Statistical Analysis Plan (SAP) - The CORTICO steroid reduction in COPD (CORTICO-COP) study

2nd April 2017

A multi-center, open label, randomized controlled trial conducted in pulmonary departments in Denmark

Estimated Primary Completion Date: December 2018
Estimated Study Completion Date: August 2019

Approved by: Ethics Committees of all participating sides (H-15012207) and the Danish Medicines Agency (EudraCT no: 201500344126) and the Danish Data Protection Agency (HGH-2015-038 and I-Suite number 04014).

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Introduction

We are conducting a prospective, multicenter, randomized, controlled, open-label study in hospitalized patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). The aim is to determine whether it is possible by applying a biomarker-guided strategy to reduce the use of systemic corticosteroids in AECOPD without influencing the outcome. Additionally, the study will explore whether this strategy reduces some of the most frequent side effects that occur with the current standard treatment.

The patients are enrolled in the trial only after obtaining informed consent. The trial is conducted at four centers (Gentofte University Hospital, Bispebjerg University Hospital, Hvidovre University Hospital, and North Zealand Hospital Hillerød).

Patients will be randomized to one of the two treatment arms:

a) Standard Care (SC) group: Intravenous methylprednisolone 80 mg on the first day followed by 37.5 mg of prednisolone tablets daily for 4 days.

b) Intervention group: Intravenous methylprednisolone 80 mg, followed by prednisolone tablet 37.5 mg daily (maximum of 4 days in all) on days where the blood eosinophil count is $\geq 0.3 \times 10^9$ cells/L. On days with eosinophil count $<0.3 \times 10^9$ cells/L systemic corticosteroid treatment will not be administered.

If a patient is discharged during the treatment period, a treatment based on the last measured eosinophil count will be prescribed for the remaining days within the 5 day-period.

The analyses described in this document will be performed by Pradeesh Sivapalan, MD, principal investigator, in cooperation with Jens Ulrik Jensen, associate professor, head of the respiratory medicine section, University of Gentofte Hospital, once the data have been entered, cleaned and released for use.

This document provides a detailed description of the statistical analyses that will be performed for the evaluation of the primary and secondary endpoints of protocolized for the CORTICO-COP study.

The analyses described in this document are compatible with the recommendations of the CONSORT 2010 statement.

The International Conference on Harmonisation (ICH) of Good Clinical Practice (GCP)(1) and leading experts recommend that randomized clinical trials should be analyzed according to predefined outcomes and a predefined detailed statistical analysis plan (2). To prevent selective reporting of outcomes and data-driven analysis results and increase transparency this paper will in detail describe the detailed statistical analysis plan for the CORTICO-COP trial(3) while enrolment of patients and collection of data is still on-going and before the database is accessed for trial results.

Analysis population

Data will be analyzed using intention-to-treat (ITT) principles. All randomized patients will be analyzed in the groups to which they were originally allocated to, regardless of whether they actually received the intended treatment or whether a protocol violation or protocol deviation occurred.

Patients who withdrew consent for use of their data will not be included in any analysis. Only the facts that they were enrolled into the trial and withdrew consent, and the original study group to which they were allocated, will be reported.

Two-sided 5% significance levels will be used to identify statistically significant results. All confidence intervals reported will be 95% confidence intervals.

A secondary analysis of the primary efficacy outcome will use a per protocol (PP) population.

A Consort diagram will be presented of participants in the present study.

Analysis Software

All analyses will be performed using SAS software version 9.4.

Descriptive analyses

The following baseline characteristics of the study population will be summarized separately within each randomized group:

- Age, median (IQR), y
- Male sex, n (%)
- Body mass index (kg/m^2, median, IQR)
- Medical Research Council dyspnea scale, n (%)
- Current smoker, n (%)
- Ex-smoker, n (%)
- Nonsmoker, n (%)
- Pack-years history (median, IQR, y)
- COPD assessment test score, median, IQR
- Support with activities of daily living at home, n (%)
- Increased dyspnea, n (%)
- Increased sputum volume, n (%)
- Increased sputum purulence, n (%)
- Increased cough, n (%)
- Disease symptoms duration
- Exacerbations frequency in previous year
- Atopy, n (%)
- Mean cumulative systemic corticosteroid dose 4 weeks before study entry (mg)
- Use of oxygen therapy, n (%)
- Use of noninvasive mechanical ventilation, n (%)
- FEV_1 (L, median, IQR)
- FEV_1 (median) % predicted
- FVC (L, median, IQR)
- FVC (median) % predicted
- FEV_1/FVC ratio, % (median, IQR)

Clinical findings

- Systolic blood pressure (mm Hg)
- Diastolic blood pressure (mm Hg)
- Heart rate, beats/min
- Oxygen saturation with nasal oxygen, median, IQR
- Respiratory rate, breaths/min
- Temperature (°C)
- Infiltrate on Chest X-ray, n (%)
- Leukocyte count, $x10^9$ cells/L

