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Study Protocol: COPD - Eosinophil-guided Reduction of Inhaled COrticoSteroids (COPERnICOS)

A randomized, double-blinded, multicenter, four-arm intervention clinical trial on eosinophil-guided time-updated person-specific reduction of inhaled corticosteroid therapy and prophylactic azithromycin therapy in patients with severe or very severe chronic obstructive pulmonary disease (COPD)

Participants

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Scientific Project Sponsor

Chronic Obstructive Pulmonary Disease Trial Network: COP:TRIN – a network of independent COPD researchers in Denmark: www.coptrin.dk

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Content

1. Background

Chronic Obstructive Pulmonary Disease (COPD) is characterized by increased mucus formation, destruction of alveoli, and constriction of the conductive airways. This causes respiratory distress, impaired lung function, and frequent lower respiratory tract infections. COPD is an incurable and potentially life-threatening disease affecting approx. 250 million people worldwide (1). Acute Exacerbation of severe Chronic Obstructive Pulmonary Disease (AECOPD) is the leading cause of death in COPD patients. Survivors often suffer from mental disabilities such as anxiety and depression and this reduces the self-rated health (2, 3)

Global Initiative for Obstructive Lung Disease (GOLD) recommends inhaled corticosteroids (ICS) for COPD patients with exacerbations and blood eosinophils >300 cells/uL, and in those with ≥100 cells/uL blood-eosinophils and persistent exacerbations while on bronchodilators. This guideline is based on several post hoc analyzes, and there are currently no randomized trials supporting this.

(4, 5). Treatment with ICS is often given in combination with Inhaled Long-acting Muscarinic Antagonist (LAMA) and Long-acting beta-agonist (LABA). The effect of the treatment varies substantially among the patients studied. In some cases, no improvement in the patients' condition is seen. Moreover, complications are seen, resulting from the use of ICS. Several studies have shown that treatment with ICS is associated with an increased risk of side effects such as pneumonia (6, 7), osteoporosis, and diabetes (8, 9). Despite GOLD recommendations and known risks, approximately 70% of COPD patients continue to use ICS even when there is no obvious indication, and the effect is discrete or absent (10). The personal consequences of these complications for the patient have not been systematically addressed but are presumably of great importance to their quality of life.

COPD symptoms vary widely in severity, which is why both the clinical phenotypes and the patient's biological information are useful in assessing the optimal treatment option. Several clinical studies have shown that the blood eosinophil count is a useful biomarker for respiratory inflammation in COPD patients (11, 12). This biomarker is an effective predictor of treatment response to ICS in COPD patients with eosinophilic inflammation. Airway inflammation is known to play a role in AECOPD, predominantly neutrophilic inflammation, but in a subset of patients, eosinophilic inflammation plays a key role (13, 14). It has been shown that ICS does not reduce the risk of AECOPD in general, although ICS reduces the risk in the sub-population of COPD patients

who have evidence of eosinophilic inflammation (15, 16). Thus, ICS should not be used for the majority of COPD patients (with blood eosinophils <300 cells/uL, approx. 80%), but on the other hand they should be used for COPD patients with blood eosinophils ≥300 cells/uL. However, this is disputed, since a strategy of eosinophil-guided ICS management in COPD patients with frequent AECOPD´s has never been tested in a randomized trial. An effective eosinophil-guided time-updated personalized reduction of systemic corticosteroid therapy has previously been shown in the CORTICO-COP study (17). We wish to study this method with ICS and create a treatment plan that optimizes the drug's therapeutic effect while reducing the use of ICS and thus the risk of side effects.

We also want to investigate, in the largest study so far, whether prophylaxis azithromycin 250 mg three times weekly can reduce the time hospitalized with AECOPD in severe COPD patients' "days alive out of hospital". It has been established that both inhaled and systemic corticosteroids increase the risk of bacterial airway infections such as pneumonia. Long-term inhaled corticosteroid treatment affects bacterial load in stable COPD. Lower eosinophil counts are associated with 9increased airway bacterial load(18, 19). Azithromycin exerts multiple effects on the structure and composition of the lower airway microbiota and increases the levels of several microbial metabolites in the emphysematous lung that have anti-inflammatory effects(20). No one has looked at the effect on the respiratory microbiota in patients receiving both treatments.

