ingredients instead of preferred terms. Non-COPD related medication will be summarized by route of administration and preferred term. Both COPD-related and non-COPD related medications will be summarized separately for prior and concomitant medications.

All summaries will be on the safety set.

2.5 Analysis of the primary objective

The primary objective of the study is to demonstrate the superiority of QVA 110/50 µg once daily compared to tiotropium 18 µg once daily in terms of trough forced expiratory volume in one second (FEV_1 in Liters) after 12 weeks treatment.

2.5.1 Primary endpoint

The primary efficacy endpoint is trough FEV_1 (L) after 12 weeks treatment, will be defined as the average of 45 and 15 min values prior to the administration of study treatment.

The analysis of the primary variable will be based on the FAS patients.

2.5.2 Statistical hypothesis, model, and method of analysis

The statistical hypothesis is to demonstrate the superiority of QVA 110/50 µg once daily to tiotropium 18 µg once daily in patients having COPD with mild to moderate airflow limitations, the following hypothesis will be tested using an analysis of covariance (ANCOVA) model for the full analysis set:

Baseline FEV_1 is defined the average of the pre-dose FEV1 measured at -45 min and -15 min at Visit 1 (Day 1).

H_0: There is no difference in trough FEV_1 (L) at Week 12 for patients treated with QVA 110/50 versus tiotropium

H_A: There is a difference in trough FEV_1 (L) at Week 12 for patients treated with QVA 110/50versus tiotropium

The primary analysis will be performed comparing treatment means with respect to trough FEV_1 (L) at Week 12 using analysis of covariance (ANCOVA) model with treatment and smoking status as fixed effects, baseline trough FEV_1 as a covariate and center 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.

In addition, the primary variable trough FEV_1 (L) will be summarized by treatment group.

The superiority of QVA to tiotropium will be demonstrated if the p-value is less than 0.05 and the confidence interval lies entirely to the right of (higher than) 0 mL.

2.5.3 Handling of missing values/censoring/discontinuations

If any of the values contributing to the trough FEV_1 are collected within 6 hours of rescue medication use or less than 7 days after systemic corticosteroid use then the individual FEV_1 value will be set to missing or if the actual measurement times were outside the 22-25 hour post-dose time window then the individual FEV_1 value will be excluded from analyzed.

If any one of the 45 min or 15 min pre-dose values is missing at Week 12, the remaining non-missing value will be considered as trough FEV_1. If both values are missing, or if the patient has withdrawn from the trial, regardless of the reason for discontinuation, then missing trough values will be imputed with the last observation carried forward (LOCF) method using the

data at Visit 2. If the trough value at Visit 2 is missing, then patient will be excluded from this analysis.

2.5.4 Supportive analyses

Supportive analyses will be performed for trough FEV1 at Week 12 using the FAS, Since some patients will discontinue the study prematurely will affecting the sample size at Week 12. Therefore the following analyses will also be performed as supplementary to support the result of the primary analysis:

1. The primary variable will be analyzed for patients who have a valid trough measurement at Week 12, without any imputation for missing data at week 12 using the FAS. The analysis will be performed using analysis of covariance (ANCOVA) model with treatment and smoking status as fixed effects, baseline trough FEV_1 as a covariate and center 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.
2. Missing value of FEV_1 at Week 12 will be imputed using LOCF method. The primary analysis will be performed at Week 12 for FAS and PPS using analysis of covariance (ANCOVA) model with treatment and smoking status as fixed effects, baseline trough FEV_1 as a covariate and center 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.
3. The primary variable will also be analyzed for patients who have been allowing by inclusion of values that fell within 6 hours of rescue medication use or within 7 days of systemic corticosteroid use using the FAS. The analysis will be performed using analysis of covariance (ANCOVA) model with treatment and smoking status as fixed effects, baseline trough FEV_1 as a covariate and center 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.
4. A sensitivity analysis of trough FEV_1 at Week 12 (with and without imputation by LOCF method) will also be performed by allowing inclusion of values that fell within 6 hours of rescue medication use or within 7 days of systemic corticosteroid use.
5. The following exploratory subgroup analyses for trough FEV_1 after 12 weeks of treatment will be performed (using the appropriate interaction term in the model and additional covariate as a fixed effect if necessary) for the FAS to explore the treatment effect in:
   - Age group (40 - < 65 years, 65 - < 75 years, and ≥ 75 years).
   - Sex (male, female).
   - Severity of COPD (50% ≤ FEV_1 < 60%, FEV_1 ≥ 60%).
   - Baseline smoking status (current smoker, ex-smoker).
   - Exacerbation (exacerbation history in previous year; 0 or 1).
   - Patient's larger value of FEV_1 reversibility after SABA (12% increase of reversibility and 200ml increase in FEV_1, 12% increase of reversibility, 200ml increase in FEV_1).
   - BMI (≤ 30.0 kg/m^2, > 30.0 kg/m^2).