- Blood eosinophil count, $x10^9$ cells/L

Arterial Blood Gas(mean ± SD)

- PCO2, mmHg
- PO2, mmHg
- HCo3
- pH

Comorbid conditions, n (%)

- Essential hypertension,
- Diabetes Mellitus
- Chronic renal insufficiency
- Hypercholesterolemia
- Heart failure
- Ischemic heart disease
- Atrial fibrillation
- Osteoporosis
- Malignancy
- Liver failure

Employment status, n (%)

- Jobseekers,
- Part-time work
- Full-time work
- Early retirement
- Retired

For continuous variables, means and standard deviations will be presented, when normally distributed, otherwise as medians and interquartile ranges (IQR). For categorical variables, the number and percentage of participants within each category will be presented. For each variable, the percent of missing values will be reported. For categorical values, chi-square, Fisher´s exact test, Cox regression and log-rank test will be used and for the latter, a corresponding Kaplan-Meier plot will be presented.

Sample size

With a power to avoid type II error (1-β) of 0.8 and a two-sided significance level (α) of 0.05, the study will be able to detect a treatment difference above 1.2 days in regards to the primary endpoint. This provides a sample size of 318 subjects.

Protocol violation

We have explicitly instructed all physicians to follow the treatment algorithm for both study arms, but completely avoidance of violation is probably not possible. Therefore, we have chosen that we can tolerate that up to 15 patients in total can violate the algorithm: Thus, ten patients in the total study population, where we accept that physicians choose to give prednisolone despite low eosinophil count in the intervention group and five patients where doctors choose to interrupt prednisolone within five days even though the patients were allocated to the SC group.

Primary objective and outcome

The primary outcome is "days alive and out of hospital (DAOH) within 14 days after recruitment" defined as the time from hospital discharge and days without hospitalization up to 14 days from recruitment where the patient is alive. To compare this outcome, we will use parametric tests if data are normally distributed, otherwise we will use non-parametric test e.g. Mann-Whitney. We do not expect that any patients will be lost to follow-up for the primary endpoint.

Secondary objective and outcomes

The secondary objective is to determine whether the clinical outcome for patients receiving eosinophil guided corticosteroid-sparing therapy will be less favorable compared to standard care, and to explore the exposure to oral corticosteroids. The endpoints and follow-up rates when assessing the clinical outcome are listed below:

1. Treatment failure (Recurrence of AECOPD resulting in emergency room visits, hospitalization or need to intensify pharmacological treatment within 30 days)
   Follow-up: 318/318 equivalent to 100%
   Analysis: Fisher's exact test or Chi squared test

   The period between index AECOPD and the next AECOPD will be calculated as the time (days) from index AECOPD and next AECOPD.
   Follow-up: 318/318 equivalent to 100%
   This endpoint will be analyzed as:
   a. Readmission with AECOPD or death within 30 days.
      Analysis: Chi-square test.
   b. Time to readmission with AECOPD or death within 30 days.
      Analysis: Cox proportional-hazards regression model. Unadjusted and adjusted (two models)

2. Cumulative corticosteroid dose (mg) from recruitment to 1 and 3-month follow-up.
   Follow-up: 318/318 equivalent to 100%
   This endpoint will be analyzed as:

a. Proportions of patients using corticosteroids during hospitalization (day 1 to day 5) between treatment arms. Analysis: Fisher's exact test or Chi squared test
b. Mean total cumulative dose from recruitment to 3-month follow-up
Analysis: t-test, Wilcoxon signed rank test or Mann-Whitney U test

3. Mortality rate 30 days
Follow-up: 318/318 equivalent to 100%
Analysis: Unadjusted: Chi-square test or Fisher´s exact test. Adjusted: Cox proportional-hazards regression model

4. Change in lung function (ΔFEV_1) on day 3, at 30 days and 3 months from recruitment
Follow-up: 250/318 equivalent to 78.6%
Analysis: Analysis of variance (ANOVA) will be used to compare outcomes for three means

5. Infections requiring antibiotic treatment within 90 days after the index of AECOPD
Follow-up: 318/318 equivalent to 100%
Analysis: Fisher's exact test or Chi squared test

6. Hyperglycemia during hospital admission.
This endpoint will be analyzed as any day (day 1 to 5)
Follow-up: 300/318 equivalent to 94%
Analysis: Fisher's exact test or Chi squared test

7. Dyspepsia or ulcer complications (gastrointestinal bleeding) 90 days
Follow-up: 318/318 equivalent to 100%
Analysis: Fisher's exact test or Chi squared test

