STATISTICAL ANALYSIS PLAN

PROTOCOL: AIFA-ICSLIFE-001

Comparison of 1-year treatment with inhaled long acting bronchodilators (LABD) plus inhaled glucocorticosteroids (ICS) versus LABD without ICS on re-hospitalizations and/or death in elderly patients with chronic obstructive pulmonary disease (COPD) recently hospitalized because of an acute exacerbation of COPD (ICS-Life study).

STATISTICAL ANALYSIS PLAN

APPROVAL PAGE

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The Statistical Analysis Plan has been completed and reviewed and the contents are approved for use for the analysis.

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Contents

Abbreviations

ADR	Adverse Drug Reaction
ADaM	Analysis Data Model
AECOPD	Acute Exacerbation Of Chronic Obstructive Pulmonary Disease
AE	Adverse Event
AF	Atrial Fibrillation
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CS	Clinically Significant
CV	Cardiovascular
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EoT	End of Treatment
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
HF	Heart Failure
ICH	International Conference on Harmonisation
ICS	Inhaled Glucocorticosteroids
ITT	Intention-to-Treat
IWRS	Interactive Web Response System
IHD	Ischaemic Heart Disease
LABA	Long-Acting Beta2-Agonist
MedDRA	Medical Dictionary for Regulatory Activities
mMRC	modified Medical Research Council
PP	Per Protocol
PT	Preferred Term
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation

SDTM	Study Data Tabulation Model
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
WHO-DD	WHO Drug Dictionary

Revision History

Document Version	Changes Made	Document Date
0.1	Draft specification based on the following documents: • Study protocol (Version 1.0 of 12.03.2018) • CRF (Version 1 of 29.06.2018)	07 Jun 2022
1.0	Final version	22 Nov 2022

1. Introduction

This document outlines the statistical methods to be implemented in the analysis of the data of AIFA-ICSLIFE-001 Clinical Trial. The purpose of this plan is to provide general guidelines from which the analysis will proceed, containing a more technical and detailed elaboration of the principal features of the analysis described in the protocol. Any changes to the protocol or Case Report Form (CRF) may necessitate updates to the Statistical Analysis Plan (SAP). In case of deviations from this updated SAP, explanations will be provided in the clinical study report.
All final study data will be considered for the analysis regulated by this SAP.

2. Study Objectives

2.1 Primary objective

The primary objective is to demonstrate that in elderly Chronic Obstructive Pulmonary Disease (COPD) patients with one or more cardiac comorbidities (heart failure, and/or ischemic heart disease, and/or atrial fibrillation) who have been recently hospitalized due to an Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD), 1-years treatment with Long-Acting Beta2-Agonist (LABD)+ Inhaled Glucocorticosteroids (ICS) will prolong the time to first re-hospitalization and/or the death for any cause when compared to 1-years treatment with LABD alone.

2.2 Secondary objectives

Secondary objectives are the following:

- to compare the number of moderate/severe exacerbations of COPD in the two patient groups;
- to compare the number of re-hospitalizations and deaths (all cause) in the two patient groups;
- to compare Quality of Life (QoL) scores measured using the COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnoea scale between the two patient groups;
- to verify if one year of treatment with combination therapy including ICS increases the risk of pneumonia;
- to compare the number of acute cardiac events in this frail, elderly COPD population;
- to compare the incidence of deaths due to cardiovascular events;
- to compare changes in lung function.

3. Study Design

3.1 General design and plan

This will be a phase IV, open label, multicenter, randomized pragmatic study in frail elderly patients with COPD. Participants will be treated with either inhaled LABD alone or LABD combined with inhaled glucocorticosteroids. The choice of the specific LABD and ICS to be used will be left to the discretion of the clinical investigator. Thus, the proposed study will be a real-life but randomized study with a 12-month treatment period followed by 3 months follow-up. The center will be considered as a unique stratifying factor, so the study will have a balanced-block center-stratified design.

