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- **Document title: Double-blind, Randomized, Placebo-controlled, Parallel-group, Phase IV Study to Evaluate the Effect of Acridinium Bromide on Long-term Cardiovascular Safety and COPD Exacerbations in Patients with Moderate to Very Severe COPD (ASCENT COPD)**
- **Version number: 3**
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**Statistical Analysis Plan**

Study Code	D6560C00002
Edition Number	Amendment 3.0
Date	23 October 2017

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AZ Study Statistician

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PAREXEL Study Statistician

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Global Product Statistician

PPD

Date

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## LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomical Therapeutic Chemical (Classification System)
AZ	AstraZeneca
BID	twice a day ( <i>bis in die</i> )
BMI	body mass index
BP	blood pressure
bpm	beats per minutes
CAT	COPD assessment test
CEC	Clinical Events Committee
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CR	copy reference
CSP	clinical study protocol
CSR	clinical study report
CV	cardiovascular
DB	database
DSMB	Data Safety Monitoring Board
DPI	dry powder inhaler/inhalation
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of treatment
FAS	full analysis set
FEV <sub>1</sub>	forced expiratory volume after one second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HLT	high level term
ICF	informed consent form
ICS	inhaled corticosteroid
IP	investigational product
IWRS	interactive web response system
J2R	jump to reference
KM	Kaplan-Meier

<b>Abbreviation or special term</b>	<b>Explanation</b>
LABA	long-acting $\beta_2$ -adrenergic agonists
LAMA	long-acting muscarinic antagonist
LTFU	lost to follow-up
MACE	major adverse cardiovascular event(s)
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed model for repeated measures
NI	non-inferior, non-inferiority
OS	overall survival
PCS	potentially clinically significant
PDE4	oral phosphodiesterase type 4
PID	patient identification number
PT	preferred term
PTFU	post treatment follow-up
QTc	QT Interval corrected for heart rate
QTcB	QT Interval corrected for heart rate using the Bazett formula ( $QTcB = QT/(RR)^{1/2}$ )
QTcF	QT Interval corrected for heart rate using the Fredericia formula ( $QTcF = QT/(RR)^{1/3}$ )
SABA	short-acting $\beta_2$ -adrenergic agonists
SAE	serious adverse event
SAMA	short-acting muscarinic antagonist
SAP	statistical analysis plan
SD	standard deviation
SMQ	standard MedDRA query
SOC	system organ class
Sponsor	AstraZeneca
TEAE	treatment-emergent adverse event
WHO DD	World Health Organization Drug Dictionary

## AMENDMENT HISTORY

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<b>Date</b>	<b>Brief description of change</b>
30 Oct 2013	Initial Approved SAP by Forest Lab
26 May 2016	Amend according to Amended Protocol #2 (15 Sep 2015), Amended Protocol #3 (29 Feb 2016) and AstraZeneca (AZ) standard
17 August 2017	Amend according to FDA comments on the SAP amendment 1 (dated May 26, 2016), JAC recommendations, and/or blind delivery reviews.
23 October 2017	Amend according to blind delivery reviews, particularly adding 2 subgroup analyses for LABA users and LABA/ICS users.

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## 1. STUDY DETAILS

### 1.1 Study objectives

Objectives:	Outcome Measure* :
<p>To assess the safety of acclidinium bromide on major adverse cardiovascular events (MACE)</p>	<p>Primary Outcome Measure:</p> <ul style="list-style-type: none"> <li>• Time to first MACE, where MACE for the analyses is defined as any adjudicated event which is a composite of the total of cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke</li> </ul> <p>Secondary Outcome Measure:</p> <ul style="list-style-type: none"> <li>• Time to first MACE or other serious CV events of interest (e.g., adjudicated serious adverse events [SAEs] based on standard MedDRA query [SMQ] of cardiac disorders [i.e. cardiac arrhythmias SMQ and cardiac failure SMQ] and of cerebrovascular disorders</li> </ul>
<p>To assess the overall safety of acclidinium bromide</p>	<p>Safety Outcome Measures:</p> <ul style="list-style-type: none"> <li>• Adverse events (AEs, includes SAEs) including chronic obstructive pulmonary disease (COPD) exacerbations</li> <li>• Vital sign measurements</li> <li>• Electrocardiograms (ECG) parameters</li> <li>• Physical examination findings</li> </ul>
<p>To assess whether acclidinium bromide reduces moderate or severe COPD exacerbations</p>	<p>Primary Outcome Measure:</p> <ul style="list-style-type: none"> <li>• Rate of moderate or severe COPD exacerbations per patient per year during the first year of treatment               <ul style="list-style-type: none"> <li>○ Primary analysis: on-treatment analysis</li> <li>○ Secondary analysis: on-study analysis</li> </ul> </li> </ul> <p>Secondary Outcome Measure:</p> <ul style="list-style-type: none"> <li>• Rate of hospitalizations due to COPD exacerbations per patient per year during the first year of treatment</li> </ul>

\* Only primary and secondary efficacy outcome measures and safety outcome measures are listed. The additional efficacy outcome measures and CAT assessment are described in Section 3.

## 1.2 Study design

This is a Phase IV, multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the effect of Acclidinium Bromide (a long-acting muscarinic antagonist delivered by the Pressair<sup>®</sup> dry powder inhalation [DPI] device) compared with placebo on long-term CV safety and COPD exacerbations in outpatients at least 40 years of age who have been diagnosed with moderate to very severe COPD (postbronchodilator % predicted forced expiratory volume in 1 second [FEV<sub>1</sub>] < 80% and FEV<sub>1</sub>/forced vital capacity [FVC] ratio < 70%) and a history of CV or cerebrovascular disease and/or significant CV risk factors.

Note: in this document

1. The term “double-blind treatment period” applies to the following 2 scenarios:
  - When used in “maximum of 36-months double-blind treatment period”
  - When used for patients who completed 36-months treatment (completer)
2. The term “during the treatment period” refers to on-treatment period.
3. The term “during the whole study period” refers to both on-treatment and off-treatment (post-treatment follow-up) periods.

The study consists of two-week washout/run-in period (for patients on a long-acting muscarinic antagonist [LAMA]) followed by a maximum of 36-month double-blind treatment period.

Signed informed consent form (ICF) from the patient or the patient’s legally authorized representative will be obtained before any study-related procedures are begun. All patients will be assigned a patient identification (PID) number via the interactive web response system (IWRS). Patients meeting the entry criteria for this study will be randomized (1:1) to acclidinium bromide 400 µg (abbreviated as acclidinium hereafter) twice a day (BID) or placebo BID. This study will conclude when 122 patients have experienced an adjudicated MACE.

Patients who prematurely discontinue investigational product (IP) will participate in a post-treatment follow-up period. The follow-up period will include on-site visits and telephone visits to collect MACE, COPD exacerbations, concomitant medications, and SAEs for the remainder of the study duration.

An independent Data Safety Monitoring Board (DSMB) will be established for this study. The DSMB will periodically monitor and review relevant clinical safety data, including adjudicated MACE.

Patients will be assessed according to the Schedule of Evaluations (See Section 2 of the clinical study protocol [CSP]).

## **1.3 Number of subjects**

### **1.3.1 Power for the primary safety endpoint: time to first MACE event**

For this study, a total of 122 patients with MACE will be needed to have 90% power, at 5% significance level, to rule out a hazard ratio of 1.8 in time to first MACE in acclidinium bromide treated patients relative to placebo, assuming the hazard rate is 1.0 under the alternative hypothesis. The justification for the hazard ratio of margin of 1.8 is provided in Appendix IV of the CSP.

This ASCENT COPD study will be recruiting patients with a FEV<sub>1</sub> below 80% and a planned maximum of 36 months double-blind treatment period. The assumption of 1.9 MACE per 100 patient years would be reasonable for this study (See Section 9.7.9.1 of the CSP for details). To obtain 122 MACE in this study with 1.9 MACE per 100 patient years of treatment, a total of 6,500 patient years of treatment (aclidinium bromide and placebo) would be needed. Assuming a treatment discontinuation rate of 40% and a study discontinuation rate of 20% at year 2, and following an exponential distributions for time to events and time to discontinuations, a sample size of 4000 is needed to ensure 90% power to observe 122 events applying the on-study analysis, and an 80% power to observe 91 events applying the on-treatment analysis.

### **1.3.2 Power for the primary efficacy endpoint: rate of moderate or severe exacerbations per patient per year during the first year of treatment**

The sample size of 4,000 patients after 1 year of treatment will have ~89% power to detect a reduction in the rate of moderate or severe COPD exacerbations per patient per year during the first year of treatment of 14% (rate ratio of 0.86 in acclidinium bromide relative to placebo) at 0.05 significance level. The 89% power was calculated assuming a treatment discontinuation rate of 30% during the first year, a placebo rate of 0.8 exacerbation per patient per year (reduced from 1 to 0.8 as not all patients will have a history of exacerbation prior to randomization), and an overdispersion factor  $k$  of 0.67 (Keene et al, 2007).

See Section 9.7.9 of the CSP for detailed information on determination of sample size and power calculation.

## **2. ANALYSIS SETS**

### **2.1 Definition of analysis sets**

Three populations will be considered in the statistical analysis of the study.

#### **2.1.1 Screened Population**

The Screened Population will consist of all patients who signed a written ICF and received a screening number.

### **2.1.2 Randomized Population**

The Randomized Population will consist of all patients in the Screened Population who were randomized to a treatment group in the study.

### **2.1.3 Full Analysis Set Population**

The Full Analysis Set (FAS) Population will consist of all patients in the Randomized Population who took at least one dose of the double-blind IP (acridinium bromide or placebo). Patients will be analyzed according to their randomized treatment.

The FAS will be used to carry out the primary analysis of both efficacy and safety data. Efficacy and safety data may be further investigated and sensitivity analyses may be performed using the Randomized Population if more than 1% of patients did not receive one dose of the double-blind IP. Any important deviations from the randomized treatment assignment and any subjects who have received double-blind IP without being randomized will be listed and considered when interpreting the data.

## **2.2 Violations and deviations**

### **2.2.1 Protocol deviations**

Only important protocol deviations (in the CSP referred to as protocol violations) will be listed and tabulated in the clinical study report (CSR). Protocol deviations that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being, will be considered as important and will include the following:

- Key eligibility criteria not fulfilled but randomized
- Concomitant use of disallowed medications. Patients who use one or more disallowed medication (for any reason, unless otherwise specified) on IP during the treatment period will be classified as protocol deviators after confirmation by an AZ physician
- Patients who received the incorrect study treatment or study dose at any time during the treatment period
- Patients who fulfilled withdrawal criteria during the study but were not withdrawn

The final list of protocol deviations will be finalized and documented prior to unblinding the study data.