A small study (N=92) has shown that azithromycin treatment for a 12-month period has been shown to reduce the annual exacerbation rate among COPD patients (21).A larger study (1,142) confirmed these results, however, 50% of the participants in this study was in GOLD risk class C/D, and it is largely unknown how azithromycin reduces exacerbation rates (22). We aim to gain a better understanding of the airway microbiota during azithromycin treatment and determine whether azithromycin can prevent AECOPD.

2. Objectives

The objectives of this study can be grouped as clinical objectives and microbiota objectives.

In the current set of studies, we aim to uncover:

Clinical objectives

1. ICS
    - Whether a strategy of "time-updated, eosinophil-guided administration of inhaled corticosteroids" in patients with severe/very severe COPD and frequent AECOPD´s can lead to non-inferior treatment responses to standard treatment with combined

ICS, LAMA, and LABA (same number of AECOPD, but with substantially lower exposure to corticosteroids).

- Whether the side effects of ICS can be reduced with the time-updated, eosinophil-guided administration of inhaled corticosteroids

2. Azithromycin: Whether the use of azithromycin can reduce the time hospitalized with AECOPD (or other cause) in severe COPD patients

Microbiota objectives

1. ICS: The change in composition of the respiratory microbiota that happen in the airways of a patient with COPD, when the patient is receiving inhaled corticosteroids continuously, compared to when a corticosteroid-sparing, biomarker-guided administration is used.
2. Azithromycin: The influence of the macrolide antibiotic azithromycin on the respiratory microbiota in patients with COPD.

3. Hypotheses

1) In severely ill COPD patients, the guidance of inhaled corticosteroids by blood-eosinophils every third month (switch-on/off-strategy) can result in a reduction of the use of inhaled corticosteroids by >25% (measured by budesonide equivalent doses) with no apparent loss of efficiency [measured by "days alive and out of hospital within 365 days"].
2) In severely ill COPD patients (GOLD C/D or FEV1<30%), guidance of inhaled corticosteroids by blood-eosinophils every third month will result in fewer ICS-induced side effects compared to side effects seen in patients receiving standard treatment
3) In severely ill COPD patients, azithromycin 250 mg three times weekly can result in a increase in "days alive and out of hospital within 365 days" of 40 days/365 days.
4) The respiratory microbiota in COPD patients have a composition of less "pathogenic" bacterial species, when the use of inhaled corticosteroids is reduced.
5) The complexity of the respiratory microbiota is lower among patients treated with an "ICS-intense" treatment regimen than among patients treated with an "ICS-sparing" treatment regimen (the eosinophil-guided group).
6) The differnece in composition of the respiratory microbiota is substantial when COPD patients are treated with long-term azithromycin
7) The degree of neutrophilic nasal airway inflammation (measured by nasosorption during bronchoscopy) is reduced in COPD patients who are treated with long-term azithromycin

4. Methods

4.1 Study design

COPERNICOS is a 4-arm facultative designed, randomized controlled, multicenter, parallel group, doubleblindednon-inferiority intervention study in participants with severe and very severe COPD study.

Participants will be randomly allocated to one of the following four following treatment groups:

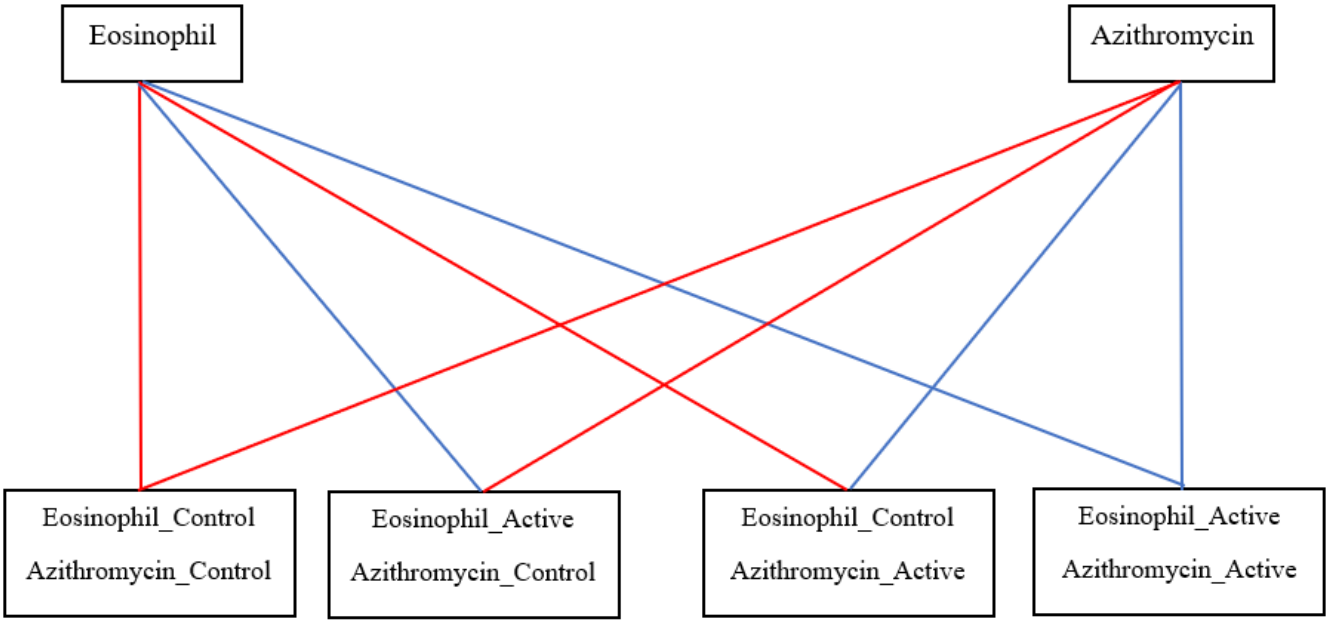

Figure 1: The four treatment groups **(Control – Active)**

1. **Eosinophil_"Control"/Azithro_"Control" group:**
    a. Azithromycin: participants are given placebo
    b. ICS: The participants are given the usual LAMA/LABA/ICS product in the usual dose.
2. **Eosinophil_"Active"/Azithro_"Control":**
    a. Azithromycin: placebo
    b. ICS: All participants will receive LABA/LAMA medication. The ICS medication will be switched on/off according to the most recent blood eosinophil count (at inclusion + every 3 months):
        i. If blood eosinophil ≥ 300 cells/µL, ICS in usual dose next 3 months. Blood eosinophils are measured every 3 months.
        ii. If blood eosinophil <300 cells/µL, ICS is discontinued.

3. **Eosinophil_"Control"/Azithro_"Active" group:**
    a. Azithromycin: 250 mg azithromycin three times weekly.
    b. ICS: The participants are given the usual LAMA/LABA/ICS product in the usual dose, where the medical treatment for severe COPD is unchanged throughout the entire project period
4. **Eosinophil_"Active"/Azithro_"Active":**
    a. Azithromycin: 250 mg azithromycin three times weekly.
    b. ICS: All participants will receive LABA/LAMA medication. The ICS medication will be switched on/off according to the most recent blood eosinophil count (at inclusion + every 3 months):
        i. If blood eosinophil ≥ 300 cells/μL, ICS in usual dose next 3 months. Blood eosinophils are measured for every 3 months.
        ii. If blood eosinophil <300 cells/μL, ICS is discontinued.