Estimates of adjusted treatment means will be displayed for each treatment along with the difference between treatments means, 95% confidence interval for treatment difference and p-value will be presented.

6. The log-transformed trough FEV_1 after 12 weeks of treatment will be analyzed for the FAS using the ANCOVA model with treatment and smoking status as fixed effects, log transformed baseline trough FEV_1 as a covariate and center as a random effect. The estimated adjusted treatment ratios, and the associated 95% confidence intervals and p-values will be displayed.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

Not Applicable.

2.6.2 Statistical hypothesis, model, and method of analysis

Not Applicable.

2.6.3 Handling of missing values/censoring/discontinuations

Not Applicable.

2.7 Analysis of secondary efficacy objective(s)

Refer to Table 1.2-1 of Section 1 for the list of secondary objectives.

2.7.1 Secondary endpoints

All the secondary efficacy evaluation will be performed on FAS population.

Refer to Table 1.2-1 of Section 1 for the list of secondary endpoints.

2.7.2 Statistical hypothesis, model, and method of analysis

Analysis of secondary endpoints:

2.7.2.1 Trough FEV1 and FVC at Week 4 and Week 12

- Trough FEV_1 (L) at Week 4 is defined as the average of FEV_1 values taken at 45 and 15 min prior to the administration of study treatment at Week 4 will be analyzed using analysis of covariance (ANCOVA) model with treatment and smoking status as fixed effects, baseline trough FEV_1 as a covariate and center 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.
- Trough FVC (L) at Week 12 is defined as the average of FVC values taken at 45 and 15 min prior to the administration of study treatment at Week 12 will be analyzed using analysis of covariance (ANCOVA) model with treatment and smoking status as fixed effects, baseline trough FVC as a covariate and center 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.

- Trough FVC (L) at Week 4 (the average of FVC values taken at 45 and 15 min prior to the administration of study treatment) will be analyzed using analysis of covariance (ANCOVA) model with treatment and smoking status as fixed effects, baseline trough FVC (L) as a covariate and center 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.
- FEV_1 (L) at Week 4 and Week 12 will be analyzed using analysis of covariance (ANCOVA) model with treatment, smoking status, visit and treatment by visit interaction as fixed effects, baseline FEV_1 as a covariate and center 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.
- FVC at Week 4 and Week 12 will be analyzed using analysis of covariance (ANCOVA) model with treatment, smoking status, visit and treatment by visit interaction as fixed effects, baseline FVC as a covariate and center 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.
- FEV_1/FVC at Week 4 and Week 12 will be analyzed using analysis of covariance (ANCOVA) model with treatment, smoking status, visit and treatment by visit interaction as fixed effects, baseline FEV_1/FVC as a covariate and center 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.

2.7.2.2 Daily rescue medication use (number of puffs) over 12 weeks

The number of puffs of rescue medication taken in the previous 24 hr is recorded in the electronic patient diary in the morning.

The total number of puffs of rescue medication per day over the full 12 weeks will be calculated and divided by the total number of days with non-missing rescue medication data to derive the mean daily number of puffs of rescue medication taken for the patient.

The mean daily number of puffs of rescue medication used over 12 weeks of treatment will be analyzed using a negative binomial regression model with treatment and smoking status as fixed effects with baseline rescue medication use as a covariates and center as a random effect. The log (exposure time) will be used as the offset variable in the model. Adjusted least square means, point estimate of difference between treatment means, 95% confidence interval for treatment difference and p-value will be presented.