All important protocol deviations will be programmatically derived. The programming produces a draft list of important protocol deviations for the medical/clinician review on an ongoing basis; a final list of important protocol deviations is determined before the database (DB) lock after a joint team review (the third bullet above is determined after the DB lock and unblinding) and include into the relevant dataset.

### **2.2.2 Visit window definitions**

For exacerbation-related analyses and MACE-related analyses, no visit windows will be applied.

For by-visit assessments (e.g., FEV<sub>1</sub>, CAT, vital signs, ECG, physical examinations, clinical laboratory), their baseline and post baseline visits may occur as per protocol at the indicated week  $\pm$  7 days throughout the treatment period. Unless otherwise specified, actual scheduled visits will be used for the summaries over time with no visit windows applied.

## **3. PRIMARY AND SECONDARY VARIABLES**

### **3.1 General principles taken for analysis variables**

#### **3.1.1 End of study date**

The study will be completed when a total of 122 patients with adjudicated MACE are observed. Based on the number of adjudicated MACE events, the sponsor will declare the end of the study date and give the study sites at least 3 months notice. At the conclusion of the treatment period, the following information will be collected for all patients (these visit procedures also apply for a patient who is discontinuing study medication before the end of the study):

- All assessments listed for the EOT visit
- Schedule a phone contact for 15 days from visit

#### **3.1.2 Censoring rules in time-to-event analyses**

In time-to-event analyses, patients who have not had the event(s) in question will be censored at the following time points as applicable, depending on whether it is an on-study or on-treatment analysis (see Section 4.1 for definitions):

For on-study analysis:

- The last visit (in this case the EOT visit) for patients who completed the treatment or patients who are still on treatment at the end of study date
- Last contact date for patients who pre-maturely discontinued IP and completed the study or patients who pre-maturely discontinued IP and are still in study at the end of study date
- Any patient who is lost to follow-up (LTFU) at the end of the study will be censored at the last study contact where all elements of the endpoint in question were assessed
- Patients who withdraw consent will be censored at date of withdrawal, except in the analysis of all-cause mortality as a single endpoint, when patients will be censored at the date of last known alive according to vital status data



For on-treatment analysis:

- Patients will be censored on the date of IP discontinuation

In analysis of time to CV death and composites including CV death, censoring will occur at date of death from non-CV causes. For endpoints not including death, all deaths are censoring events.

### 3.1.3 Definition of baseline measurements

For each safety variable, the last assessment made before the first dose of the double-blind IP will be used as the baseline for all analyses of that safety variable. For physical examination and ECG, baseline is defined as Visit 1A assessment.

Body mass index (BMI) is calculated as weight [kg]/(height [m])<sup>2</sup>, and will also be categorized as follows:

- Underweight: BMI < 18.5 kg/m<sup>2</sup>
- Normal range: BMI ≥ 18.5 kg/m<sup>2</sup> and < 25 kg/m<sup>2</sup>
- Overweight: BMI ≥ 25 kg/m<sup>2</sup> and < 30 kg/m<sup>2</sup>
- Obese: BMI ≥ 30 kg/m<sup>2</sup>

Weight and height measured at Visit 1A will be used in calculation of baseline BMI.

For pre-dose trough FEV<sub>1</sub>, the average of the two pre-dose values measured prior to the administration of the first dose of the double-blind IP at Visit 1B will be used as baseline. If one of the two measurements at Visit 1B is missing, then the available one will be used as baseline value. If both values at Visit 1B are missing, then the pre-bronchodilator value from Visit 1A will be used as baseline instead.

Baseline COPD severity based on airflow obstruction is assessed using postbronchodilator FEV<sub>1</sub> measured at Visit 1A or unscheduled visit prior to Visit 1B as follows:

- GOLD Grade 1 (mild): FEV<sub>1</sub> ≥ 80% predicted
- GOLD Grade 2 (moderate): FEV<sub>1</sub> ≥ 50% predicted and < 80% predicted
- GOLD Grade 3 (severe): FEV<sub>1</sub> ≥ 30% predicted and < 50% predicted
- GOLD Grade 4 (very severe): FEV<sub>1</sub> < 30% predicted

Baseline COPD severity, when used as a factor in the statistical model, will be classified into 3 levels above: moderate, severe, and very severe. In case any patient has baseline COPD severity as mild (a protocol deviation, and expected very limited), the value of mild will be pooled into the moderate to avoid convergence problem in the statistical model.

The COPD assessment test (CAT) assessments at Visit 1B will be used for calculating the respective baseline.

The new Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2017) for the assessment of COPD disease has been refined to separate spirometric grades from the ABCD groups. The assessment of airflow limitation is based on percent predicted FEV1 and is classified into 4 grades (see COPD severity classification above). The assessment of symptoms/risk of exacerbations is classified into the 4 groups as shown in table below.

<b>Group</b>	<b>Exacerbation history</b>	<b>CAT at baseline</b>
A	0 or 1 (not leading to hospital admission)	<10
B	0 or 1 (not leading to hospital admission)	≥10
C	≥2 or ≥1 leading to hospital admission	<10
D	≥2 or ≥1 leading to hospital admission	≥10

Therefore, there are 16 potential categories with A, B, C and D phenotypes being further subdivided by 4 severities of airflow obstruction.

### **3.1.4 Repeated or unscheduled assessments**

Extra assessments (vital signs, or ECG parameters associated with non-protocol clinical visits or obtained in investigating or managing AEs) will be included in listings, but not summaries of the data.

For summary tables, if repeated measurements are taken for either time point, then the last measurement will be used for the value for that time point. If it is not possible to determine which is the last measurement due to missing times then the average of all measurements for that time point will be used for the value for that time point.

However, all postbaseline assessments, including repeated or unscheduled visits, will be used for potentially clinically significant (PCS) value determinations.

### **3.1.5 Handling missing data**

#### **3.1.5.1 Data convention for FEV<sub>1</sub>**

For FEV<sub>1</sub>, refer to Section 3.1.3 for handling missing data in determination of baseline FEV<sub>1</sub>.

### **3.1.5.2 Data convention for CAT**

The CAT total score for each patient at each visit will be computed as the summation of scores for all 8 questions. If one or two responses are missing, then the average of the remaining non-missing responses will be used for missing values; if more than two responses are missing, then the total score will be treated as missing.

### **3.1.5.3 Missing end date of exacerbations**

For duration of COPD exacerbations, if end date of the exacerbation is completely missing, then the last contact date will be used as the end date of the event. If end date of the exacerbation is partially missing with month and year available, then the last day of that month will be used.

### **3.1.5.4 Missing date of the last dose of the double-blind IP**

When the date of the last dose of the double-blind IP during treatment period is missing for a patient in the FAS Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, then the last available dosing record date will be used as the last dose date in calculation of treatment duration.

### **3.1.5.5 Missing severity assessment for AEs**

If severity is missing for an AE that started before the date of the first dose of the double-blind IP, then an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of the double-blind IP, then an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

### **3.1.5.6 Missing causal relationship to the double-blind IP for AEs**

If the causal relationship to the IP is missing for an AE that started on or after the date of the first dose of the double-blind IP, then a causality of Yes (reasonable possibility) will be assigned. The imputed values for causal relationship to the double-blind IP will be used for the incidence summary; the actual values will be presented in the data listings.

### **3.1.5.7 Missing date information for AEs**

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partial missing).

#### Missing Month and Day

- If the year of the incomplete start date is the same as the year of the first dose of the double-blind IP, then the month and day of the first dose of the double-blind IP will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the first dose of the double-blind IP, *December 31* will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the first dose of double-blind IP, *January 1* will be assigned to the missing fields.

#### Missing Month Only

- If only the month is missing, then the day will be treated as missing and both the month and the day will be replaced according to the procedure above.

#### Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of the double-blind IP, then the day of the first dose of the double-blind IP will be assigned to the missing day.
- If either the year of the incomplete start date is before the year of the date of the first dose of the double-blind IP or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of the double-blind IP, then the last day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of the double-blind IP or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of the double-blind IP, then the first day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date as above is after the stop date, then the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, then the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of the double-blind IP, then the date of the first dose of the double-blind IP will be assigned to the missing start date.
- If the stop date is before the date of the first dose of the double-blind IP, then the stop date will be assigned to the missing start date.

### **3.1.5.8 Missing date information for prior and concomitant medications**

For prior and concomitant medications, incomplete (i.e., partial missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first.

#### **Incomplete start date**

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

### Missing Month and Day

- If the year of the incomplete start date is the same as the year of the first dose of the double-blind IP, then the month and day of the first dose of the double-blind investigational product will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the first dose of the double-blind IP, *December 31* will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the first dose of the double-blind IP, *January 1* will be assigned to the missing fields.

### Missing Month Only

- If only the month is missing, then the day will be treated as missing and both the month and the day will be replaced according to the procedure above.

### Missing Day Only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of the double-blind IP, then the day of the first dose of the double-blind IP will be assigned to the missing day.
- If either the year of the incomplete start date is before the year of the date of the first dose of the double-blind IP or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of the double-blind IP, then the last day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of the double-blind IP or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of the double-blind IP, then the first day of the month will be assigned to the missing day.

### **Incomplete stop date**

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of the double-blind IP is missing, then replace it with the last visit date in the imputations described below. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

### Missing Month and Day

- If the year of the incomplete stop date is the same as the year of the last dose of the double-blind IP, then the month and day of the last dose of the double-blind IP will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of the last dose of the double-blind IP, *December 31* will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the last dose of the double-blind IP, *January 1* will be assigned to the missing fields.

#### Missing Month Only

- If only the month is missing, then the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

#### Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of the double-blind IP, then the day of the last dose of the double-blind IP will be assigned to the missing day.
- If either the year of the incomplete stop date is before the year of the date of the last dose of the double-blind IP or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of the double-blind IP, then the last day of the month will be assigned to the missing day.
- If either the year of the incomplete stop date is after the year of the date of the last dose of the double-blind IP or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of the double-blind IP, then the first day of the month will be assigned to the missing day.

#### **3.1.5.9 Character Values of Clinical Laboratory Parameters**

Not applicable since there will be no report of the laboratory data.

#### **3.1.6 Definition of COPD exacerbations**

The onset and end of a COPD exacerbation is defined by the investigators in their assessment of patient symptoms and initiation/finalization of treatment (as defined below for the severity of exacerbation), and recorded on COPD Exacerbation page of electronic case report forms (eCRFs).