A microbiological study within the framework of the randomized study aims to investigate the respiratory microbiota in participants from the four randomized groups from bronchial lavage fluid. 40 participants from each group will participate in the microbiota analysis. The bronchial lavage will be performed at lingula, if not possible then the middle lobe, if not possible then left or right lower lobe. A total of 50 ml bronchial lavage fluid will be collected- Diagnostic bronchoscopy with bronchial lavage fluid (is a routine procedure at Section of Respiratory Medicine. Serious complications are rare participants' data and laboratory specimens will be assigned a coded identification number to maintain participant confidentiality.

4.2 Recruitment and inclusion criteria

Participants for the trial will be recruited through advertisements and announcements in local newspapers, daily newspapers, and via the Danish Lung Association and its member magazine. Participants can contact trial staff by e-mail or telephone to receive the written participant information. Furthermore, patients at the outpatient clinic at each center will be consecutively screened and assessed on inclusion and exclusion criteria. If a patient matches the criteria for the study, the patient will be invited to a screening meeting with a Good Clinical Practice nurse (GCP) or a PhD student. This meeting will take place in an undisturbed office. Participants will be thoroughly screened and informed of the right to an assessor and companion in the first contact during an information meeting with trial staff. A 24-hour reflection period will be given to every participant, and informed consent will be obtained upon the signed consent declaration, provided that the participant will participate in the project. Only after receiving oral and written participant information

can informed consent be obtained. The consent to collect blood samples and bronchial lavage fluid samples to research biobank and future-research biobank is a part of the informed consent.

At recruitment health files regarding inclusion and exclusion criteria will be accessed for screening purposes before informed consent is obtained according to the Danish Health Care Act §46 (1). The following contact to possible participants will be at the next planned visit to the outpatient clinic. During the project health files will be accessed by investigators for the following information:

- Medication
- Hospital admissions

If informed consent are obtained sponsor, investigator, monitor and the Danish Medicines Agency (Lægemiddelstyrelsen) will have access to health files, including electronic files, as part of the trial surveillance, quality control etc.

Participants are randomized by chance via RedCap to one of the four arms, prior to randomize the participant the inclusion and exclusion criteria will have to be entered.

Participants compliance to Azithromycine/placebo are monitored by medicine diaries. Blood eosinophil count will be monitored every 3 months from inclusion and participants will receive a phone call from a nurse every 3 months to ensure that participants have taken the inhaled corticosteroid according to the physician's prescription and plan the next 3 months inhalation treatment according to protocol.

Inclusion criteria:

- COPD (verified by a specialist in respiratory medicine + spirometry)
- GOLD risk class C/D or FEV1<30%
- Must receive at least during last 4 weeks: LAMA, LABA and ICS
- Informed consent

Exclusion criteria:

- Known asthma
- Male <40 years
- Female<55 years (in order to exclude fertile women)
- Non-menopausal women>55 years (Had menstruation within the last 12 months)
- Non-bacterial* exacerbation per investigator judgement in the last 3 months
- Severe mental illness which considerably complicates co-operation
- Language problems that considerably complicate co-operation.

- Current treatment with systemic corticosteroids corresponding to >5 mg prednisolone per day
- Antibiotic treatment within 14 days
- Allergy to inhaled corticosteroids
- Contra-indication to treat with azithromycin (e.g. prolonged QTc > 480 msec, interactions with other medications).
- * Non-bacterial exacerbation per investigator judgement may be guided byExacerbation with blood eosinophil > 0.3 x 10^9 cells
- Exacerbation with CRP under 100 mg/L
- Exacerbation with chest x-ray without sign of pneumonia

4.3 Examinations

The following clinical tests will be performed during the project cf. figure 2.