3.2 Visit Schedule and Visit Windows

Assessments and study visits will be performed as listed in the table below:

Procedure	**Screening (up to 10 days before Day 1)**	**Intervention Period [months]**					**Follow-up (3 months after last study treatment)**
		day 1 (randomization)	**3 months**	**6 months**	**9 months**	**12 months (or early withdrawal)**	
Visit number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Informed consent	X						
Inclusion and exclusion criteria	X	X					
Spirometry*		X				X	
COPD assessment test (CAT)	X	X	X	X	X	X	X
mMRC dyspnea scale	X	X	X	X	X	X	X
Demography	X						
Physical examination including height and weight	X	X	X	X	X	X	X
Medical history (including substance usage).	X	X	X	X	X	X	X
History of COPD and cardiovascular disease (particularly HF, IHD or AF)	X	X	X	X	X	X	X
Past and current medical conditions	X						
Laboratory assessments	X						
12-lead ECG	X					X	
Chest x-ray	X (Optional)						
Vital signs (blood pressure and heart rate)	X	X	X	X	X	X	
Randomization		X					

Procedure	Screening (up to 10 days before Day 1)	Intervention Period [months]					Follow-up (3 months after last study treatment)
		day 1 (randomization)	3 months	6 months	9 months	12 months (or early withdrawal)	
Visit number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Study treatment checked and prescribed		X	X	X	X		
Assessment of symptoms and hospitalizations			X	X	X	X	X
Vaccination check		X	X	X	X		
Adverse event review		X	X	X	X	X	
Serious adverse event review		X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X

CV = cardiovascular, HF = heart failure, IHD = ischemic heart disease, AF = atrial fibrillation, CAT = COPD Assessment Test, mMRC = modified Medical Research Council.
* Participants with a diagnosis of COPD confirmed by spirometry within the last 3 years, will be immediately eligible for the study after hospital discharge. Participants without a previous spirometric confirmation must have a spirometry test, which must be performed at least 8 weeks after discharge. If confirmed then they can be recruited to the study.
**Participants will be contacted by telephone each month, by the clinical investigator or by a research staff member, to check compliance with the study procedures, vaccination and treatment. Information about any hospitalizations or any unexpected medical events, particularly moderate exacerbations treated with antibiotics and/or steroids will be collected

Paragraph no. 8 “Study Assessments and Procedures” of Study Protocol contains additional details about scheduled visits and time windows.

3.3 Sample size justification

The sample size calculation is based on the superiority criteria of the LABD+ICS group versus LABD alone group in terms of re-hospitalization and/or death. With 464 patients in each group, the percentage of patients experiencing the composite event (re-hospitalization and/or death) is expected to be 9% in the LABD+ICS group and 15% in the LABD alone group. A log-rank test (two-sided 5% significance level) will have 80% power to detect a difference between treatment groups in terms of time to first re-hospitalization and/or death (primary efficacy endpoint). Adjusting for an expected 10% dropout rate, a total of 516 patients per group will need to be randomized.

3.4 Randomization and blinding

All participants will be centrally assigned to randomized study intervention using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and instructions for the IWRS will be provided to each site.
The center will be considered as a unique stratifying factor, so the randomization will follow a balanced-block center-stratified design.
Study intervention will be dispensed at the study visits summarized in the Schedule of Activities (SoA).

This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IWRS. The site will contact the IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form.
Potential bias will be reduced by using central randomization.
Since this is an open label study, no unblinding procedures are foreseen.

3.5 Efficacy endpoints

3.5.1 Primary endpoint

The primary efficacy endpoint is the time to first re-hospitalization and/or death (all cause).

3.5.2 Secondary efficacy endpoints

The secondary efficacy endpoints are the following:

- number of moderate/severe COPD exacerbations;
- number of re-hospitalizations and deaths (all cause);
- QoL variation measured as change in CAT total score from baseline to end of treatment period;
- change in mMRC dyspnea score from baseline to end of treatment period;
- number of pneumonia events;
- number of acute cardiac events;
- number of cardiovascular deaths;
- change in FEV1 from baseline to the end of treatment period;
- change in FVC from baseline to the end of treatment period.

3.6 Safety endpoints

The safety endpoints are the following:

- Adverse Events (AEs);
- Vital Signs (blood pressure, heart rate);
- Electrocardiogram (ECG);
- Laboratory parameters;

3.7 Other endpoints

Not foreseen.