In addition, the mean daily number of puffs of rescue medication used over 12 weeks of treatment will be summarized by treatment group.

2.7.2.3 Percentage of ‘days with no rescue medication use’ over 12 weeks

A ‘day with no rescue use’ is defined from diary data as any day where the patient does not

use any puffs of rescue medication.

The total number of 'days with no rescue use' over the 12 weeks treatment will be divided by the total number of days in order to derive the percentage of 'days with no rescue use'.

The percentage of 'days with no rescue use' will be analyzed using analysis of covariance (ANCOVA) model with treatment and smoking status as fixed effects, baseline percentage of 'days with no rescue use' as a covariate and center 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.

In addition, the percentage of 'days with no rescue use' over 12 weeks of treatment will be summarized by treatment group.

2.7.2.4 Dyspnea index

Dyspnea is measured at baseline using the baseline dyspnea index (BDI) and at the end of the treatment period (Week 12) using the transition dyspnea index (TDI), which captures changes from baseline.

The BDI and TDI each have three domains: functional impairment, magnitude of task and magnitude of effort. The BDI domains are rated from 0 (severe) to 4 (unimpaired) and the rates are summed for the baseline focal score ranging from 0 to 12; the lower the score the worse the severity of dyspnea. The TDI domains are rated from -3 (major deterioration) to 3 (major improvement) and the rates are summed for the transition focal score ranging from -9 to 9; minus scores indicate deterioration. A TDI focal score of 1 is considered to be a clinically significant improvement from baseline. If the data are missing or insufficient for any one of the domains, a focal score cannot be imputed.

TDI focal score

The TDI focal score after 12 weeks of treatment will be analyzed using analysis of covariance (ANCOVA) model with treatment and smoking status as fixed effects, BDI focal score as a covariate and center 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.

In addition, dyspnea index data will be summarized.

Proportion of patients with a clinically important improvement in TDI focal score at Week 12

A TDI focal score of ≥ 1 is defined a clinically important improvement from baseline. The proportion of patients who achieve a clinically important improvement will be analyzed using logistic regression with treatment and smoking status as fixed effects, BDI focal score as a covariate and center as a random effect. Estimated odds ratio along with associated 95% confidence interval and p-value will be presented.

2.7.2.5 COPD Assessment Test (CAT)

The CAT score at Week 12 will be analyzed using analysis of covariance (ANCOVA) model with treatment and smoking status as fixed effects, baseline CAT score as a covariate and

center 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.

In addition, CAT score data will be summarized by visit and category.

2.7.3 Handling of missing values/censoring/discontinuations

No missing imputation will be performed for secondary endpoint.

2.8 Safety analyses

Safety measurements include ECG, vital signs, laboratory data and adverse events. All safety endpoints will be summarized by treatment for the safety set. All safety data will be included in the summaries or analysis regardless of rescue medication.

2.8.1 Adverse events (AEs)

All adverse events including COPD exacerbations will be listed.

Events which start on or after the time of the first administration of study drug but not later than 7 days (30 days in the case of a Serious Adverse Event (SAE)) after the last administration of study drug will be classified as treatment emergent AEs.

AEs that start during the study before the first administration of study drug will be classified as pre-treatment and will be listed only. In addition, all the treatment emergent AEs will also be listed.

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 system organ class, the preferred terms will be sorted in descending frequency within the QVA 110/50 treatment arm. In addition, number and percentage of patients with the most frequent AEs with atleast 5% in each treatment arm will also be summarized.

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 primary system organ class level.

AEs by severity

All treatment emergent adverse events will be summarized by primary system organ class, preferred term and maximum 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 will be counted once by maximum severity and treatment.

AEs suspected to be related to study drug

All 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 treatment is considered as suspected for those events where "Relationship to study treatment" is answered by the investigator as "Suspected".

AEs leading to permanent study drug discontinuation

All 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.

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. In addition, number and percentage of patient mortality and CCV SAE events will also be summarized.