Figure 2: An overview of examinations that each participant will undergo:

	Enrollment	Inclusion (Baseline)	After 3 months	After 6 months	After 9 months	After 12 months
Informed consent	X					
Eligibility screening	X					
Blood sample		X	X	X	X	X
Microbiota and inflammation analysis (Bronchoscopy with bronchial lavage and nasosoption)				X		
Lung function measurement (Spirometry)		X				X
Weight		X				X
Height		X				
COPD Assessment Test (CAT)		X	X	X	X	X
MRC-dyspnea scale		X	X	X	X	X

Blood tests: Electrolyte parameters (sodium, potassium, albumin, creatinine, hemoglobin, liver parameters (conjugated bilirubin, ALT, alkalic phosphatase, INR, LDH), infection parameters (CRP, white blood cell differential count, thrombocytes), D-dimer and HbA1c

Questionnaires: Standardized questionnaires are used. CAT and MRC dyspnea scale are short and simple tests that provide an understanding of the severity and impact of COPD on the participant's daily life.

4.4 Data Collection

Inclusion of participants, data collection, data processing, statistical analysis and publication of the data material will be performed by a PhD student (Coordinating investigator) together with health professionals (Primary and secondary investigators) from the participating pulmonary medical outpatient clinic. The randomized trial is expected to start with the inclusion of participants from 1/9/2020, and the last participant is expected to be included by 31/12/2022. Data collection ceases 31/12/2023, and the project is scheduled to run until 31/8/2025. A nurse will be responsible for blood sampling, questionnaires, and lung function examination at baseline and at three-, six- and nine-month follow-ups. Other information required for data analysis will be taken from the National Patient Register. Medical decisions are made by doctors only. Proper handling, storage, and delivery of medication and the primary daily project management is handled by the coordinating investigator. Recruitment, medical examinations, and distribution and accounting of medication will be assisted by primary investigators at each center. Information on survival and death rates are obtained from the Cause of Death Register.

The data collected will be treated confidentially and only by personnel associated with the project. This includes demographic data, health status, current illnesses, medications, medicinal side effects, hospital admissions, and results from various examinations during the trial. Data will be reported in Electronic Case Report Forms (eCRF) specific for each participant. The data is encrypted, stored in online servers and protected by the Data Protection Authority through various security precautions. The physical copies of the CRF are kept in locked archives on the departments involved for 15 years. Data in eCRF will be handled by the investigator at each center and in accordance to the Law for Data Protection and the Danish Law for Privacy Regulation.

4.5 Research Biobank

The purpose of establishing a research biobank is to investigate the frequency of ICS-induced side effects and the changes in respiratory microbiota in different treatment groups. This biobank will clarify the hypotheses and provide biological materials for future research (Providing that future projects can obtain a separate approval from the Danish National Committee on Health Research Ethics).

The research biobank will store blood samples and bronchial wash samples. Blood samples are taken from each participant at inclusion and at follow-up every 3 months during the 12-month study period. Approximately240 ml of blood will be collected from each participant during the entire study period

corresponding to a maximum of 40 ml per blood draw. All blood samples are stored in a freezer at -80 degrees Celsius within 24 hours of blood sampling for analysis prior to completion of the project. The freezers are kept in a locked room at each of the six participating pulmonary medicine departments. Sputum samples are stored and analyzed at the State Serum Institute.

All samples are pseudonymized and kept for 15 years in accordance with present legislation and data protection laws. Establishment of this research biobank ends 31/08/2023. Following the end of this study and the research biobank, all surplus biological material will be transferred to a future-research biobank. These samples will also be pseudonymized and kept for 15 years. Permission to create a research biobank and future-research biobank with the excess biological material will be sought from The Danish National Committee on Health Research Ethics and The Danish Data Protection Agency. Permission to store biological material from participants in the research biobank and future-research biobank is a part of the informed consent to participation in the project.

5. Statistical Considerations (Power Calculation)

Participants will be randomized using stratified block randomization (www.redcap.com) to ensure equal distribution of participants at the site, age (<70 years vs. 70 years or more), smoking status (Previous smoker vs. current smoker), and number of hospital-requiring exacerbations within the past 12 months (1 or more vs. 0).

The trial will have a target of 444 participants from the pulmonary outpatient clinic at Herlev-Gentofte Hospital, Amager-Hvidovre Hospital, North Zealand Hospital, Bispebjerg Hospital, Esbjerg Hospital, Roskilde Hospital and Næstved-Ringsted-Slagelse Hospital will be included in the project within 30 months, and 111 participants will be allocated to each of the four groups to be examined.