4. Statistical Analysis

4.1 General

Descriptive statistics will be provided for all variables in the summary tables for the treatment according to the type of variable summarized.

Quantitative variables will be summarised by using n, arithmetic mean, SD, median, minimum and maximum.
Categorical variables will be summarised by using frequency distributions and percentages.

Hypothesis testing will be carried out at the alpha = 0.05 level (two-sided) when comparing treatments. For all inferential analyses, p-value will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value will be less than or equal to 0.05.

All data collected in the CRF will be presented in the listings.

4.2 Analysis sets

4.2.1 Randomised population

All randomised patients will be included in the Randomised population.
The Randomised population will be considered for descriptive purposes.

4.2.2 Safety population

All randomized patients who receive at least one administration of the study treatment in a given treatment period will be included in the Safety population.
Analysis of safety variables will be performed in the Safety population.

4.2.3 Intention-to-Treat population (ITT)

All randomized patients from the safety population with at least one available post-baseline efficacy evaluation during the treatment period.
Since this is a superiority study, the ITT will be considered the primary analysis set. The primary and secondary efficacy variables will be analysed on the ITT.
The primary efficacy variable will also be analysed on the ITT for sensitivity purposes.

4.2.4 Per Protocol population (PP)

All randomized patients from the ITT population without any major protocol deviations.
The exact definition of major protocol deviations will be discussed with the clinical team case by case during the review of the data and will be described in the Data Review Report.
The primary efficacy variable will be analysed on the PP.

In case an error occurs in treatment allocation, the following rule will be followed: if a patient was randomised but received the incorrect treatment, he/she will be reported under his/her randomised treatment group for all analyses performed on the ITT population, but he/she will be reported under the treatment actually received for all analyses performed on the safety population. The patient will be excluded from the PP population.

4.3 Sub-group analyses

The following subgroup will be defined:

- Patients treated with triple therapy: subjects who were treated with "LAMA+LABA" or "LAMA+LABA+ICS". Considering that LABD category of treatments can be subdivided in "LAMA", "LABA" or "LABA+LAMA", this subgroup will be selected. Other subgroup analyses may be performed during post-hoc analyses for efficacy and safety endpoints based on baseline disease characteristics which could provide evidence to assess effectiveness, adherence levels and the true value of adding ICS treatment to LABD.

4.4 Covariates

All the analysis of covariance (ANCOVA) models will include the baseline value of the variable and age as quantitative independent variables, treatment group and centre as qualitative independent variables.
The Poisson regression model and the Cox proportional hazards model will include center and treatment group as qualitative independent variables and age as quantitative independent variable.

The baseline to be considered in the statistical analysis for each variable is reported in the table below:

Endpoint	**Baseline**
Spirometry	Visit 2 (randomization)
COPD Assesment test (CAT)	Visit 2 (randomization)
mMRC dyspnea scale	Visit 2 (randomization)
Height and weight	Visit 1 (screening)
Physical examination	Visit 1 (screening)
Laboratory assessments	Visit 1 (screening)
12-lead ECG	Visit 1 (screening)
Vital signs (blood pressure and heart rate)	Visit 2 (randomization)

4.5 Pooling of sites

Not foreseen.

4.6 Interim analyses

No formal interim analysis is planned for the study.

4.7 Handling of missing and incomplete data

Missing values will be included in the denominator count when computing percentages. The number of patients with missing data will be presented under the "Missing" category, if present.
Only the non-missing values will be evaluated for computing summary statistics.
Missing or incomplete data will be treated as described in chapters 5, 6, 7 and 8.

Other critical missing data will be discussed prior to database lock, if any. Decisions will be taken during the data review and will be fully documented in the Data Review Report.

4.8 Changes in the planned analysis

The following changes were implemented in this SAP with respect to the analyses planned in the protocol:

- P-values of paired t-tests will not be provided for the mean change from baseline because the information is considered redundant with the one provided by the 95% confidence intervals.
- Vital signs and physical examination data will be listed only.

4.9 Data Review Meeting

A Data Review Meeting will be held after Database lock and before the Database freeze.