2.8.1.1 Adverse events of special interest / grouping of AEs

Not Applicable.

2.8.2 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. In addition, deaths occurring after the first dose of study treatment till the date of last treatment will also be summarized.

2.8.3 Laboratory data

All laboratory data will be listed with abnormal values flagged.

Laboratory data measured more than 7 days after last dose of study drug is regarded as post-treatment data and will not be summarized or analyzed, only listed.

For all continuous laboratory parameters, summary statistics for absolute and change from baseline at each scheduled visit and treatment will be provided and all laboratory data (including any unscheduled assessments) will be listed with abnormal values flagged.

For categorical urinalysis laboratory parameters, a frequency table of results will be produced by laboratory parameter, scheduled visit and treatment.

Shift tables for laboratory parameters will be provided in order to compare a subject's baseline value to the value at each timepoint at each study visit, relative to the normal reference range for each lab parameter. Normal reference ranges provided by the local lab will be used to evaluate whether a particular laboratory test value for each timepoint at each visit is normal, low or high relative to the baseline value also categorized as normal, low or high. These summaries will be presented by laboratory parameter, visit, timepoint, and treatment group.

In addition, shift tables relative to the normal reference ranges will be used to summarize the change from baseline to the most extreme post-baseline for each laboratory parameter. For each laboratory test, the subjects will be classified into one of the four mutually exclusive groups (low, normal, high, and low + high), defined as follows:

- Low: at least one post-baseline value below the normal range and none above the normal range
- High: at least one post-baseline value above the normal range and none below the normal range
- Normal: all the post-baseline values within the normal range
- Low + High: at least one post-baseline value below the normal range and at least one above the normal range

Categorical parameters in the urinalysis panel will also be summarized with shift tables showing the shift from one categorical result to another. The shift from baseline to most extreme post baseline value will also be summarized, with the least to most extreme scale assumed to be negative, trace, +, ++, +++, ++++.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Data from the electrocardiogram will be summarized by treatment at all time-points

Data measured more than 7 days after last dose of study drug will be regarded as posttreatment data and will not be summarized but listed only.

The following quantitative variables will be summarized by treatment at each scheduled postdose visit: ventricular rate, QT interval, RR interval, PR interval, QRS duration and Fridericia's QTc (QTcF). The maximum QTcF will also be summarized.

The changes from baseline will be summarized by ECG parameter, scheduled visit and timepoint where baseline and post-baseline values are both available.

Notable value is defined as a QTc interval of greater than 450 ms. The categories used for the change from baseline in QTc are less than 30 ms, 30 to 60 ms and greater than 60 ms.

For a subject to meet the criterion of a newly occurring clinically notable value, the subject needs to have a baseline value which is not clinically notable for that parameter. For a subject to meet the criterion of a worsening clinically notable value, the subject needs to have a baseline value which is clinically notable and also have a worse post-baseline value. For subjects with a missing value at baseline, post-baseline values meeting the notable criterion will be considered as newly occurring. The number and percentage of subjects who have newly occurring or worsening clinically notable values, or notable changes from baseline, will be presented by scheduled post-baseline visit. A listing of all newly occurring or worsening abnormalities will be provided.

2.8.4.2 Vital signs

Data measured more than 7 days after last dose of study drug will be regarded as posttreatment data and will not be summarized or analyzed, but listed only.

Data from the vital signs (systolic blood pressure, diastolic blood pressure, pulse rate and weight) will be summarized by treatment at the scheduled visits. The maximum and minimum systolic blood pressure, diastolic blood pressure, and pulse rate post-baseline will also be summarized by treatment.

Vital signs will also be summarized by categories:

• systolic blood pressure: < 75 mmHg, 75 – 200 mmHg, and > 200 mmHg
• diastolic blood pressure: < 40 mmHg, 40 – 115 mmHg, and > 115 mmHg
• pulse rate: < 40 bpm, 40 – 130 bpm, and > 130 bpm

Notable values for vital signs will also be summarized by categories:

• 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

The change from baseline to each scheduled post-baseline visit will be summarized similarly as the laboratory parameters where baseline and post-baseline values are both available. The summary will be presented by vital sign parameter, scheduled visit, and treatment with standard descriptive statistics.