The severity of a COPD exacerbation is assessed according to the following scale:

- Mild: Increase in COPD symptoms (e.g., dyspnea, cough, sputum volume, sputum purulence) during at least 2 consecutive days, managed by the patient at home by increasing short-acting bronchodilator and/or inhaled corticosteroid (ICS) use
- Moderate: Increase in COPD symptoms (e.g., dyspnea, cough, sputum volume, sputum purulence) during at least 2 consecutive days that does not lead to hospitalization but is treated with antibiotics and/or systemic corticosteroids

- Severe: Increase in COPD symptoms (e.g., dyspnea, cough, sputum volume, sputum purulence) during at least 2 consecutive days that leads to hospitalization (overnight stay at hospital or emergency room) or death

### Definitions of New and/or Relapsed COPD exacerbations

The interval between 2 consecutive COPD exacerbations must be at least 7 days. Therefore, if 2 COPD exacerbations occur within 7 days of each other, then they will be considered as 1 event (i.e., the second one is considered as a relapse). Inpatient hospitalization due to COPD occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted as a new exacerbation it must be preceded by at least 7 days in which none of the exacerbation criteria is fulfilled.

A COPD exacerbation will be derived as a new COPD exacerbation if and only if either of the following conditions is met:

- The exacerbation is the first episode, or
- The start date of the exacerbation is greater than or equal to 7 days since the previous exacerbation

All reported exacerbations will be combined with any reported relapses. Relapses will be considered as a continuation of the previous event. That is, the onset of exacerbation event will be the same as the onset of first exacerbation event with a resolution date being derived as the resolution date of last relapse. The severity of exacerbation event derived in this way will be the most severe of first exacerbation or any derived relapse.

### 3.1.7 Derived variables

#### 3.1.7.1 Rate of event

The rate of event per patient per year during a given period (e.g., during the first year of treatment) is calculated as the sum of all available events in that period divided by the sum of all patients follow-up time in that period, i.e.,  $\frac{\sum_{i=1}^n e_i}{\sum_{i=1}^n t_i}$ , where  $e_i$  is the number of event in patient  $i$  and  $t_i$  is the follow-up time in patient  $i$ . The follow-up time in patient  $i$ ,  $t_i$ , is calculated as  $d_i/365.25$ , where  $d_i$  is the number of days patient  $i$  exposed, calculated as (*follow-up date – randomization date + 1*).

#### 3.1.7.2 Duration of event

For the production of summary statistics, the duration (in days) of event per patient per year during a given period is calculated as the sum of duration of all available events in that period divided by the sum of all patients follow-up time in that period, i.e.,  $\frac{\sum_{i=1}^n p_i}{\sum_{i=1}^n t_i}$ , where  $p_i$  is the duration (in days) of all events in patient  $i$ . The duration of each event is calculated as (*end date – onset date + 1*).

See Section 3.1.7.1 for calculation of the follow-up time in patient  $i$ ,  $t_i$ .



### 3.1.7.3 Time to first event

Time (in days) to first event in a given period is calculated as follows:

*Start date of first event in a given period – Date of randomization + 1.*

### 3.1.7.4 Other derived variables

#### Selection of spirometric measurements

Spirometric measurements data for each maneuver attempt must be entered into the electronic data capture system. Throughout the study, the reading of spirometric values is to be performed by the PI, or appropriately trained designee, to ensure the values meet the American Thoracic Society and European Respiratory Society criteria for acceptability. At each time point, only the greatest acceptable FEV<sub>1</sub> value and other corresponding spirometric measures (FVC, FEV<sub>1</sub>/FVC) will be used for all analyses. See Appendix III of the CSP for details.

Reversible is defined as % bronchial reversibility  $\geq$  12% and change from pretest  $\geq$  200 mL in FEV<sub>1</sub>, where

*% bronchial reversibility = 100 × (postbronchodilator FEV<sub>1</sub> – prebronchodilator FEV<sub>1</sub>) / prebronchodilator FEV<sub>1</sub>*

*Change from pretest (in liters) = postbronchodilator FEV<sub>1</sub> – prebronchodilator FEV<sub>1</sub>*

#### Other variables

Baseline ICS use, when used as a factor in statistical model, will be derived as follows:

- ‘Yes’ if any ICS use was reported (as a monotherapy or in combination) within 15 days prior the first dose of the double-blind IP.
- ‘No’ otherwise

The CV severity at baseline, when used as a factor in statistical model, will be defined as 2 categories:

- Patients who had 2 CV risk factors, and
- Patients who had more than 2 CV risk factors or at least one documented cerebrovascular disease, coronary artery disease or peripheral vascular disease or history of claudication

The CV risk factors will be defined as following atherothrombotic risk factors as determined by the PI:

- Male  $\geq$  65 years or female  $\geq$  70 years
- Diabetes



- Dyslipidemia
- Hypertension
- Waist circumference in males  $\geq 40$  inches or in females  $\geq 38$  inches.
- Evidence of renal dysfunction (eGFR  $< 60$ ) and microalbuminuria (eGFR is based on modification of diet in renal disease equation, microalbuminuria is defined as  $\geq 30$ -300 mcg/mg creatinine on a spot urine or  $\geq 30$  mg creatinine on a 24hr urine test)

Number of cigarettes per day is calculated as  $(20 * Total\ pack\text{-}years) / Smoking\ duration$  (in years).

Age is also categorized as a categorical variable as follows:

- $\geq 40$  and  $< 60$  years
- $\geq 60$  and  $< 70$  years
- $\geq 70$  years old

### **3.2 Primary efficacy variable**

The primary efficacy variable is rate of moderate or severe COPD exacerbation per patient per year during the first year of treatment. COPD exacerbations are evaluated by the PI throughout the study.

For the production of summary statistics, the rate of moderate or severe COPD exacerbation per patient per year during the first year of treatment is calculated by applying the following in the general formula defined in Section 3.1.7.1.

- Event is moderate or severe COPD exacerbation
- Period refers to the first year of treatment

### **3.3 Secondary efficacy variable**

The secondary efficacy variable is rate of hospitalization due to COPD exacerbation per patient per year during the first year of treatment.

For the production of summary statistics, the rate of hospitalization due to COPD exacerbation per patient per year during the first year of treatment is calculated by applying the following in the general formula defined in Section 3.1.7.1.

- Event is hospitalization due to COPD exacerbation
- Period refers to the first year of treatment

### **3.4 Additional efficacy variables**

#### **3.4.1 COPD exacerbation variables**

The following COPD exacerbation variables use data collected during the whole study period. Maximum follow-up time for a patient is approximately 36 months.

##### **3.4.1.1 Rate of moderate or severe COPD exacerbations per patient per year**

For the production of summary statistics, the rate of moderate or severe COPD exacerbation per patient per year is calculated by applying the following in the general formula defined in Section 3.1.7.1.

- Event is moderate or severe COPD exacerbation
- Period refers to the whole study period

##### **3.4.1.2 Rate of mild, moderate, or severe COPD exacerbations per patient per year**

For the production of summary statistics, the rate of mild, moderate, or severe COPD exacerbation per patient per year is calculated by applying the following in the general formula defined in Section 3.1.7.1.

- Event is mild, moderate, or severe COPD exacerbation
- Period refers to the whole study period

##### **3.4.1.3 Duration of moderate or severe COPD exacerbations per patient per year**

For the production of summary statistics, the duration (in days) of moderate or severe COPD exacerbation per patient per year is calculated by applying the following in the general formula defined in Section 3.1.7.2.

- Event is moderate or severe COPD exacerbation
- Period refers to the whole study period

##### **3.4.1.4 Duration of mild, moderate, or severe COPD exacerbations per patient per year**

For the production of summary statistics, the duration (in days) of mild, moderate, or severe COPD exacerbation per patient per year is calculated by applying the following in the general formula defined in Section 3.1.7.2.

- Event is mild, moderate, or severe COPD exacerbation
- Period refers to the whole study period

##### **3.4.1.5 Proportion of patients with at least one COPD exacerbation**

- Number and percentage of patients with at least one COPD exacerbation

- Number and percentage of patients with at least one mild COPD exacerbation
- Number and percentage of patients with at least one moderate COPD exacerbation
- Number and percentage of patients with at least one severe COPD exacerbation
- Number and percentage of patients with at least one moderate or severe COPD exacerbation

#### **3.4.1.6 Time to COPD exacerbation**

- Time to first COPD exacerbation

Time to first COPD exacerbation is calculated by applying the following in the general formula defined in Section 3.1.7.3.

- Event is mild, moderate, or severe COPD exacerbation
- Period refers to the whole study period

For patients who do not experience a COPD exacerbation during the study, start date of the first COPD exacerbation will be censored per general censoring rules described in Section 3.1.2, i.e., the event in question refers to a COPD exacerbation.

- Time to first moderate or severe COPD exacerbation during the first year of treatment

Time to first moderate or severe COPD exacerbation during the first year of treatment is similarly calculated and censored as time to first COPD exacerbation, by considering moderate or severe COPD during the first year of treatment only, i.e., patients will be censored on the date of IP discontinuation or at the end of the first year, whichever is earlier.

- Time to first moderate or severe COPD exacerbation

Time to first moderate or severe COPD exacerbation is similarly calculated and censored as time to first COPD exacerbation, by considering moderate or severe COPD only.

- Time to second COPD exacerbation

Time to second COPD exacerbation is calculated as follows:

*Start Date of the second COPD exacerbation – Date of randomization + 1.*

Time to second COPD exacerbation will be analyzed in patients who experience at least one COPD exacerbation. For patients who experience < 2 COPD exacerbations during the study, start date of the second COPD exacerbation will be censored per general censoring rules described in Section 3.1.2, i.e., the event in question refers to the second COPD exacerbation.

- Time to second moderate or severe COPD exacerbation

Time to second moderate or severe COPD exacerbation is similarly calculated and censored as time to second COPD exacerbation, by considering moderate or severe COPD only.

- Time to third COPD exacerbation

Time to third COPD exacerbation is calculated as follows:

*Start Date of the third COPD exacerbation – Date of randomization + 1.*

Time to third COPD exacerbation will be analyzed in patients who experience at least two COPD exacerbations. For patients who experience < 3 COPD exacerbations during the study, date of the third COPD exacerbation will be censored per general censoring rules described in Section 3.1.2, i.e., the event in question refers to the third COPD exacerbation.

- Time to third moderate or severe COPD exacerbation

Time to third moderate or severe COPD exacerbation is similarly calculated and censored as time to third COPD exacerbation, by considering moderate or severe COPD only.

#### **3.4.1.7 Time to Withdrawal from the double-blind IP due to COPD exacerbation**

Time (in days) to withdrawal from the double-blind IP due to COPD exacerbation is calculated as follows:

*Date of withdrawal from the double-blind IP due to COPD exacerbation – Date of randomization + 1.*

- For patients who do not withdraw from the double-blind IP, date of withdrawal from the double-blind IP due to COPD exacerbation will be censored at the last dose date.
- For patients who withdraw from the double-blind IP due to reasons other than COPD exacerbation, patients will be censored at the date of withdrawal from the double-blind IP (due to reasons other than COPD exacerbation).