Type 1 error limit (α) of 5%. Power (1-β) of 80% (α=0.05, β=0.2).

The expected standard deviation of 150 days within 365 days.

Mean "days alive out of hospital" is expected to be 290 days in the intervention arms and 250 days for the control group (both primary analyses in the facultative design).

This gives a sample size of 444 participants (111+111+111+111).

Forty participants from each group will participate in the microbiota analysis.

Scheduled analyzes of data (Interim analysis) will be assessed when half of the participants are recruited. These assessments will be made by the independent Data and Safety Monitoring Board

(DSMB). Data on primary and secondary power targets will be used for this purpose. DSMB will review the protocol, monitor the guideline, evaluate the trial concerning the recruitment of participants, participants' risk and, based on interim analyses, make recommendations to the investigators on whether to continue or cease the study. DSMB may at any time require an extraordinary interim analysis

5.1 Primary Endpoints

The primary outcome targets admissions and death within 12 months of randomization. This is calculated in two ways:

1. "Days alive and out of hospital within 365 days after recruitment" (Continuous data: Analysis with T-test)
2. Number of hospitalization-requiring exacerbations within 12 months (Continuous data: Analysis with T-test)

5.2 Secondary Endpoints (After 3, 6, 9, and 12 months)

- Death within 12 months (Death equates to 3 exacerbations in data analysis when an exacerbation is not antecedent to death)
- Number of moderate/severe exacerbation within 12 months
- Number of mild exacerbations within 12 months
- The cumulative ICS dose
- Change in blood eosinophils (eosinophilic trajectories)
- Difference in respiratory microbiota abundance and diversity at 6 months between treatment arms
- Antibiotic-requiring infections within 90 days (0 vs. 1)
- Need for treatment with systemic corticosteroids
- Change in lung function (ΔFEV1) from baseline
- One or more ICS-induced side effects as listed below
    - Debut or worsening of diabetes mellitus (At baseline and 3 months follow-ups)
        - HbA1c ≥ 6.5% (does not apply to participants with chronic renal failure, recent transfusion or haematological disorders) * or
        - Venous fasting plasma glucose ≥ 7.0 mmol / l * or
        - Initiation or intensification of antidiabetic therapy
    - Pulmonary infections

- Change in following from baseline
    - Body mass index (of more than 1 unit) over 12 months
    - MRC-dyspnea score from < 3 to 3 ≥, over 3 months
    - COPD-related quality of life (Based on COPD Assessment Test - CAT)
- Treatment failure: Recurrence of COPD leading to emergency room visit, hospitalization or need to intensify pharmacological treatment within 30 days

- Mortality within 365 days (Access via patient journal)
- Worsening of COPD symptoms (approach via patient journal and questionnaire). This endpoint is analyzed as:
    - Recurrence of COPD exacerbation or death within 30 days
    - Time to exacerbation or death within 30 days
    - Number of admission-requiring NIV treatment or admissions to intensive care or death within 30 days

5.3 Data analysis

The four treatment groups will be compared in terms of endpoints at inclusion and follow-up visits every 3 months from trial inclusion with standard statistical tests such as t-test (Dichotomous outcomes), chi-squared test, Fisher's exact test, and time-to-event analyses.

Recurrence of AECOPD, the period between index AECOPD and the next AECOPD, and number of admission-requiring NIV treatment within 30 days are analyzed using Fisher's exact test or Chi-squared test. Time to readmission with AECOPD within 365 days and number of hospitalization-requiring exacerbations within 365 days will be analyzed with t-test and Cox proportional-hazards regression model (unadjusted and adjusted). Mortality rate with 365 days will be analyzed with Chi-squared test or Fisher's exact test (unadjusted) and with Cox proportional-hazards regression model (adjusted).