The number and percentage of subjects with newly occurring or worsening notable values, including notable change from baseline, will be summarized by vital sign parameter, scheduled post-baseline visit and treatment group. Subjects with any newly occurring or worsening value meeting the clinically notable criteria will be counted under the applicable criteria.

For a subject to meet the criterion of a newly clinically notable occurrence, the subject needs to have a baseline value which does not meet the criteria for categorizing a value as notable. For a subject to meet the criterion of a worsening occurrence, the subject needs to have a baseline value which is clinically notable and also have a worse post-baseline value. For subjects with a missing value at baseline, post-baseline values meeting the notable criterion will be considered as newly occurring. For subjects with both baseline and post-baseline values which are clinically notable but in opposing directions (e.g. Low at baseline and high at post-baseline, or vice versa), the post-baseline notable value will be considered as newly occurring.

Absolute body weight and change from baseline will be summarized by visit and treatment group.

2.9 Pharmacokinetic endpoints

Not Applicable.

2.10 PD and PK/PD analyses

Not Applicable.

2.12 Biomarkers

Not Applicable.

2.14 Interim analysis

No interim analysis is planned for this study.

3 Sample size calculation

The primary objective is to demonstrate superiority of QVA149 110/50 µg once daily compared to tiotropium 18 µg once daily in terms of pre-dose trough FEV_1 (L) after 12 weeks of treatment. Based on the results of QVA149A2303 (SHINE) study, it was assumed that the estimated treatment difference between QVA149 and tiotropium is 82 mL and corresponding standard deviation is 271 mL (Bateman et al 2013). With these estimates, a sample size of 173 patients in each treatment arm would be required to achieve 80% power on a 2-sided test with 5% level of significance.

Therefore assuming a dropout rate of 11%, approximately 404 patients will be enrolled in the study.

4 Change to protocol specified analyses

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	**NC** Uncertain	**NC** Uncertain	**NC** Uncertain	**NC** Uncertain
YYYY < TRTY	**(D)** Before Treatment Start	**(C)** Before Treatment Start	**(C)** Before Treatment Start	**(C)** Before Treatment Start
YYYY = TRTY	**(B)** Uncertain	**(C)** Before Treatment Start	**(A)** Uncertain	**(A)** After Treatment Start
YYYY > TRTY	**(E)** After Treatment Start	**(A)** After Treatment Start	**(A)** After Treatment Start	**(A)** After Treatment Start

The following table is the legend to the logic matrix.

If AE end date is complete and AE end date < Treatment start date or AE end date is partial and AE imputed end date < Treatment start date, then AE start reference = min (informed consent date, earliest visit date from SV) Else if AE end date is partial,AE end date > = Treatment start date or AE is ongoing , then AE start reference = treatment start date.

Relationship		Time imputation
Before AE start reference	Partial date indicates AE start date prior to AE start reference	
After AE start reference	Partial date indicates AE start date after AE start reference	
Uncertain	Partial date insufficient to determine relationship of AE start date to AE start reference	
Imputation Calculation		
NC/Blank	No convention	
(A)	MAX(01MONYYYY, AE start reference+1 day)	
(B)	AE start reference+1	
(C)	15MONYYYY	
(D)	01JULYYYY	
(E)	01JANYYYY	
Complete date	No date imputation	If time is cuptured for the study Case1: if AE start date is not equal to AE start reference then do the following: If minutes missing then AESTMF = M and time is imputed to hh:00 If minutes missing then AESTMF = H and time is imputed to 00:00 Case2: if AE start date = AE start reference then AESTMF = H and time is imputed to treatment start time + 1 hour

Adverse Event End Date Imputation

Imputed date = date part of original date, if complete date

Imputed date = min (completion/discontinuation visit date, DEC 31, date of death), if month is missing

Imputed date = min (completion/discontinuation visit date, last day of the month, date of death), if day is missing

Adverse Event End Time Imputation

If the AE end date is complete and time is captured in the study then:

Case 1. if AE end date is not equal to Treatment end date, then do the following:

if minutes missing then time is imputed to hh:00 if time missing then time is imputed to 00:00

Case 2: if AE end date = Treatment end date then time is imputed to treatment end time

If the AE end date is partial then end time is imputed to 00:00.