#### **3.4.1.8 Rate of hospitalization due to COPD exacerbations per patient per year**

For the production of summary statistics, the rate of hospitalization due to COPD exacerbation per patient per year is calculated by applying the following in the general formula defined in Section 3.1.7.1.

- Event is hospitalization due to COPD exacerbation
- Period refers to the whole study period

#### **3.4.1.9 Number of days hospitalized due to COPD exacerbations**

The number of days hospitalized due to COPD exacerbations is calculated as follows:

*Number of days hospitalized due to COPD exacerbations = Sum of duration for all hospitalizations due to COPD exacerbations*

where

*Duration for each hospitalization due to COPD exacerbations = end date – onset date + 1*

Hospitalizations during the whole study period are counted in the calculation.

#### **3.4.1.10 Time to first hospitalization due to COPD exacerbations**

Time (in days) to first hospitalization due to COPD exacerbations is calculated by applying the following in the general formula defined in Section 3.1.7.3.

- Event is hospitalization due to COPD exacerbation
- Period refers to the whole study period

For patients who do not experience a hospitalization during the study, date of first hospitalization due to COPD exacerbation will be censored at the last dose date (or study closure date for patients who did not discontinue from study treatment). For patients who experience a hospitalization due to reasons other than COPD exacerbation during the study, patients will be censored at the date of first hospitalization (due to reasons other than COPD exacerbation).

#### **3.4.2 Spirometry outcome variable**

- Change from baseline in morning pre-dose trough FEV<sub>1</sub> at visits 2, 3, 4, 5, 6, 8, 10, and 12 (on-treatment analysis)

Changes from baseline in morning pre-dose FEV<sub>1</sub> at a specified visit will be calculated as follows:

*Morning pre-dose FEV<sub>1</sub> at a specified visit – baseline FEV<sub>1</sub>.*

### **3.5 Safety variables**

The following safety data will be collected: AEs (including COPD exacerbations reported in the AE/SAE page of eCRFs), vital sign measurements, 12-lead ECGs, and physical examination findings.

#### **3.5.1 MACE and other serious CV events of interest**

Major adverse cardiovascular event is a composite of the total of CV death, non-fatal MI and non-fatal stroke.

Other serious CV events of interest are SAEs based on SMQs of cardiac disorders (i.e. cardiac arrhythmias SMQ and cardiac failure SMQ) and of cerebrovascular disorders, adjudicated to

‘Non-fatal other: Other cardiovascular event’. See the Clinical Events Committee [CEC] charter for details.

Adverse events based on SMQ for MACE and other serious CV events of interest (includes cardiac events and cerebrovascular events) are as follows:

Events of interest	Standard MedDRA Query Category plus additional High Level Terms or Preferred Term, if applicable	
Cardiac events	Ischemic Heart Disease:	
	Myocardial infarction	Narrow search SMQ
	Other Ischemic Heart Disease	Narrow search SMQ
	Tachyarrhythmias	Tachyarrhythmias (narrow and broad search SMQ) plus additional PTs: tachycardia, heart rate increase and palpitation
	Cardiac failure	Narrow search SMQ
	Bradycardia	Bradycardia terms, non-specific (narrow search SMQ) plus additional PTs: sinus arrest and sinus bradycardia
	Conduction defects	Narrow search SMQ
Cerebrovascular events	Hemorrhagic and Ischemic disorders	Haemorrhagic central nervous system vascular conditions (narrow search SMQ) plus Ischaemic central nervous system vascular conditions (narrow search SMQ)
Major adverse cardiovascular events (MACEs)	All Adjudicated MACE by CEC: cardiac death, non-fatal myocardial infarction and non-fatal stroke	

### 3.5.1.1 Adjudication of clinical endpoints

A CEC will be formed to assess and adjudicate all MACE. This committee will be blinded to treatment assignment and composed of independent cardiologists. A charter outlining the communication flow and the criteria to classify and adjudicate MACE will be established.

The committee will adjudicate the following events occurring from randomization to end of study (last contact visit):

- All death cases
- Myocardial infarction defined as any non-fatal case that was coded to a preferred term (PT) in the SMQ “myocardial infarction”
- Stroke defined as any non-fatal case that was coded to a PT in the SMQ “central nervous system hemorrhages and cerebrovascular conditions”

Additionally, the SMQs of cardiac disorders (i.e. cardiac arrhythmias SMQ and cardiac failure SMQ) and cerebrovascular disorders will also be assessed by the CEC.

### **3.5.1.2 Primary safety variable**

The primary safety variable is time to first MACE event (i.e., time to first occurrence of any event from the composite of CV death, non-fatal MI, or non-fatal stroke) using only events adjudicated as such by the CEC. Time will be calculated as the number of days plus one between the date of randomization and date of the first occurrence of the MACE event, or, event free patients will be censored at the time as described in Section 3.1.2 for on-study analysis.

A patient may suffer more than one event during the study. For composite endpoints only a patient's first occurring event contributes to the analysis of the component. For example, if a stroke precedes an MI, only the stroke will be used for the analysis of the primary composite endpoint. However, the MI will be used in separate analysis of time to components of the composite endpoint. Multiple events for a patient will be included in tabulations at episode level, and may be included in exploratory analyses.

When the first event is MI or stroke, the time of a composite endpoint will be the time of the MI or stroke, irrespective of whether or not the patient dies as a sequel of the event. Analysis of the individual components will include all MI/strokes at the time of the event. Thus, the qualifier 'non-fatal' used for MI and stroke throughout the composite endpoint definitions can be ignored. The qualifier was used to clarify that fatal MI and fatal strokes would not be counted twice (e.g., as an MI and as a CV death) in tallying the composite endpoint.

The individual components (CV death, non-fatal MI, non-fatal stroke) of the primary endpoint will be examined in exploratory fashion.

### **3.5.1.3 Secondary safety variable**

The secondary safety variable is time to first MACE or other serious CV events of interest.

## **3.5.2 Adverse events**

Adverse events will be coded using the MedDRA version 18.0 or newer.

Adverse event data will be categorized according to their onset date, as occurring during washout/run-in, during on treatment, or during off treatment.

An AE will be considered a treatment-emergent adverse event (TEAE) if it started on or after the date of the first dose of double-blind IP or it started before the date of the first dose of double-blind IP and continued during the study with increased severity. An AE that occurs more than 15 days after the date of the last dose of double-blind IP will not be counted as a TEAE.

A TEAE with cause Reasonable Possibility related to the double-blind IP as judged by the investigator is defined as a treatment related AE.

### 3.5.3 Clinical laboratory variables

Local laboratories will be used to evaluate all urine and blood samples. Any clinically significant abnormalities in laboratory values as determined by the investigator are reported as adverse events.

Study center personnel must report every patient that meets potential Hy's law criteria, i.e.: ALT or AST  $\geq 3xULN$  and Total Bilirubin  $\geq 2xULN$  and Alkaline Phosphatase  $< 2xULN$ . An event that potentially meets Hy's law criteria should be reported as an SAE using the most relevant SAE criteria, as judged by the Investigator.

### 3.5.4 Vital signs

Vital signs will be assessed including pulse rate (beats per minute [bpm]), systolic and diastolic blood pressure (BP; mmHg), and weight in accordance with the schedule of evaluations as specified in the CSP.

Blood pressure (systolic and diastolic), pulse rate, and weight values meeting criteria for PCS vital signs will be considered with special attention.

#### Criteria for Potentially Clinically Significant Vital Signs

Vital sign	Flag	Criteria
Systolic BP, mmHg	High	( $\geq 180$ and increase over baseline $\geq 20$ ) or ( $\geq 200$ and baseline $< 200$ )
	Low	( $\leq 90$ and decrease over baseline $\geq 20$ ) or ( $\leq 75$ and baseline $> 75$ )
Diastolic BP, mmHg	High	( $\geq 105$ and increase over baseline $\geq 15$ ) or ( $\geq 115$ and baseline $< 115$ )
	Low	( $\leq 50$ and decrease over baseline $\geq 15$ ) or ( $\leq 40$ and baseline $> 40$ )
Pulse rate, bpm	High	( $\geq 110$ bpm and increase over baseline $\geq 15\%$ ) or ( $\geq 120$ bpm and baseline $< 120$ bpm)
	Low	( $\leq 50$ bpm and decrease over baseline $\geq 15\%$ ) or ( $\leq 40$ bpm and baseline $> 40$ bpm)
Weight <sup>a</sup> , kg	High	Increase of $\geq 7\%$
	Low	Decrease of $\geq 7\%$

<sup>a</sup> Weight change is relative to Screening (Visit 1A).

bpm = beats per minute.

### 3.5.5 Electrocardiogram

ECG measurements include ventricular heart rate (bpm), RR interval (ms), PR interval (ms), QRS duration (ms), QT interval (ms), and QTc (ms). QTc will be used for the data interpretation. Commonly used techniques including Bazett's (QTcB) and Fridericia's (QTcF) methods are applied.



Categorical analyses of absolute QTc interval prolongation and change from baseline in QTc interval meeting criteria for PCS ECGs will be considered with special attention.

### Criteria for Potentially Clinically Significant Electrocardiograms

ECG Parameter	Criteria 1	Criteria 2
QTcB, and QTcF		
Absolute values	> 480 ms	> 500 ms
Absolute change from baseline	> 30 ms	> 60 ms
QRS duration	≥ 100 ms and an increase of ≥ 25% over baseline value	≥ 150 ms if baseline is < 150 ms
PR interval	≥ 200 ms and an increase of ≥ 25% over baseline value	≥ 250 ms if baseline is < 250 ms
Heart Rate		
Tachycardia event	≥ 110 bpm and an increase of ≥ 15% over baseline value	≥ 120 bpm if baseline is < 120 bpm
Bradycardia event	≤ 50 bpm and a decrease of ≥ 15% over baseline value	≤ 40 bpm if baseline is > 40 bpm

bpm = beats per minute; ms = millisecond.

QTcB = QT interval corrected for heart rate using the Bazett formula ( $QTcB = QT/(RR)^{1/2}$ );

QTcF = QT interval corrected for heart rate using the Fridericia formula ( $QTcF = QT/(RR)^{1/3}$ ).

#### 3.5.6 Physical examination

Clinically significant finding occurring at Visit 1A are considered Medical History and any changes thereafter considered AEs.

#### 3.5.7 All-cause mortality

Patient's vital status will be collected and used for all-cause mortality analysis. Death/alive status, date of death, and date last known to be alive will be collected at either 3 years post subject randomization date or study completion is announced. The overall survival (OS) time is censored on the last date they were known to be alive.

### 3.6 Health economic and outcomes research assessments

The CAT is a validated, patient completed, questionnaire to measure the impact of COPD on a patient's health status. It is comprised of 8 questions to be answered independently by patient

via a paper questionnaire (See Appendix V of the CSP). Each question, except for total CAT score, ranges from 0 to 5 (5 indicates the worst health status). The total scores range from 0 to 40 (40 indicates the worst health status). Refer to Section 3.1.5.2 for scoring the CAT total score.