4.10 Software

All statistical analyses and data processing will be performed using Statistical Analysis Systems (SAS®) Software (release 9.4) on a Windows 7 operating system.

5. Evaluation of Demographic and Baseline Characteristics

5.1 Subject enrolment and disposition

Statistical analysis
Disposition of patients will be presented by treatment and overall for all subjects.
The number of patients included in each of the Randomised, Safety, ITT will be summarised for each treatment.

5.2 Protocol violations

Not foreseen.

5.3 Study discontinuations

Definitions and data conventions

Date of completion/discontinuation
Date of study completion will be the date of study end recorded in the study conclusion/withdrawal form.
If the date of study completion is missing, the date of last study visit performed (i.e. Date of Visit 6) will be used.

Date of discontinuation will be the date of withdrawal recorded in the study conclusion/withdrawal form.

Statistical analysis
Randomised patients who completed the study will be presented by treatment and overall for the Randomised population. Randomised patients who discontinued from the study prematurely will also be presented with a breakdown of the reasons for discontinuation by treatment and overall for the Randomised population.

5.4 Demographics and baseline characteristics

Definitions and data conventions

Race
Race as it is recorded on the CRF will be considered. If more than one race is ticked, Race will be set equal to "Other".

Body Mass Index (BMI) (kg/m^2)
BMI will be calculated using the following formula:

$$\text{BMI} = \frac{\text{Body weigh t (kg)}}{\text{height (m)}^2}$$

Time since disease diagnosis
Time since disease diagnosis (years) will be calculated using the following formula:

Time since disease diagnosis (years) = (Date of Visit 1 – first COPD diagnosis + 1)/365.25

Statistical analysis
The baseline demographic characteristics will be summarised by treatment and overall by means of descriptive statistics.

The following characteristics will be provided for the ITT population:

- Age (years)
- Sex (male/female)
- Ethnicity (Hispanic or Latino, Non-hispanic or non-latino, Not reported, Unknown)
- Race (White (Caucasian), Asian, Black or African American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Smoking status (Non-smoker, Ex-smoker, Current smoker)
- Number of pack-years
- Alcoholic consumption (Yes, No, Former)

- Average number of units/week
- Caffeine consumption (Yes, No, Former)
- Average number of cups of coffee/week
- Time since disease diagnosis (years)

5.5 Medical and surgical history

Definitions and data conventions

Medical history

A disease is considered as medical history if it is not ongoing at screening visit ("ongoing" box is not ticked).

Concomitant disease

A disease is considered as concomitant disease if it is ongoing at screening visit ("ongoing" box is ticked). Concomitant cardiovascular diseases will be considered as they are recorded on the CRF separate form.

Statistical analysis

Medical history and concomitant diseases will be coded using Medical Dictionary for regulatory activities (MedDRA) dictionary (version 21.0) and frequency distributions and percentages will be summarised by treatment group for the ITT by System Organ Class (SOC) and Preferred Term (PT).

Counts will be given for both SOC and PT by subject. Subjects experiencing more than one past/concomitant disease event will be counted only once within each SOC and PT.

Concomitant cardiovascular diseases (Heart Failure, Ischemic Heart Disease, Atrial Fibrillation) will be separately summarised by treatment group for the ITT through frequency distributions and percentages.

5.6 Prior and concomitant medications

Definitions and data conventions

Date of first randomised study medication intake

The date of first randomised study medication intake is the first Start date recorded in the Study Medications Log.

Previous/Concomitant

The following categories of medications will be identified:

- previous medication (stop date ≤ date of first medication intake);
- concomitant medication (stop date > date of first medication intake or ongoing);

In case of missing or incomplete dates not directly allowing allocation to any of the two categories of medications, a worst-case allocation will be done according to the available parts of the start and the end dates. The medication will be allocated to the first category allowed by the available data, according to the following order:

- concomitant medication;

- previous medication.

Statistical analysis
Medications will be coded using World Health Organization Drug Dictionary (WHO DD), version March 2018 B3.
Previous medications and concomitant medications will be summarised by treatment group for the ITT through frequency distributions and Anatomical Main Group (1st level of the Anatomical Therapeutic Chemical (ATC) classification), Chemical Subgroup (4th level of the ATC classification) and Preferred Name.
Subjects experiencing more than one medication classified in the same category (previous medications, concomitant medications) within the same anatomical main group, chemical subgroup and preferred name will be counted only once.