Imputed Date Flag

If year of the imputed date is not equal to YYYY then date flag = Y
else if month of the imputed date is not equal to MON then date flag = M
else if day of the imputed date is not equal to day of original date then date_flag = D
else date flag = null

Imputed Time Flag

If hours of the imputed time is not equal to hours of original time then time flag = H
else if minutes of the imputed time is not equal to minutes of original time then time flag = M
else time flag = null.

Cardiovascular risk factors

Seven cardiovascular risk factors were defined. The first four, CCV history/condition, hypertension, hyperlipidemia, type 2 diabetes are taken from the CRF page of Medical History – Protocol solicited events – Cardiovascular events.
The remaining cardiovascular risk factors 5. Obesity at baseline (i.e. BMI > 30 kg/m2), 6. Age ≥ 65 years, and 7. Current smoker at baseline will be identified directly from the data recorded in the eCRF.

5.1.2 Concomitant medication date imputation

This algorithm is used when *event* is the partial start date of the concomitant medication. The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CM Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSDT)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	**(C2)** Uncertain	**(C1)** Uncertain	**(C1)** Uncertain	**(C1)** Uncertain
YYYY < TRTY	**(D)** Before Treatment Start	**(A)** Before Treatment Start	**(A)** Before Treatment Start	**(A)** Before Treatment Start
YYYY = TRTY	**(C2)** Uncertain	**(A)** Before Treatment Start	**(C1)** Uncertain	**(B)** After Treatment Start
YYYY > TRTY	**(E)** After Treatment Start	**(B)** After Treatment Start	**(B)** After Treatment Start	**(B)** After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment Start	Partial date indicates CMD start date **prior** to Treatment Start Date
After Treatment Start	Partial date indicates CMD start date **after** Treatment Start Date

Uncertain	Partial date **insufficient to determine** relationship of CMD start date relative to Treatment Start Date
Imputation Calculation	
(A)	15MONYYYY
(B)	01MONYYYY
(C1 or C2)	IF relative reference start = before treatment start THEN TRTSDT-1 ELSE IF relative reference start = ' ' THEN TRTSDT+1
(D)	01JULYYYY
(E)	01JANYYYY

Concomitant Medication End Date Imputation

If not ongoing then -

Imputed date = date part of CMENDTC, if complete date

Imputed date = min(completion/discontinuation visit date, DEC 31) , if month is missing, (C2, D, E)

Imputed date = min(completion/discontinuation visit date, last day of the Month) , if day is missing. (A, B, C1)

Concomitant Medication Date Flag

If not a complete date then

Y - If year of the imputed date is not equal to YYYY else M – If month of the imputed date is not equal to MON else D.

5.1.2.1 Prior therapies date imputation

Same as above.

5.1.2.2 Post therapies date imputation

Same as above.

5.1.2.3 Other imputations

Same as above.

5.2 AEs coding/grading

NA

5.3 Laboratory parameters derivations

NA

5.4 Statistical models

5.4.1 Primary analysis

The SAS procedure PROC MIXED, will be used to perform ANCOVA with the following SAS code:

```
PROC MIXED DATA = ....  ORDER = internal;
 CLASS usubjid acenter trtpn smkst;
 MODEL aval = trtpn smkst bl / DDFM=kr;
 RANDOM acenter;
 LSMEANS trtpn / CL DIFF;
 ESTIMATE "QVA149 - Tiotropium" 1 -1/diff cl alpha=0.05;
RUN;
```

where aval = dependent variable, e.g. Trough FEV_1
trtpn = Treatment
smkst = Smoking status
usubjid = Patient identifier
bl = Baseline value
acenter = Center