8. New onset or worsening of diabetes during the study period (defined as HbA1c $\geq$ 48 mmol/mol or initiation / intensification of anti-diabetic treatment) 30 days
Follow-up: 318/318 equivalent to 100%
Analysis: Fisher's exact test or Chi squared test

9. Increase in Body Mass Index between hospitalization, at 30 days, and 3-month follow-up
Follow-up: 300/318 equivalent to 94%
Analysis: ANOVA

10. Changes in health-related quality-of-life measured by COPD Assessment Test between hospitalization, at 30 days, and 3-month follow-up
Follow-up: 300/318 equivalent to 94%
Analysis: ANOVA

11. Changes in level of dyspnea using the Medical Research Council (MRC) Dyspnoea Scale between hospitalization, at 30 days and 3-month follow-up
    Follow-up: 300/318 equivalent to 94%
    Analysis: ANOVA

12. Changes in PTH and Vitamin D status between hospitalization and 3-month follow-up
    Follow-up: 300/318 equivalent to 94%
    Analysis: t-test, Wilcoxon signed rank test or Mann-Whitney U test

Long-term outcome to be assessed in 1, 2 and 5 years follow-up

Defined secondary long-term endpoints will be published when long-term follow-up is available (after due time) in a separate publication.

1. Mortality
   Analysis: Unadjusted: Chi-square. Adjusted: Cox proportional-hazards regression model
   Follow-up: 318/318 equivalent to 100%

2. Hospitalization or death
   Analysis: Unadjusted: Chi-square. Adjusted: Cox proportional-hazards regression model
   Follow-up: 318/318 equivalent to 100%

3. Changes in Bone Turnover Markers (C-terminal telopeptide of type 1 collagen (CTX) and procollagen type 1 N propeptide (P1NP)) between hospitalization and follow-up
   Analysis: ANOVA
   Follow-up: 300/318 equivalent to 94%

4. Osteoporotic fractures
   Analysis: Fisher's exact test or Chi squared test
   Follow-up: 318/318 equivalent to 100%

5. Infections requiring antibiotic treatment after the index of AECOPD
   Analysis: Fisher's exact test or Chi squared test
   Follow-up: 318/318 equivalent to 100%

6. Hospital admissions with infections
   Analysis: Fisher's exact test or Chi squared test
   Follow-up: 318/318 equivalent to 100%

7. New onset or worsening of diabetes mellitus
   Analysis: Fisher's exact test or Chi squared test
   Follow-up: 300/318 equivalent to 94%

All-cause mortality and time to next exacerbation

Differences in time to next exacerbation or time to death will be calculated using the Kaplan-Meier method in combination with the log-rank test and as an adjusted analysis using Cox proportional hazards models.

Figures and tables

The first figure will be a Consolidated Standards of Reporting of Randomized Trials (CONSORT) flow chart. The second figure will be a Kaplan-Meier plot to describe the process of death by treatment arms. The first table will be the baseline characteristics of the ITT population. The second table will be of the primary and secondary outcomes according to the two groups and pair-wise comparisons.

Blinding of the statistician

The detailed analysis plan was written in strict concordance with the trial protocol approved by the regulatory authorities prior to recruitment initiation. The entire statistical analysis plan was published at www.coptrin.dk before the trial was finalized (while the database was closed). All analyses will be done prior to breaking of the randomization code (analysis comparisons between "arm A" and "arm B" (random names). The principal investigator (PS) and the study sponsor (JUJ) will conjointly perform all the data analyses according to this plan, except analyses involving eosinophil counts and use of oral corticosteroids, which will be performed by investigator Josefin Eklöf (not to unblind the analysis of the primary and secondary endpoints).

Abbreviations

AECOPD	Acute exacerbations of chronic obstructive pulmonary disease
ANOVA	Analysis of variance
CAT	COPD Assessment Test
CONSORT	Consolidated Standards of Reporting of Randomised Trials
DAOH	Days alive and out of hospital
FEV_1	Forced expiratory volume in 1 second
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ITT	Intention-to-treat
IQR	Interquartile range

MRC Medical Research Council dyspnea scale

References

1. ICH Harmonised Tripartite Guideline. Guideline for good clinical practice E6(R1). ICH Harmon Tripart Guidel. 1996;1996(4):i-53.

2. Finfer S, Bellomo R. Why publish statistical analysis plans? Crit Care Resusc [Internet]. 2009 Mar [cited 2018 Sep 20];11(1):5–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19281437

3. Sivapalan P, Moberg M, Eklöf J, Janner J, Vestbo J, Laub RR, et al. A multi-center randomized, controlled, open-label trial evaluating the effects of eosinophil-guided corticosteroid-sparing therapy in hospitalised patients with COPD exacerbations - The CORTICO steroid reduction in COPD (CORTICO-COP) study protocol. BMC Pulm Med. 2017;17(1).