5.7 Other baseline characteristics

Not foreseen.

6. Evaluation of Treatment Compliance and Exposure

6.1 Compliance to study drug and treatment

Compliance will be listed only.

6.2 Exposure to study drug

Not foreseen.

6.3 Evaluation of pharmacokinetics

Not foreseen.

7. Evaluation of Efficacy

7.1 Analysis of primary endpoint

Definitions and data conventions

First re-hospitalization and/or death
The event "first re-hospitalization and/or death" is identified as the first occurrence between the first re-hospitalization (as collected in the "COPD EXACERBATION FORM") and death, if any of them occurred.

Time to first re-hospitalization and/or death

In patients with at least one event, time to first re-hospitalization and/or death will be calculated as the weeks between baseline (Visit 2) and the date at which the first re-hospitalization (i.e., Date of admission/prolonged hospitalization in the 'COPD Exacerbation Form') and/or death occurs.

Time to first re-hospitalization and/or death (weeks) = (date of first re-hospitalization and/or death - Visit 2 + 1)/7

Patients without first re-hospitalization and/or death or who are discontinued before having it will be considered as "censored" at the end of the study visit (Visit 6) or at the time of the withdrawal during the treatment period (i.e., the date of withdrawal). For the analysis, the following formula will be applied:

Censoring time (weeks) = (date of Visit 6/withdrawal - Visit 2 + 1)/7

Time to first re-hospitalization and/or death for the sensitivity analysis.

The crossover occurrence is identified as patients that switch from one treatment group to the other adding or stopping ICS and it will be identified as protocol deviation.
In patients without the crossover occurrence , time to first re-hospitalization and/or death will be calculated as described above.
In patients with the crossover occurrence:

- if they experienced first re-hospitalization and/or death before or at the crossover occurrence date, time to first re-hospitalization and/or death will be calculated and considered as for the patients without the crossover occurrence;

- if they experienced first re-hospitalization and/or death after the crossover occurrence date, time to first re-hospitalization and/or death will be censored at the time of crossover occurrence;

- patients without first re-hospitalization and/or death will be considered as "censored" at the cross-over start date. For the analysis, the following formula will be applied:

Censoring time (weeks) = (date of cross-over start - Visit 2 + 1)/7

Primary efficacy analysis
Analysis will be performed on ITT population.

Time to first re-hospitalization and/or death will be analysed using the Kaplan-Meier estimator. The number of re-hospitalization and/or death-free patients at the beginning of the period, the cumulative number of patients with re-hospitalization and/or death at the end of the period and the probability of being re-hospitalization and/or death-free at the end of the period with the associate 95% CIs will be presented by treatment for the following study periods: (0-12] weeks, (12-24] weeks, (24-36] weeks and (36 weeks-EoT]. The point estimates and the relative 95% CIs will be

presented by treatment for the 75th, 50th and 25th percentiles. Comparison between treatments will be performed using the log-rank test stratified by center.
The LABD(s)+ICS group will be declared to prolong time to first re-hospitalization and/or death, compared to the LABD(s) group, if the difference between the two treatments is significantly in favour of LABD(s)+ICS (i.e., the p-value from the log-rank test is ≤ 0.050).
Plots of first re-hospitalization and/or death-free survival by treatment will also be presented.

The following SAS® code will be used to provide the Kaplan-Meier estimates for time to first re-hospitalization and/or death:

```
proc lifetest data=dataset TIMELIST=(12 24 36 EOT_A, EOT_B);
time TIME*EVENT(1);
strata CENTER / group=TMT;
run;
```

where TIME represents the time to first re-hospitalization and/or death or time to censoring, EVENT the censoring indicator (1 = censored patient), CENTER the center and TMT the treatment group; EOT_A, EOT_B, have to be replaced by the last time to first re-hospitalization and/or death or last time before EOT for each treatment group (if any).