5.4.2 Key secondary analysis

The SAS procedure PROC MIXED, will be used to perform ANCOVA along with interaction term with the following SAS code:

```
PROC MIXED DATA = ....  ORDER = internal;
 CLASS usubjid acenter trtpn smkst avisit;
 MODEL aval = trtpn smkst avisit trtpn*avisit bl / DDFM=kr;
 RANDOM acenter;
 LSMEANS trtpn / CL DIFF;
 ESTIMATE "QVA149 - Tiotropium" 1 -1/diff cl alpha=0.05;
RUN;
```

where aval = dependent variable, e.g. FEV_1
trtpn = Treatment
smkst = Smoking status
avisit = Visit number
usubjid = Patient identifier
bl = Baseline value
acenter = Center

The SAS procedure PROC GENMOD, will be used to perform Negative Binomial model with the following SAS code:

```
PROC GENMOD DATA = ....  internal;
 CLASS usubjid acenter trtpn smkst;
 MODEL aval = trtpn smkst bl / dist=nb link=log offset=lrisk lrci type3 wald;
 RANDOM acenter;
 LSMEANS trtpn / CL DIFF EXP;
```

```
 ESTIMATE "QVA149 - Tiotropium" 1 -1/diff cl alpha=0.05;
RUN;
```

where aval = dependent variable, e.g. Number of puffs of rescue medications
trtpn = Treatment
smkst = Smoking status
avisit = Visit number
usubjid = Patient identifier
bl = Baseline value
lrisk = log (exposure time)
acenter = Center

The SAS procedure PROC LOGISTIC, will be used to perform Logistic regression with the following SAS code:

Certain binary outcome variables, e.g. response outcomes, will be evaluated using a logistic regression model with treatment, smoking status, BDI focal score. Odds ratios will be computed for comparisons of QVA149 versus Tiotropium utilizing the logistic regression model fitted.

```
PROC LOGISTIC DATA = .... ;
CLASS usubjid acenter trtpn smkst / param=glm;
MODEL aval = trtpn smkst bl;
RANDOM acenter;
LSMEANS trtpn / diff cl exp;
Ods output diffs=lsm_diff;
Run;
```

In cases where separation is a concern, e.g. 0% response in one treatment (sub)group, an exact logistic regression model will be applied. To ensure convergence, this model will not include any continuous covariates.

```
PROC LOGISTIC DATA = .... exactonly;
CLASS usubjid acenter trtpn smkst / param=glm;
MODEL aval = trtpn smkst;
EXACT trtpn / estimate=both;
Ods output exactoddsratio=exactoddsratio;
Run;
```

The SAS procedure PROC CORR, will be used to perform pearson's product moment correlation with the following SAS code:

```
PROC CORR DATA = .... OUTP=CORR;
      VAR VAR1 VAR2;
Run;
```

5.5 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
INCL01	Signed informed consent not obtained	Excluded from PP analysis	1
INCL02	Patients' s age less than 40 years Or, DOB missing	Excluded from PP analysis	1
INCL03	COPD not diagnosed according to GOLD guidelines	Excluded from PP analysis	1
INCL03A	Post-bronchodilator FEV1 less than 50 percentage of the predicted normal value Or, post-bronchodilator FEV1 value divided by FVC value is greater than or equal to 0.7	Excluded from PP analysis	1
INCL03B	Smoking history less than 10 pack years	Excluded from PP analysis	1
INCL04	CAT score less than 10 at Visit 0 and Visit 1	Excluded from PP analysis	1
INCL05	Patients not on tiotropium monotherapy for the past 3 months	Excluded from PP analysis	1
INCL06	More than 1 COPD exacerbations in the previous 12 months or, 1 COPD exacerbations leading to hospitalization, in previous months	Excluded from PP analysis	1
EXCL01	Treatment with any ICS in the 3 months prior to Visit 1	Excluded from PP analysis	1
EXCL02	Pregnant or nursing (lactating) women.	Excluded from PP analysis	1
EXCL04	Presence of any contraindication, warning, precaution, hypersensitivity to LABA and LAMA	Excluded from PP analysis	1
EXCL05	History or current diagnosis of clinically significant ECG abnormalities.	Excluded from PP analysis	1
EXCL06	Patients not achieved an acceptable spirometry result at Visit 1	Excluded from PP analysis	1
EXCL07	Patients with Type I diabetes	Excluded from PP analysis	1
EXCL07A	Patients with uncontrolled Type II diabetes	Excluded from PP analysis	1
EXCL08	Patients with narrow angle glaucoma, symptomatic BPH or bladder neck obstruction, moderate or severe renal impairment or urinary retention.	Excluded from PP analysis	1
EXCL09	Patient has active cancer or has been cancer free for less than 5 years	Excluded from PP analysis	1
EXCL10	As per Investigator, History of clinically significant diseases will put safety of patients at risk through study participation or will compromise patient compliance or preclude completion of study.	Excluded from PP analysis	1
EXCL11	Uncontrolled hypothyroidism and hyperthyroidism, hypokalemia.	Excluded from PP analysis	1
EXCL12	Patients with neurological, endocrine, immunological, psychiatric,	Excluded from PP analysis	1