- Change from baseline in CAT score at visits 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12

Changes from baseline in CAT score at a specified visit will be calculated as follows:

*CAT score at a specified visit – baseline CAT.*

- Proportion of patients with an improvement of 2 or more units from baseline in CAT total score at visits 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12

## **4. ANALYSIS METHODS**

### **4.1 General principles**

Unless otherwise stated, descriptive summaries will be presented by treatment group. The treatment groups will be presented in the order of Acridinium 400 µg and Placebo in tables.

Continuous data will be summarized in terms of the number of nonmissing observations (n), mean, standard deviation (SD), median, minimum, and maximum, unless otherwise stated. Where data are collected over time, both the observed data and change from baseline (refer to Section 3.1.3 for baseline definitions) will be summarized at each time point.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database, unless a decision has been made to report the summary statistics to a lesser number of decimal places than the original data. Unless otherwise specified in the actual table shells, the mean, SD, standard error of the mean (SEM), median, the upper and the lower limits of confidence interval (CI) will be displayed to the one more decimal place than the raw data in the database. In general, the maximum number of decimal places reported shall be three for any summary statistic.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. A percentage of 100% will be reported as 100%. Percentages will not be presented for zero counts. Unless otherwise stated, percentages will be calculated using n as the denominator.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as “<0.001”. P-values greater than 0.999 will be presented as “>0.999”.

All report outputs will be produced using SAS<sup>®</sup> version 9.2 or a later version in a secure and validated environment.

All statistical tests will be two-sided hypothesis tests performed at a 0.05 significance level for main effects. All CIs will be two-sided 95% CIs, unless otherwise stated.

The on-study analysis is defined as all events that occurred while the patient was in the study, irrespective of treatment exposure (i.e., this includes all events that occurred during which the patient was on treatment or off treatment). The on-treatment analysis is defined as only events that occurred while the patient has received at least one dose of study double-blind IP during the treatment period excluding off treatment period/post treatment follow-up (PTFU) period.

The status of patients off treatment during the study period is referred to as the PTFU period.

**Handling professional/duplicate patients.** Professional patients are individuals who, in violation of protocol entrance criteria and enter into the same study more than once and/or enter into more than one study at the same or in close succession.

Unless otherwise stated, the first incidence of patient entering trial is used in analysis and summary. All data is listed for transparency, with flags for duplicate patients to ensure clarity which records are in/out of the analysis.

For handling of AEs, if a patient is on same treatment throughout (across all incidences), include all data in the analysis. If patient is on different treatments (i.e., different randomised treatment received at the second incidence vs the first incidence), the first incidence of patient entering trial is used in analysis.

**Handling data from patients with missing investigator signatures.** These patients will be excluded from the FAS and would be included in screened and randomized patient population.

## 4.2 Analysis methods

### 4.2.1 Patient disposition

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion. Summaries of patient disposition will be presented by treatment and overall (column), while summaries in the Screened Population (when applicable) will be presented only by overall (column). The following patient disposition summaries will be provided:

- Number and percentage of patients in the Screened, Randomized, and FAS populations by country and overall (row) (Analysis Population: Screened).
- Number and percentage of screen-failure patients (i.e., patients screened but not randomized), further classified by reasons for screen failure (Analysis Population: Screened).

- Number and percentage of patients who complete the double-blind treatment period and who prematurely discontinue from the double-blind IP, further classified by reasons for premature discontinuation from the double-blind IP (as recorded on Subject Status [IP Usage] page of the eCRFs); number and percentage of patients who prematurely discontinue from the double-blind IP and entered into post-treatment follow-up period and who prematurely discontinued from the double-blind IP and did not enter into post-treatment follow-up period will also be summarized (Analysis Population: FAS).
- Number and percentage of patients who complete the study and who withdraw from the study, further classified by reasons for withdrawal from the study (as recorded on Termination/Death page of eCRFs). Patients who complete the study are those who by the time the study is stopped 1) complete the 36-months double-blind treatment period, 2) prematurely discontinue the double-blind IP and complete the PTFU period, 3) are on treatment, or 4) prematurely discontinue the double-blind IP and are in the PTFU period. Number and percentage of patients who prematurely discontinued treatment, entered into PTFU, but prematurely discontinued the PTFU will also be summarized (Analysis Population: FAS).
- Number and percentage of patients who complete the first year of treatment and who prematurely discontinue from the double-blind IP during the first year, further classified by reasons for premature discontinuation from the double-blind IP during the first year (as recorded on Subject Status [IP Usage] page of eCRFs); number and percentage of patients who prematurely discontinued from the double-blind IP during the first year and entered into post-treatment follow-up period and who prematurely discontinued from the double-blind IP during the first year and did not enter into post-treatment follow-up period will also be summarized (Analysis Population: FAS).
- Number and percentage of patients characterized at the key time point (e.g., one year) who remained on treatment through that time point, discontinued treatment but remained in study through that time point, withdrew from the study prior to that time point, or did not reach that time point due to study closure (Analysis Population: FAS).
- Time (in days) to premature discontinuation from the double-blind IP based on Kaplan-Meier (KM) method and displayed graphically using KM curves. A log-rank test (two-sided) will be used to compare time to premature discontinuation from the double-blind IP between the two treatment groups (Analysis Population: FAS). Patients who did not discontinue from the double-blind IP will be censored at their last dose of IP.
- Time (in days) to withdrawal from the study will be analyzed using the same methods as described above for analysing time to premature discontinuation from the double-blind IP (Analysis Population: FAS). Patients who did not discontinue from the study will be censored at their last visit date on the study.
- A plot of time to discontinuation from the double-blind IP versus reasons for discontinuation from the double-blind IP will be presented to illustrate patterns of

missing data, with different symbols for treatment groups (Patients who discontinued from the double-blind IP).

The following by-patients listings will be provided:

- Patients who prematurely discontinued the double-blind IP during the first year of treatment will be listed, including, but not limited to, reason for premature discontinuation from the double-blind IP, exposure (days), day of last visit, and status of entering into post-treatment follow-up period (Analysis Population: FAS). Where  
*Exposure (days) = Date of the last dose of the double-blind IP – Date of the first dose of the double-blind IP + 1.*  
*Day of last visit = Last visit date – Date of the first dose of the double-blind IP + 1.*
- Patients who prematurely discontinued the double-blind IP after the first year of treatment will be listed separately (Analysis Population: FAS).
- Patients who withdraw from the study will be listed, including, but not limited to, reason for withdrawal from the study, exposure (days), and day of last visit (Analysis Population: FAS).

## **4.2.2 Demographics and other baseline characteristics**

### **4.2.2.1 Demography data**

**Demography data** such as age (at informed consent), race, ethnicity, sex, waist circumference, weight, height, and BMI will be summarized by treatment group (Analysis Population: FAS).

Demography data will also be summarized in a separate table before and after implementing the protocol amendment 2.

### **4.2.2.2 Other baseline characteristics**

Various baseline characteristics will also be summarized descriptively by treatment group (Analysis Population: FAS). These include medical and surgical histories, COPD history, smoking status and history, pre-bronchodilator and post-bronchodilator tests at Screening, FEV<sub>1</sub> at baseline, CAT score at baseline, prior medications, and COPD related prior medications. No statistical tests will be performed.

**Medical and surgical histories** will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 18.0 or newer, and will be summarized by MedDRA SOC, HLT and PT. It will also be summarized in a separate table before and after implementing the protocol amendment 2.

COPD **history** will be summarized as follows:

- Duration of COPD in years

- Patient known to have either chronic bronchitis or emphysema (Yes, No)
- COPD exacerbation in the previous 12 months (Yes, No)
- Number of COPD exacerbations in the previous 12 months
- COPD severity based on airflow obstruction
- Combined assessment of COPD per GOLD (see Section 3.1.3 for categories)

COPD history will also be summarized in a separate table before and after implementing the protocol amendment 2

**Smoking status and history** will be summarized as follows:

- Smoking status
- Smoking duration in years
- Number of cigarettes per day
- Total pack-years

Smoking status and history will also be summarized in a separate table before and after implementing the protocol amendment 2.

**Pre-bronchodilator, post-bronchodilator tests, and reversibility at Screening** will be summarized as follows:

- Pre-bronchodilator tests:
  - FEV<sub>1</sub>
  - FEV<sub>1</sub> % predicted
  - FVC
  - FVC % predicted
- Post-bronchodilator tests:
  - FEV<sub>1</sub>
  - FEV<sub>1</sub> % predicted
  - FVC
  - FVC % predicted
  - Ratio of FEV<sub>1</sub>/FVC
- Change from pre-bronchodilator test:

- % bronchodilator reversibility
- Change from pre-test FEV<sub>1</sub>
- Reversible (Yes, No)

Pre-bronchodilator, post-bronchodilator tests, and reversibility at Screening will also be summarized in a separate table before and after implementing the protocol amendment 2.

FEV<sub>1</sub> at baseline will be summarized descriptively. It will also be summarized in a separate table before and after implementing the protocol amendment 2.

CV risk factors will be summarized descriptively. It will also be summarized in a separate table before and after implementing the protocol amendment 2.

The **CAT score at baseline** will be summary descriptively by individual question and total CAT score. It will also be summarized in a separate table before and after implementing the protocol amendment 2.

#### **4.2.2.3 Prior and concomitant medications**

The World Health Organization Drug Dictionary (WHO DD), enhanced version of March 2011 or newer, will be used to classify prior and concomitant medications by therapeutic class.

Prior medication is defined as any medication taken 15 days before signing ICF, regardless of stop date. Concomitant medication is defined as any medication taken during the treatment period between the date of the first dose of the double-blind IP and the date of the last dose of the double-blind IP, inclusive.

Prior and concomitant medications will be tabulated by the third level of Anatomical Therapeutic Chemical (ATC) classification code, preferred name, and treatment group.

All concomitant medications will be classified for each one of the two following periods and will be summarized by the third level of ATC classification code, preferred name, and treatment group (Analysis Population: FAS):

- 1) Medications that the patient started to take before the randomization and continued after the first double-blind IP administration, and
- 2) Medications that the patient started to take during the treatment period (from the first double-blind IP administration to the last double-blind IP administration).

In addition, medications that were used between the last double-blind IP administration and to the study end will be summarized by the third level of ATC classification code, preferred



name, and treatment group (Analysis Population: patients who discontinued the double-blind IP and entered into post-treatment follow-up period).