Time to first re-hospitalization and/or death will also be analyzed using a Cox proportional hazards regression analysis with center and treatment group as qualitative independent variables and age as quantitative independent variables. The inclusion of any other potential confounding factors in the model will be evaluated during the Data Review, verifying the homogeneity of factors distributions among treatment groups.
The number of patients and the number of patients considered in the model will be provided by treatment. P-values of the independent variables based on Wald chi-square test will also be presented.
Treatment effect will be presented as a hazard ratio with the associated 95% Wald CI and p-value.

The following SAS® code will be used to estimate the Cox proportional hazards regression model:

```
proc phreg data=dataset;
class CENTER TRT;
model TIME*EVENT(1) = CENTER TRT AGE / ties=exact;
hazardratio TRT / cl=wald;
run;
```

where TIME represents the time to first re-hospitalization and/or death or time to censoring, EVENT the censoring indicator (1 = censored patient), TMT the treatment group, CENTER the center and AGE the age.
The variable TMT will be ordered in SAS in the following order:

- 1 = LABD;
- 2 = LABD + ICS.

If the option "ties=exact" requires a considerable amount of computer resources, the Efron approximation will be used ("ties=efron").

A sensitivity analysis will also be carried out excluding efficacy data (i.e., hospitalization and death) collected after the crossover occurrence date. The same analyses described above will be repeated on this modified dataset.

Finally, the same analyses described above will be repeated in the subgroup of patients treated with triple therapy.

7.2 Analysis of secondary efficacy endpoints

Definitions and data conventions

Number of re-hospitalizations and death
The number of re-hospitalizations and deaths will be calculated per-subject as the sum of the number of hospitalizations as recorded in the 'COPD Exacerbation Form' and the deaths (all cause).

Number of moderate/severe COPD exacerbations
The number of moderate/severe COPD exacerbations will be calculated per-subject as the sum of the number of COPD exacerbations recorded as "Moderate" or "Severe" in the 'COPD Exacerbation Form'.

Number of pneumonia events
The number of pneumonia events will be calculated per-subject as the sum of adverse events classified with the following System Organ Classes/Preferred Terms:

System Organ Class	Preferred Term
Respiratory, thoracic and mediastinal disorders	• Pneumonia NOS • Acute pneumonia • Lung infection • Multilobar pneumonia • Bronchopneumonia • Pneumonia lobar • Pneumonia, organism unspecified • Bronchopneumonia NOS • Acute bronchopneumonia • Community acquired pneumonia • Lobar pneumonia NOS • Ventilator associated pneumonia • Healthcare associated pneumonia • Pneumonia recurrent • Bronchopulmonary infection

	• Pulmonary suppuration • Lung infection NOS • Pleuropneumonia • Bronchopneumonia, organism unspecified • Bilateral bronchopneumonia • Infectious pneumonitis • Nosocomial pneumonia • Bronchial pneumonia • Bilateral pneumonia • Hospital acquired pneumonia • Right middle lobe pneumonia • Lobar pneumonia

Number of acute cardiac events

The number of acute cardiac events will be calculated per-subject as the sum of adverse events classified with the following System Organ Classes/Preferred Terms:

System Organ Class	Preferred Term
Cardiac disorders	• Heart failures • Coronary artery disorders • Cardiac arrhytmias • Embolic stroke • Haemorrhagic stroke • Thrombotic stroke

Time on study

Time on study (years) will be calculated using the following formula:

Time on study (years) = (Date of patient completion or withdrawal - Date of randomization +1)/365.25.

Log-time on study (years)

The log-time on study in years will be calculated using the following formula:

Log-time on study = ln(time on study)

Statistical analysis

Analysis will be performed on the ITT population.

Number of re-hospitalizations and deaths

The number of re-hospitalizations and deaths of all cause (1, 2, 3, 4, >4) will be summarised by using frequency distributions and percentages.

Comparison between treatments will be performed using a Poisson regression model. The model will include the number of events as dependent variable, treatment group and center as qualitative independent variables and age as quantitative independent variable. Log-time on study (in years)

will be used as an offset. The overdispersion parameter based on the deviance will be considered in order to account for between-patient variability in the event rate and standard errors will be estimated allowing for extra-Poisson variation.
The number of patients and the number of patients considered in the model will be provided by treatment. P-values of the independent variables based on Wald chi-square test will also be presented.
The adjusted mean rates per patient per year in each treatment group and their 95% CIs will be presented, and the adjusted rate ratio between treatments will be provided with the associated 95% Wald CI and p-value.