	gastrointestinal, hepatic, or hematological abnormalities.		
EXCL13	Patients who are, in the opinion of the investigator, known to be unreliable or non-compliant.	Excluded from PP analysis	1
EXCL14	Long term oxygen therapy of more than 12 hrs. per day prescribed to patient.	Excluded from PP analysis	1
EXCL15	Patients reported with COPD exacerbation between Visit 0 and 1, can be re screened after a minimum of 6 weeks after resolution of the exacerbation if the exacerbation did not require hospitalization.	Excluded from PP analysis	1
EXCL16	Onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years	Excluded from PP analysis	1
EXCL17	History of respiratory infection within 4 weeks prior to Visit 0.	Excluded from PP analysis	1
EXCL17A	Patients develops respiratory tract infection between Screening and prior to treatment will be permitted to be re-enrolled 4 weeks after the resolution of the respiratory tract infection	Excluded from PP analysis	1
EXCL18	Patient with concomitant pulmonary diseases.	Excluded from PP analysis	1
EXCL19	Patients with lung lobectomy, or lung volume reduction or lung transplantation	Excluded from PP analysis	1
EXCL20	Patient has a history of Asthma	Excluded from PP analysis	1
EXCL21	Treatments for COPD and allied conditions: the following class of medications should be washed out prior to randomization (Visit 1) or prohibited during the study period.	Excluded from PP analysis	1
EXCL22	Patients with COPD and allied conditions.	Excluded from PP analysis	1
EXCL23	Patients had live attenuated vaccinations within 30 days prior to the screening visit.	Excluded from PP analysis	1
EXCL23A	Patients had inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine is administered within 48 hours prior to screening and randomization visits.	Excluded from PP analysis	1
EXCL24	Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half lives of Visit 1, whichever is longer.	Excluded from PP analysis	1
EXCL25	Patients unable to use a dry powder inhaler.	Excluded from PP analysis	1
EXCL25A	Patients unable to use a MDI.	Excluded from PP analysis	1
WITH01	Patients, who either become pregnant, while taking study medication.	Excluded from PP analysis	1
OTH02	Reversibility test not performed as required per protocol	Excluded from PP analysis	1
OTH03	Spirometry test not performed as	Excluded from PP analysis	1

	required per protocol		
OTH04	Treatment Compliance less than 80 percentage or greater than 120 percentage.	Excluded from PP analysis	1
OTH05	Time of spirometry outside of 22 to 25 hrs.	Excluded from PP analysis	1
OTH06	Assigned IMP via NIRT but subject took Non-IMP.	Excluded from PP analysis	1
OTH07	Time zone for treatment group Xoterna is greater than 37hrs or lesser than 22hrs.	Excluded from PP analysis	1
OTH08	Time zone for treatment group Spiriva is greater than 25hrs or lesser than 22hrs.	Excluded from PP analysis	1

Table 2 Subject Classification

Analysis Set	**PD ID that cause subjects to be excluded**	**Non-PD criteria that cause subjects to be excluded**
RAN	NA	Not randomized
FAS	NA	Not in RAN; Mistakenly randomized and no post-baseline taken
PPS	All specified PD in Table 1	Not in FAS;
SAF	NA	No study drug taken

6 Reference