Number and percentage of patients who used any medication for COPD will be presented by therapeutic categories as follows (but not limited to) by treatment groups:

- Long-Acting  $\beta$ 2-Agonists (LABA)
- LAMA
- Short-Acting  $\beta$ 2-Agonists (SABA)
- Short-Acting Muscarinic Antagonist (SAMA)
- ICS
- LABA and ICS combination (free and fixed)
- LABA and LAMA combination
- SABA and SAMA combination
- Leukotriene modifiers
- Oral phosphodiesterase type 4 (PDE4)
- Systemic corticosteroid
- Oxygen
- Methylxanthines
- Influenza vaccine
- Pneumococcal vaccine

Specifically, medication in the reporting by therapeutic categories is presented for each of the two following periods:

- 1) Prior medication for COPD the patient is taken at the time of signing ICF, regardless of the onset or stop date , and
- 2) Concomitant medication for COPD that the patient started to take before the randomization and continued after the first double-blind IP administration.

In addition, medications for COPD that were used between the last double-blind IP administration and to the study end will be summarized by therapeutic categories (Analysis Population: patients who discontinued the double-blind IP and entered into post-treatment follow-up period).

Multiple medications used by a patient will only be counted once.



### **4.2.3 Extent of Exposure and Treatment Compliance**

#### **4.2.3.1 Extent of Exposure**

Exposure to the double-blind IP will be summarized for treatment duration (in days), calculated as *date of the last dose of the double-blind IP taken - date of the first dose of the double-blind IP taken + 1* (Analysis Population: FAS).

Duration of exposure before and after implementing the CSP amendment 2 will also be summarized.

#### **4.2.3.2 Measurement of Treatment Compliance**

Dosing compliance for a given period is calculated as follows:

*100 × (total number of treatment applications [puffs] of the double-blind IP actually taken / number of treatment applications [puffs] of the double-blind IP expected to be taken) by a patient during a given period.*

The number of puffs actually taken is obtained from “Double Blind Study Drug Record” page of eCRFs.

The number of puffs expected to be taken in a given period is calculated as follows:

*2 × (End date - Start date + 1 for that period)*

i.e., a patient is expected to inhale 2 puffs per day. For those patients who complete the study, 1 puff is subtracted from the number of puffs expected to be taken since no evening dose is administered on the date of the last dose.

A patient is defined as compliant with treatment if treatment compliance rate is at least 75%.

Descriptive statistics for treatment compliance rate will be presented by treatment group for two periods (Analysis Population: FAS):

- Treatment period, and
- The first year of treatment.

Number and percentage of patients compliant with treatment will also be presented by treatment group for two periods above (Analysis Population: FAS).

#### **4.2.4 Efficacy analyses**

All efficacy analyses will be based on the FAS Population. All statistical tests will be two-sided hypothesis tests performed at the 0.05 significance level for main effects. All CIs will be two-sided 95% CIs. No multiplicity adjustment will be made to CIs as they will be interpreted descriptively and used as a measure of precision. All p-values will be unadjusted.

To control for multiplicity, the primary and secondary efficacy variables will be tested sequentially, i.e., the secondary efficacy endpoint will be tested only when both primary and secondary analyses on the primary efficacy endpoint achieved statistical significance, and the secondary analysis on the primary efficacy endpoint will be tested only when the primary analyses on the primary efficacy endpoint achieved statistical significance. Otherwise, nominal p-values will be provided and should be interpreted descriptively.

Analyses on COPD exacerbations will be based on definitions as described in Section 3.1.6.

#### 4.2.4.1 Primary efficacy outcome variable

The primary efficacy variable is rate of moderate or severe COPD exacerbation per patient per year during the first year of treatment. The primary analysis (on-treatment analysis) is to compare rate of moderate or severe COPD exacerbation per patient per year during the first year of treatment between aclidinium and placebo in patients in the FAS. Patients will be analyzed according to randomized treatment.

The null hypothesis is that the exacerbation rate on aclidinium is equal to the exacerbation rate on placebo. The alternative hypothesis is that the exacerbation rate on aclidinium is not equal to the exacerbation rate on placebo, i.e.:

$$H_0: \text{Rate ratio (aclidinium over Placebo)} = 1$$

versus

$$H_a: \text{Rate ratio (aclidinium over Placebo)} \neq 1$$

Exacerbation rate in aclidinium group will be compared to exacerbation rate in the placebo group using a negative binomial regression model. The response variable in the model will be the number of moderate or severe COPD exacerbations experienced by a patient during the first year of treatment. The model will include treatment group, baseline ICS use, baseline COPD severity, history of at least one exacerbation in the past year, and smoking status as factors. In order to adjust for the exposure for each patient, the natural logarithm of the exposure time (in years) during the first year of treatment will be used as an offset variable. When used as the offset variable, the exposure time will be adjusted by subtracting the time when a patient experienced COPD exacerbation(s) (i.e., not at risk during an exacerbation). The model is as follows:

*Number of moderate or severe exacerbations during the first year of treatment = treatment group + baseline ICS use + baseline COPD severity + history of at least one exacerbation in the past year + smoking status*

The estimated treatment effect (i.e., the rate ratio of aclidinium over placebo), corresponding 95% CI, and two-sided p-value for the rate ratio will be presented. In addition, the exacerbation rate and the corresponding 95% CI within each treatment group will be presented.

If the Negative Binomial regression model does not converge, the Poisson regression model with robust variance estimate using sandwich method will be applied. A scale parameter will be included to take overdispersion into account in fitting Poisson regression model. This would be a similar SAS GENMOD model to the one used for the Negative Binomial, but will specify Poisson as the distribution and include a scale parameter (DSCALE).

The primary analysis on the primary efficacy endpoint will be based on on-treatment analysis. For those patients who prematurely discontinue IP during the first year of treatment and have follow-up assessments, the primary analysis described above will be based on the data (events) collected before treatment discontinuation.

The secondary analysis on the primary efficacy endpoint will be based on on-study analysis using the same model as for the primary analyses of the primary efficacy endpoint. For those patients who prematurely discontinue IP during the first year of treatment and have follow-up assessments, the secondary analysis will include the events collected during the PTFU period up to one year.

The individual exacerbation criteria (use of systemic corticosteroids, use of antibiotics, and inpatient hospitalization due to COPD) will also be analysed using the same method as the primary analysis for on-treatment analysis during the first year of treatment, and will be summarized descriptively for on-study analysis over the whole study period.

The frequency of events and descriptive statistics of moderate or severe COPD exacerbations will also be provided by analysis method and period:

- On-treatment analysis during the first year of treatment
- On-study analysis during the first year of treatment
- On-treatment analysis over the whole study period
- On-study analysis over the whole study period.

### **Sensitivity analyses**

To assess the robustness to variations of the data assumptions underlying the primary analysis on the primary efficacy endpoint, several sensitivity analyses will be conducted as follows:

- Jump to reference (J2R) approach (see Appendix 1 for details)
- Copy reference (CR) approach (Keene et al, 2014; see Appendix 1 for details)
- Tipping point analysis (see Appendix 2 for details)

### **Subgroup analyses**

To evaluate the consistency in the primary efficacy endpoint over demographics and baseline characteristics, subgroup analyses will be performed. The subgroups are described below:

- Age group ( $\geq 40$  and  $< 60$  years,  $\geq 60$  and  $< 70$  years,  $\geq 70$  years old)
- Sex (Female, Male)
- Race (White, Other)
- Smoking status (Current smoker, Ex-smoker)
- Baseline ICS use (Yes, No)
- Baseline COPD severity (moderate, severe, and very severe)
- History of at least one exacerbation in the past year ( $0, \geq 1$ )

Exacerbation rate in aclidinium group will be compared to exacerbation rate in the placebo group for each subgroup (on-treatment analysis) using a negative binomial regression model. The response variable in the model will be the number of moderate or severe COPD exacerbations experienced by a patient during the first year of treatment. The model will include treatment group, each subgroup, and the interaction term. In order to adjust for the exposure for each patient, the natural logarithm of the exposure time (in years) during the first year of treatment (subtracting the time when a patient experienced COPD exacerbation) will be used as an offset variable.

The estimated treatment effect (i.e., the rate ratio of aclidinium over placebo) and corresponding 95% CI will be presented graphically.

In addition, the primary efficacy endpoint will be analyzed (on-treatment analysis) for the following 2 subgroups:

- LABA users (with and without ICS): include patients who took LABA and/or LABA/ICS during the treatment period.
- LABA/ICS users: include patients who took LABA/ICS during the treatment period.

That is, data for each subgroup will be extracted first, then do analysis on each set of data using the same approach as the corresponding primary analysis.

#### **4.2.4.2 Secondary efficacy variable**

The secondary efficacy endpoint of rate of hospitalizations due to COPD exacerbations per patient per year during the first year of treatment will be analyzed (on-treatment analysis) using the same model as for the analyses of the primary efficacy endpoint, including on-study analysis as sensitivity analysis.

#### **4.2.4.3 Additional efficacy variables**

Unless otherwise specified, the following variables will use data collected during the whole study period using on-treatment analysis.

### **Analyses for COPD Exacerbations**

The rate of COPD exacerbations per patient per year (any, and moderate or severe) and rate of hospitalizations due to COPD exacerbations per patient per year will be analyzed using a Negative Binomial regression model (or Poisson regression model taking overdispersion into account for analyses that Negative Binomial regression does not converge) similar to the primary analysis of the primary efficacy variable. The exposure time will be re-calculated based on the last data collection during the whole study period.

The number of patients with at least one COPD exacerbation (any, mild, moderate, severe, and moderate or severe) will be analyzed based on a logistic regression model with treatment group, baseline ICS use, baseline COPD severity, history of at least one exacerbation in the past year, and smoking status as factors. The estimated treatment effect (i.e., the odds ratio of aclidinium over placebo), corresponding 95% CI, and two-sided p-value for the odds ratio will be presented. The model is as follows:

*Response (Yes=1/No=0) = treatment group + baseline ICS use + baseline COPD severity + history of at least one exacerbation in the past year + smoking status*

Time (in days) to first COPD exacerbation (any, and moderate or severe), time (in days) to second COPD exacerbation (any, and moderate or severe), time (in days) to third COPD exacerbation (any, and moderate or severe), time (in days) to first hospitalization due to COPD exacerbation, and time (in days) to withdrawal of the double-blind IP due to COPD exacerbation will be analyzed by means of Kaplan-Meier estimators and Cox Proportional Hazards model. The estimates of the hazard ratio comparing aclidinium with placebo will be derived using the Cox proportional hazard model for the time in terms of the number of days served as a response variable and treatment group, baseline ICS use, baseline COPD severity, history of at least one exacerbation in the past year, and smoking status as factors. The hazard ratio (aclidinium over placebo), corresponding 95% CI, and two-sided p-value for the hazard ratio will be presented. The model is as follows:

*Survival time = treatment group + baseline ICS use + baseline COPD severity + history of at least one exacerbation in the past year + smoking status*

In addition, the Kaplan-Meier survival curves will be displayed for each treatment group along with p-value for differences (aclidinium over placebo) based on the Log-Rank test stratified by baseline COPD severity and smoking status.