New onset or worsening of diabetes during the study period or occurrence of antibiotic-requiring infections within 90 days (0 vs. 1) will be analyzed using Fisher's exact test or Chi-squared test. Changes in lung function, Body Mass Index, health-related quality-of-life (CAT), and level of dyspnea (MRC) will be analyzed using analysis of variance (ANOVA). The cumulative ICS dose will be analyzed as mean total cumulative dose from recruitment to end of the study period using t-test, Wilcoxon signed-rank test or Mann-Whitney U test.

6. Risks and Side Effects

Possible side effects from the use of ICS according to pro.medicin.dk are:

Common (1-10%): Pharyngitis, Coughing, Hoarseness, Headache, Candidiasis.

Uncommon (0.1-1%): Blurry vision, Dizziness, Tremor.

Rare (0.01-0.1%): Allergic reactions, Angioedema, Bronchospasm.

Very rare (<0.01%): Adrenal insufficiency. Eosinophilic pneumonia. Erythemas, purpura. Decrease in bone mineral density. Glaucoma, cataract. Growth retardation.

Unknown prevalence: Disturbed behavior, Aggressiveness, Anxiety, Delirium, Hallucinations, Hyperactivity, Hypercorticism.

Possible side effects from the use of azithromycin according to pro.medicin.dk are:

Very common (>10%): Abdominal pain, diarrhoea, flatulence, nausea.

Common (1-10%): Tiredness or weakness. Decreased appetite. Vomiting, taste perversion. Decreased lymphocyte count. Decreased serum bicarbonate. Arthralgia. Headaches, Paresthesia, Dizziness. Skin itching, rash. Visual disturbances.

Uncommon (0.1-1%): Pain. Hepatitis, Oral candidiasis. Dyspnea, Pneumonia, Edema. Eosinophilia, Leukopenia, Neutropenia. Elevated serum bicarbonate, Hyperchloremia, Hyperglycemia, Hyperkaliemia, Hypernatremia, Hypokalemia, Hyponatremia. Arthritis, Back Pain. Nervousness, Somnolence. Facial oedema, Dermatitis, Photosensitivity. Candidiasis, Infections. Metrorrhagia, Kidney Pain, Testicular Disease, Vaginitis. Hearing loss, Tinnitus.

Rare (0.01-0.1%): Cholestasis, Liver Impact. Agitation. Acute generalized exanthemata, pustulosis. Allergic reactions, Angioedema, Hypersensitivity.

Unknown prevalence: Fulminant hepatitis, Hepatotoxicity, Hepatic insufficiency, Pancreatitis, Pseudomembranous colitis. Arrhythmias, Extended QT interval, Hypotension, Torsades de pointes tachycardia. Hemolytic anaemia, Thrombocytopenia. Aggravated myasthenia gravis. Aggressiveness, Anxiety, Delirium, Hallucinations, Hyperactivity, Hypesthesia, Seizures, Syncope. DRESS - drug reaction with eosinophilia and systemic symptoms, Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis. Anaphylactic reaction. Acute renal failure, Interstitial nephritis.

When taking blood, there is a small risk of infection, slight discolouration at the puncture site, and transient pain/discomfort. Bronchoscopy is associated with a small risk of minimal bleeding, infection, temporary breathing difficulties, and a low blood oxygen level during the examination. There are no known risks associated with nasosorption collection.

The Summary of Product Characteristics of ICS and Azithromycin is used as a reference when assessing whether a serious adverse reaction (SAR) is expected/unexpected and thus may be a suspected unexpected serious adverse reaction (SUSAR). Only adverse events and reactions not listed in the Product Characteristics and/or not listed as primary or secondary endpoints will be registered. Investigator must report all eligible serious side effects (SAR) to the sponsor within 24 hoursAn immediate report ensures a duly and timely report to the Danish Medicines Agency and the Scientific Ethics Committee (VEK) if it is deemed to be a SUSAR.