The following SAS® code will be used to estimate the Poisson regression model:

```
proc genmod data = dataset;
class TMT CENTER;
model VAR = TMT CENTER AGE / offset=log_time dist=poisson link=log dscale wald type3;
lsmeans TMT / exp cl;
lsestimate 'LABD vs LABD + ICS' TMT 1 -1 / exp cl;
run;quit;
```

where VAR represents the number of re-hospitalizations and deaths, TMT the treatment group, CENTER the center, AGE the age and log_time the logarithm of the time on study in years.
The variable tmt will be ordered in SAS in the following order:

- 1 = LABD;
- 2 = LABD + ICS.

Number of moderate/severe COPD exacerbations
The same analyses described for the number of re-hospitalizations and deaths will be performed for the number of moderate/severe COPD exacerbations (1, 2, 3, 4, >4).

Number of pneumonia events
The same analyses described for the number of re-hospitalizations and deaths will be performed for the number of pneumonia events (1, 2, 3, 4, >4).

Number of acute cardiac events
The same analyses described for the number of re-hospitalizations and deaths will be performed for the number of acute cardiac events (1, 2, 3, 4, >4).

Number of deaths
Patients who died will be presented with a breakdown of the causes of death (Cardiovascular death/Other) by treatment and overall.

QoL variation (change in CAT total score from baseline to end of treatment period)
CAT total score, the change from baseline will be summarised by treatment at each visit by means of descriptive statistics. 95% CIs for the mean change will also be calculated.

A comparison between treatment groups will be performed with an ANCOVA model with the change from baseline of the CAT total score to the end of treatment period (i.e. Visit 6) as dependent variable, treatment group and centre as qualitative independent variables and age and baseline value of the variable as quantitative independent variables.
The number of patients and the number of patients considered in the model will be provided by treatment. P-values of the independent variables will also be presented.
The adjusted means for treatments and the relative 95% CIs will be presented. The difference between the adjusted means for LABD and LABD + ICS will be calculated with the relative 95% CI and p-value.

The following SAS® code will be used to estimate the ANCOVA model:

```
proc mixed data = dataset;
class TMT CENTER;
model CHG = TMT CENTER AGE BASELINE;
lsmeans TMT / cl;
lsestimate 'LABD vs LABD + ICS' TMT 1 -1 / cl;
run;
```

where CHG represents the change from baseline of the CAT total score at Visit 6, TMT the treatment group, CENTER the center, AGE the age and BASELINE the baseline value of the variable.
The variable TMT will be ordered in SAS in the following order:

- 1 = LABD;
- 2 = LABD + ICS.

Change in mMRC dyspnea score from baseline to end of treatment period
The same analyses described for the change in CAT total score will be performed for the change in mMRC dyspnea score.

Change in FEV1 from baseline to the end of treatment period
The same analyses described for the change in CAT total score will be performed for the change in FEV1.

Change in FVC from baseline to the end of treatment period
The same analyses described for the change in CAT total score will be performed for the change in FVC.

7.3 Analysis of exploratory efficacy endpoints

Not foreseen.

7.4 Evaluation of pharmacodynamics

Not foreseen.

8. Evaluation of Safety

8.1 Adverse events

Definitions and data conventions

Pre-treatment adverse events

An AE will be classified as pre-treatment AE if it starts before the date of randomization (AE onset date < date of randomization).

Treatment-emergent adverse event (TEAE)

An AE will be classified as a TEAE if it starts on or after the date of randomization (AE onset date ≥ date of randomization).

In case of missing or incomplete dates not allowing a direct allocation to any of the two categories of AEs, a worst-case allocation will be done according to the available parts of the onset and the end dates. The AE will be allocated to the first category allowed by the available data, according to the following order:

- TEAE
- Pre-treatment.

Serious adverse event (SAE)

A SAE is an AE judged as serious.