The durations of COPD exacerbation (any, and moderate or severe; in days) will be summarized descriptively for only the patients who had exacerbations during the treatment period.

Number of days hospitalized due to COPD exacerbations will be summarized for only the patients who had exacerbations during the treatment period. The descriptive statistics of number of days hospitalization due to COPD exacerbations will be summarized by unit type (any, hospitalization unit, intensive care unit, emergency room).

#### **Analyses for spirometry variable**

Change from baseline in morning pre-dose (trough) FEV<sub>1</sub> by visit (on-treatment analysis) will be compared between aclidinium group and placebo using a MMRM model on patients with a baseline pre-dose/pre-bronchodilator FEV<sub>1</sub> and at least one post-randomization pre-dose FEV<sub>1</sub> in the FAS Population. The dependent variable will be the change from baseline in pre-dose FEV<sub>1</sub> at postbaseline protocol-specified visits (up to Visit 12 or EOT visit). Treatment group will be fitted as the explanatory variable, and pre and post-bronchodilator (albuterol/salbutamol) FEV<sub>1</sub> at screening visit (Visit 1A), and baseline FEV<sub>1</sub> as covariates, and smoking status, baseline ICS use, visit, and treatment group-by-visit interaction as fixed effect factors. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. Kenward Roger approximation will be used to estimate denominator degrees of freedom. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is as follows:

*Change in FEV<sub>1</sub> = treatment group + pre-bronchodilator FEV<sub>1</sub> at Screening + post-bronchodilator FEV<sub>1</sub> at Screening + baseline FEV<sub>1</sub> + smoking status + Baseline ICS use + visit + treatment\*visit*

Each treatment effect and treatment difference between aclidinium and placebo at each visit will be estimated by their least squares (LS) means and the differences in LS means on the treatment-by-visit interaction, along with their standard errors (SEs), and 95% CIs and the p-value corresponding to the between-treatment-group difference. In addition, the overall treatment effect and treatment difference over the treatment period will be estimated by the LS means and the difference in LS means on the treatment factor, along with the SEs, and 95% CIs and the p-value corresponding to the between treatment group difference.

A longitudinal plot will be used to display the change from baseline in FEV<sub>1</sub> at each visit by treatment group.

In addition, change from baseline in morning pre-dose (trough) FEV<sub>1</sub> by visit (on-treatment analysis) will be analyzed for the following 2 subgroups:

- LABA users (with and without ICS)
- LABA/ICS users

That is, data for each subgroup will be extracted first, then do analysis on each set of data using the same approach as the corresponding primary analysis.

#### **4.2.5 Safety analyses**

All safety analyses will be based on the FAS Population. No multiplicity adjustment will be made to CIs. All p-values will be unadjusted. The analyses of the secondary safety endpoint of the time to first MACE or other serious CV events of interest will not be adjusted for multiple comparisons.



#### 4.2.5.1 Primary safety variable

The null hypothesis is that treatment with acclidinium is inferior to treatment with placebo with regard to the risk of developing a MACE for a non-inferior (NI) margin of 1.8, i.e.:

$$H_0: \text{Hazard ratio (aclidinium over Placebo)} \geq 1.8$$

versus

$$H_a: \text{Hazard ratio (aclidinium over Placebo)} < 1.8$$

The primary safety variable of time to first MACE will be based on on-study analysis. Only events adjudicated by the Clinical Events Committee (CEC) will be included.

The primary safety variable of time to first MACE will be analyzed based on Cox-proportional hazards regression model including baseline CV severity, smoking status, and treatment group as covariates. The model is as follows:

$$\text{Time to first MACE} = \text{treatment group} + \text{baseline CV severity} + \text{smoking status}$$

This model will provide point estimate for the hazards ratio (aclidinium over placebo), as well as corresponding 95% CI and two-sided p-value (p-value will be presented for composite MACE endpoint only). The upper bound of the 95% CI (based on Cox regression) for the hazard ratio (aclidinium over placebo) of time to first MACE will be used to rule out the null hypothesis of hazard ratio of 1.8 for the primary test on MACE. If the upper bound of the 95% CI is less than the 1.8 margin of the hazard ratio, then the hazard ratio of 1.8 or higher will be ruled out (justification for the hazard ratio of 1.8 is provided in Appendix IV of the CSP).

In addition, the KM survival curves will be displayed for each treatment group.

To examine the contribution of the components of the composite endpoint to the overall treatment effect, time to first non-fatal MI, non-fatal stroke and CV death will be analyzed individually and presented in the same way as for the primary endpoint.

The results from the primary safety analysis will also be evaluated considering a superiority hypothesis.

#### Model assumption checking

The assumption of proportional hazards will be assessed visually using log-cumulative hazard plots. The effect of any departures from proportional hazards will be discussed as part of the presentation of results of the analyses.

#### Sensitivity analysis

To account for the relation of the occurrence of an event and treatment exposure, an on-treatment analysis will be conducted and this will include only events that occurred while the patient was exposed to study treatment, i.e., events that occurred after the patient's last

treatment dose will be censored. Two ascertainment windows, 0 and 15 days, will be evaluated in the on-treatment analyses. The on-treatment and on-treatment +15 days analyses will censor events that occur after and more than 15 days after, respectively, after the last treatment dose (see Section 9.7.6.1 of the CSP for consideration on totality of evidence from on-study and on-treatment analyses in evaluation of MACE).

To assess possible effects of informative censoring, sensitivity analysis (on-study analysis) will be done as follows: based on the missing follow-up time in drop-outs, i.e. the time from censoring to study closure, the expected number of events that might have been observed if the drop-outs had completed the study can be calculated using an event rate similar to that observed in the study. The test (aclidinium versus placebo) will be recalculated with these residual events allocated in different proportions to the treatment groups to assess the robustness of the results with regard to the censoring of drop-outs.

Sensitivity analysis of the primary composite endpoint will also include analysis with CV death replaced with all-cause mortality.

**Subgroup analysis.** To evaluate the consistency in the primary safety endpoint over selected baseline characteristics, subgroup analysis will be performed. The subgroup is described below:

- History of at least one exacerbation in the past year ( $0, \geq 1$ )

The subgroup analysis on time to first adjudicated MACE will be analyzed using the same method as the primary analysis on the primary safety endpoint using a 95% CI and without statistical testing for NI (NI margin will not be used).

#### 4.2.5.2 Secondary safety variable

The secondary safety endpoint of time to first MACE or other serious CV events of interest will be analyzed using the same method as the primary safety endpoint using a 95% CI and without statistical testing for NI (NI margin will not be used).

Supportive listings will be provided for all adjudicated events with adjudication conclusions.

#### 4.2.5.3 Adverse Events

High-level summaries of AEs and TEAEs will be presented separately. The tables will include the number and percentage of patients for the following categories:

- Any AE/TEAE
- Any AE/TEAE with outcome = death
- Any SAE/TEAE
- Any AE/TEAE leading to discontinuation of IP



Summaries on event counts will also be presented by categories above.

The number and percentage of patients reporting any TEAE will be summarized

- by system organ class (SOC), high level term (HLT), and PT;
- by SOC, HLT, PT, and severity;
- by SOC, HLT, PT, and relationship to the IP

If more than one AE is coded to the same PT for the same patient, the patient will be counted only once for that PT using the most severe and most related occurrence in the summarization by severity and by causal relationship to the IP.

The incidence of common ( $\geq x\%$  of patients in any treatment group, 'x' to be determined prior to the DB lock) TEAEs will be summarized by PT (sorted by decreasing frequency of PT [total]).

All AEs will be provided in a by-patient listing which will include both the term reported on the eCRF (verbatim term) and the PT and SOC to which it is coded. Relative start and stop days will be included along with the actual onset and resolution dates.

#### **Deaths, Serious Adverse Events, and Other Significant Adverse Events**

An SAE that occurs on or after the date of the first dose of double-blind IP and within 15 days of the date of the last dose of double-blind IP will be considered an on-treatment SAE/TEAE.

An SAE that occurs after 15 days of the date of the last dose of double-blind IP will be considered an off-treatment SAE.

The following summaries will be produced:

- Number and percentage of patients with any SAEs by SOC, HLT, and PT
- Number and percentage of patients with adverse events with outcome of death by SOC and PT
- Number and percentage of patients with off-treatment SAEs by SOC, HLT, and PT
- Number and percentage of patients with AEs leading to premature discontinuation of the IP by SOC and PT

In addition, separate listings will be provided for the following:

- Deaths
- SAEs
- Permanent discontinuations of study treatment due to AEs

Adjudicated MACEs and other serious CV events of interest will be summarized as follows:

- Number, percentage, and incidence (per 1000 patient-years of exposure to IP) of patients with adjudicated MACE by MACE category, adjudicated subcategory, and PT (on-study analysis and on-treatment analysis).
- Number, percentage, and incidence (per 1000 patient-years of exposure to IP) of patients with adjudicated cardiac disorders (i.e. cardiac arrhythmias SMQ and cardiac failure SMQ) and cerebrovascular disorders by specific SMQ category and PT (on-study analysis and on-treatment analysis).
- Number, percentage, and incidence (per 1000 patient-years of exposure to IP) of patients with adjudicated non-fatal other CV events by PT (on-study analysis).

Supportive listings to summaries described above will be provided.

#### **Adverse events of special interest (AESI)**

The summaries on the following AESI will be produced by SOC and PT.

Events of interest	Standard MedDRA Query Category plus additional High Level Terms or Preferred Term, if applicable
Anticholinergic events	Anticholinergic syndrome (narrow and broad search SMQ) Glaucoma (narrow search SMQ) Additional PTs: sinus tachycardia, supraventricular tachycardia, ventricular tachycardia, heart rate increased, palpitations, pupillary reflex impaired, pupils unequal, visual disturbance, constipation, gastrointestinal obstruction, ileus paralytic, urinary tract infection, cystitis, urinary incontinence, incontinence, dysuria, urge incontinence, urine flow decreased, bladder irritation, oropharyngeal pain, dysphonia, laryngitis, pharyngitis, and throat irritation
Pneumonia	All PTs that contain the term pneumonia

#### **4.2.5.4 Clinical laboratory variables**

There will be no report of the laboratory data.

Patients who meet the potential Hy’s Law criteria from the first dose of double-blind IP to within 15 days after the last dose of double-blind IP will be summarized. A supportive listing will be provided. Related data collected in the eCRF (e.g., abnormal liver biochemistry risk factors, liver disease signs and symptoms, liver diagnostic tests) will be listed.

#### **4.2.5.5 Vital signs**

Descriptive statistics for vital signs (pulse rate, systolic and diastolic BP, and weight) and changes from baseline values at each visit and at the end of study will be presented.

The number and percentage of patients with PCS postbaseline values will be tabulated. The percentages will be calculated relative to the number of patients with available baseline values and at least one postbaseline assessment in the treatment period. The numerator will be the total number of patients with available baseline values and at least one PCS postbaseline value in the treatment period. A supportive tabular display of patients with PCS postbaseline values

will be provided, including the PID number and baseline and all postbaseline (including non-PCS) values. A tabular display of all AEs occurring in patients who have PCS postbaseline vital sign values will also be provided.

#### **4.2.5.6 Electrocardiogram**

Descriptive statistics for ECG parameters (i.e., ventricular heart rate, RR interval, PR interval, QRS duration, QT interval, QTcB, and QTcF) and changes from baseline values at each assessment time point to the end of study will be presented.

The number and percentage of patients with PCS postbaseline ECG values will be tabulated. The percentages will be calculated relative to the number of patients with available baseline values and at least one postbaseline assessment in the treatment period. The numerator will be the total number of patients with available baseline values and at least one PCS postbaseline value in the treatment period. A supportive tabular display of patients with PCS postbaseline values will be provided, including the PID number, baseline, all postbaseline (including non-PCS) values, and change from baseline. In addition, a tabular display showing all AEs that occurred in patients who had postbaseline PCS ECG values will be provided.

A shift table from baseline to the end of study in the Investigator's overall interpretation of the ECG will be presented for the following categories: normal; abnormal, not clinically significant (NCS); and abnormal, clinically significant (CS).

Shift tables for ECG abnormal findings will be presented overall (in subjects with normal baselines and all subjects in FAS) and by visit.

#### **4.2.5.7 Physical examination**

A listing of physical examination findings at Screening (Visit 1A) will be provided as a part of the medical and surgical history listing. Any new physical examination finding or change (worsening) since the previous physical examination during the treatment period will be provided as part of the AE listing.

#### **4.2.5.8 All-cause mortality**

All-cause mortality based on patient's vital status data will be analyzed using the same method as the primary safety endpoint using a 95% CI and without statistical testing for NI (NI margin will not be used).

### **4.2.6 Health economics and outcomes research analyses**

#### **4.2.6.1 COPD assessment tests (CAT) by visit**

Descriptive statistics will be provided at baseline (actual scores) and each postbaseline visit (actual and change from baseline scores).

Change from baseline in CAT total score by visit will be compared between aclidinium group and placebo using a MMRM model on patients with a baseline CAT total score and at least

one post-randomization CAT total score in the FAS Population. The dependent variable will be the change from baseline in CAT total score at postbaseline protocol-specified visits (up to Visit 12 or EOT visit). Treatment group will be fitted as the explanatory variable, and baseline CAT total score as covariate, and baseline ICS use, smoking status, visit, and treatment group-by-visit interaction as fixed effect factors. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. Kenward Roger approximation will be used to estimate denominator degrees of freedom. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is as follows:

*Change in CAT total score = treatment group + baseline CAT total score + baseline ICS use + smoking status + visit + treatment\*visit*

Each treatment effect and treatment difference between aclidinium and placebo at each visit will be estimated by their LS means and the differences in LS means on the treatment-by-visit interaction, along with their SEs, and 95% CIs and the p-value corresponding to the between-treatment-group difference. In addition, the overall treatment effect and treatment difference over the treatment period will be estimated by the LS means and the difference in LS means on the treatment factor, along with the SEs, and 95% CIs and the p-value corresponding to the between treatment group difference.

A longitudinal plot will be used to display the change from baseline in CAT total score at each visit by treatment group.

Change from baseline in CAT total score by visit will be analyzed for the following 2 subgroups:

- LABA users (with and without ICS)
- LABA/ICS users

That is, data for each subgroup will be extracted first, then do analysis on each set of data using the same approach as the primary analysis.

In addition, the number (%) of patients experiencing response (improvement of 2 or more units from baseline in CAT total score) will be presented by visit. The number of patients who experience response will be analyzed based on a logistic random effect model with baseline CAT total score as covariate, and treatment group, baseline ICS use, smoking status, visit and treatment group-by-visit interaction as fixed effects and a random intercept to account for the variability between subjects. The estimated treatment effect (i.e., the odds ratio of aclidinium over placebo), corresponding 95% CI, and two-sided p-value for the odds ratio will be presented. The model is as follows:

*Response (Yes=1/No=0) = treatment group + baseline CAT total score + baseline ICS use + smoking status + visit + treatment\*visit*

## **5. CHANGES OF ANALYSIS FROM PROTOCOL**

The primary efficacy endpoint, rate of moderate or severe COPD exacerbations per patient per year during the first year of treatment, will be analyzed using on-treatment analysis as primary analysis and on-study analysis as secondary analysis (per the CSP, on-treatment analysis as primary analysis and on-study analysis as sensitivity analysis).

The covariates or factors included in the models are harmonized.

The incidence of common (e.g.  $\geq 2\%$  of patients in any treatment group) TEAEs will be summarized by preferred term (per the CSP, by SOC and PT).

Number (%) of patients with any SAEs is summarized by SOC, HLT, and PT (per the CSP, by PT).

Number (%) of patients with adverse events with outcome of death is summarized by SOC and PT (per the CSP, by PT).

Number (%) of patients with AEs leading to premature discontinuation of the IP is summarized by SOC and PT (per the CSP, by PT).

The denominator and numerator for PCS vital sign and ECG values are re-defined.

## **6. REFERENCES**

Global initiative for chronic obstructive lung disease (GOLD). Pocket guide to COPD diagnosis, management, and prevention. 2017

Keene OH, Rogers JH, Hartley BF, Kenward MG. Missing data sensitivity analysis for recurrent event data using controlled imputation. *Pharmaceutical Statistics* 2014 13(4): 258-264.

Keene ON, Jones MR, Lane PW, Anderson J. Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the Tristan Study. *Pharmaceutical Statistics*. 2007 6(2): 89 – 97.

## **7. APPENDIX**

The changes in the appendices only will not need a SAP amendment, instead the revised appendix will be considered as an addendum of the SAP.

## Appendix 1: Imputation of unobserved exacerbations

Assume a patient has  $y_1$  exacerbations during period 1 and then withdraws. We want to estimate  $y_2$ , the number of unobserved exacerbations, given what we have actually seen. Numbers of events before and after withdrawal are seen as two periods with a joint negative multinomial distribution, with  $Y_1$  observed and  $Y_2$  unobserved. For a given patient, distribution  $Y_2|Y_1$  is a function of:

- Observed  $y_1$
- Estimated dispersion (assumed same in both periods)
- Estimated mean (model predicted) rate period 1
- Imputed mean rate period 2 – options for this depends on the method: missing at random (MAR), CR, J2R chosen)

In the CR approach, a patient's expected event rate both before and after withdrawal is assumed to be the same as the reference group. This mimics the case where those withdrawing are in effect nonresponders. When a patient on test treatment has more events before withdrawal than expected for them if they had been in the reference arm, then this 'positive residual' will feed through into a higher than expected event rate in the postwithdrawal period. This is because their earlier observed higher than normal event rate suggests a personal high propensity to events. Postwithdrawal data in the reference arm are imputed under randomized arm MAR.

In the J2R approach, dropouts on test treatment are assumed to have been on test treatment rather than the reference prior to dropout. In the FDA's opinion, this may be more reasonable than the CR approach, given that the CR approach may carry forward a treatment effect (i.e., if a patient had a decreased rate while on treatment). The CR approach is likely inappropriate since effects of bronchodilators are expected to diminish within a few weeks of discontinuation and because such patients will not benefit from the drug in the long-term.

Whichever imputation model is chosen, the subsequent procedure follows that of standard MI. For each imputation, a single set of data is created for each subject's missing data conditional upon their observed data. After summing observed and imputed values for each subject, each imputed data set is analyzed using the model used for the primary analysis. At least 1000 imputations are recommended and more should be considered, to provide sufficiently stable and reproducible results.

Multiple imputation:

- Take a random sample from  $Y_2|Y_1$ , add this to the  $y_1$  we observed for the patient
- Analyse the data using PROC GENMOD as usual
- Repeat analysis multiple times
- Combine estimates using Rubin's rules

### Implementation in SAS:

This approach to sensitivity analysis as described above can be implemented in the SAS system using the GENMOD procedure to derive and sample from the posterior distribution for  $k$ ,  $\beta$  and the other covariate regression parameters. A sample can be drawn from the conditional distribution for the unobserved period using a DATA step. Results can be summarized using the MIANALYZE procedure, which applies Rubin's formula.

The following SAS code extracts samples from the posterior distribution of model parameters including the dispersion parameter using a Bayesian negative binomial log-link model with an offset variable which holds the log of the exposure time for each patient:



Specifically for the sensitivity analysis using copy reference approach on the primary analysis of the primary efficacy endpoint in this study, using only the data from the placebo, run genmod using the primary analysis model (including all the covariates and offset) without treatment, and using Bayes statement with "coeffprior = normal", output a posterior sample of the model parameters of size N. The rationale of using only the placebo's group data is that when we explore the effect of the missing values we assume the missing values are treatment related. Therefore, when estimate the model parameters we do not want the missing values from the active group to contaminate the estimates.

For each draw (after thinning) the expected number of events is calculated for the period before and after withdrawal for each subject. This depends upon the length of time before and after withdrawal. Denote these as  $y1\_hat$  and  $y2\_hat$ .

The design matrices for an individual patient are modified to assign the withdrawing patient to the desired treatment arm for the observed or unobserved period (depending on the method: MAR, CR, J2R chosen).

Then according to the derivation for the conditional distribution  $Y2|Y1$ , we can sample using the following statement:



where  $invK\_hat$  is the inverse of the sampled dispersion parameter, and  $y1$  is the actual count before withdrawal.

The entire number of exacerbations (observed and unobserved) is then:

CCI

CCI

These imputed numbers are then analyzed in a new series of further GENMOD runs (one for each draw), using the standard model (same covariates etc.) and a negative binomial model. However an offset will usually now not be required as the effective period at risk is the same for every patient. Derived parameters from the model such as least squares means for treatment and their differences are then combined across imputation data sets using Rubin's formula, as implemented in the MIANALYZE procedure. These and their confidence interval limits are then exponentiated to derive relative rates.



## **Appendix 2: Tipping point analysis**

Missing counts for a subject will be imputed according to the mean of the arm that the subject belongs to, multiplied by a factor delta. The deltas for the two arms can be varied until the result crosses some relevant threshold (e.g., different statistical significance levels). That is, to do multiple imputation and apply the imputation to the unobserved period only. Since this will be computationally demanding a suggestion is to only multiply deltas to Acridinium 400 µg group (to make it worse) and keep the placebo “delta” fixed to 1.