Adverse drug reaction (ADR)

An ADR is an AE with relationship to study treatment equal to "Yes".

Severe adverse event (SAE)

A SAE is an AE judged as severe intensity.

Adverse event leading to study withdrawal

An AE leading to study withdrawal is an AE with action taken equal to "Drug withdrawn" or "Drug interrupted".

Count of adverse events

Two AEs with the same Preferred Term (PT) and classified in the same category (pre-treatment AE or TEAE) will be considered as two different events when calculating the "number of events" in the tables.

Statistical analysis

Pre-treatment AEs and TEAEs will be presented separately. Pre-treatment AEs will be presented in the listings only.

The number of treatment-emergent AEs, SAEs, ADRs, severe AEs and AEs leading to discontinuation, and the number and the percentage of patients experiencing treatment-emergent AEs, SAEs, ADRs, severe AEs and AEs leading to discontinuation will be summarised by treatment group. Differences between groups will be evaluated using Chi-square test or Fisher's exact test (if more than 20% of the cells in a contingency table have expected counts less than 5).

AEs will be coded using the MedDRA dictionary (version 21.0). The SOCs and PTs will be used for tabulation. The number of treatment-emergent AEs and the number and the percentage of patients with at least one treatment-emergent AE will also be presented by SOC and PT by treatment group.

8.2 Clinical laboratory evaluation

Statistical analysis
Laboratory data will be listed only.

8.3 Vital signs

Statistical analysis
Vital signs will be listed only.

8.4 ECGs

Statistical analysis
ECG data will be listed only.

8.5 Physical examination

Statistical analysis
Physical examination data will be listed only.

8.6 Other safety evaluations

Not foreseen.

9. Tables, Figures and Listings

9.1 Programming conventions

All tables/figures/listings will be presented in landscape format.

Titles will be center-aligned; footnotes will be left-aligned.
Each table/figure/listing will have 2 titles:

- The 1st title will be the table/figure/listing number with the description of the table/figure/listing;
- The 2nd title will be a description of the study set presented in the table/figure/listing.

Some tables will have a third title (before 2nd title) with a description of the statistical method used in those tables.

Any footnote added to explain the table/listing/figure contents will be presented in the following format:

Note 1: Percentages are calculated on the number of patients (N).
Note 2: A serious adverse event is an ....
Note 3: …….

The last two footnotes of each table/figure will be footers indicating:

- the reference listing of the data;
- the program name, the date and time of generation and the SAS® version used.

The last footnote of each listing will be a footer indicating the program name, the date and time of generation and the SAS® version used.

In the tables, listing and figures the treatment under comparison will be labelled as "LABD" and "LABD + ICS".

Unless otherwise stated, listings will be presented by randomised treatment, and sorted by the patient number.

All the listings will be based on the randomised population.

In all the listings on safety variables, a column with a flag (§) for treatment misallocation will identify the treatment misallocations.
The derived variables will be identified in the listings with a flag (*).

In general, dates will be presented on listings in the format ddmmmyyyy (date9.) and time in the format hh:mm (time5.). In case of partial dates or times, missing information will be replaced by dashes. Numeric variables will be listed generally with the same number of decimal places as in the actual data.

The following rules on decimal places will be considered in the listings for the derived variables (in the analyses approximations will not be performed):

- BMI (kg/m^2), time since disease diagnosis (years), time to event: 1 decimal place;
- change from baseline: same as the variable considered.

The following rules on decimal places will be considered for the results of the analyses (if the analyses are performed on derived variables, the level of precision of the actual data is derived from the previous list):

- Min, max: same as actual data;
- Mean and its confidence limits (unadjusted and adjusted), adjusted difference between means and its confidence limits, SD, median: actual data + 1 decimal;
- Percentage: 1 decimal place;
- P-value: 3 decimal places.

10. Literature

- CROS NT Standard Operating Procedure SOP ST03/V01 “Statistical Analysis Plans”;
- European Medicines Agency (EMA), International Conference on Harmonisation (ICH) E3 Harmonised Guideline (1996) “Structure and Content of Clinical Study Reports”;
- EMA, ICH E9 Harmonised Guideline (1998) “Statistical Principles for Clinical Trials”.