The sponsor must ensure that all information about SUSARs that are fatal or life-threatening is registered and reported to the Danish Medicines Agency as soon as possible and no later than 7 days after the sponsor has learned of such suspected adverse reaction. Within 8 days of the report file, the sponsor must notify the Danish Medicines Agency of all relevant information about the sponsor's and investigator's follow-up on the report. All other SUSARs must be reported to the Danish Medicines Agency within 15 days after initial notification of them, and all test managers at other centers are to be made aware of these SUSARs.

An annual list of all SARs and SUSARs that have occurred during the trial period and a report on the safety of the subjects are submitted to the Danish Medicines Agency and the Scientific Ethics Committee. In addition, all adverse reactions and events are reported at the end of the trial in the final report to the Danish Medicines Agency.

Adverse reactions and events are registered and reported only in the time frame of the trial when participants are enrolled.

7. Exclusion from or interruption of the trial

Participants may at any time terminate the study if the physician responsible for the study deems it necessary with medical justification (allergy to the medicine, safety risk, or other adverse circumstances). This must be done in agreement with the coordinating investigator of the project. The investigator can furthermore at all hours unblind the Azithromycin/placebo treatment by contacting Region Hovedstadens Apotek. The participant in question will be informed immediately of health concerns, project termination, and future treatment plan. Additionally, participants may, at any time, withdraw their informed consent. This will not have any consequence on further treatment.

8. Economy

The initiative for the trial was taken by the steering committee of COP:TRIN (Chronic Obstructive Pulmonary Disease: Trial Network) and department of pulmonary medicine at Gentofte Hospital, Herlev Hospital, Hvidovre Hospital, Bispebjerg Hospital, Nordsjælland Hospital, and Aalborg Hospital. The project budget is approximately DKK 7.433.600. This amount will cover salary to researchers, supervisors, nurses and auxiliary staff, the cost of data collection, equipment, medication, laboratory analyses and diagnostic tests, and potential hospitalizations.

Funding has been sought from various foundations, including Region H Research Fund. The Scientific Ethics Committee and the trial participants will be informed of the sponsors, their financial contribution and its part in the project, and information on grant recipient (Whether the support is paid directly to the investigators or their department/institute).

The Novo Nordisk Foundation have supported the initiative with 4.6 million DKK by a grant to Jens-Ulrik Stæhr Jensen.

The investigators have no economic interests in the research project in question and are not financially linked to private companies, foundations etc. with economic interests in the study.

8.1 Remuneration

Participants will not receive remuneration for project participation, but the cost of Azithromycin/placebo treatment during the trial period will be covered by the sponsor.

9. Publications of Trial Results

The trial is a part of a PhD thesis. The results from the trial will be published regardless of whether they are positive, negative, or inconclusive. The trial will be registered and published at clinicaltrials.gov as well as published in an international peer-reviewed scientific journal and in The Journal of the Danish Medical Association. At least one publication in a high impact scientific journal is expected. If publication in a scientific journal is not possible, the results will be published as an online report.

10. Scientific Perspective

AECOPD are often accompanied by markedly reduced lung function and increased likelihood of progression in COPD and mortality. In many cases, the illness progression following an exacerbation is irreversible. Therefore, the everyday life of COPD patient is often characterized by fear and anxiety of these acute exacerbations. In addition to the risk of exacerbations, the risk of side

effects from the medical treatment of COPD symptoms often creates additional concerns for COPD patients. Corticosteroids in the dosages given both for maintenance and for AECOPD carry high risks for the patient: dysregulation of glucose hemostasis(17), high risk of pneumonia and other infections (23, 24), and emergence or worsening of osteoporosis and the consequent fractures (8). Such side effects can lead to a vicious cycle of anxiety, physical deconditioning, muscle wasting, loss of social life, increased risk of further AECOPD, more corticosteroids and again more side effects. We believe that this trial has the potential to impact the current COPD guidelines seeing that it can provide relevant information for the development of a treatment plan that has the potential to reduce the usage of ICS by 80%[1], minimize ICS-induced complications and increase the quality of life.

As for Azithromycin, little is known about the mechanism of its effect. Only one large randomized trial has been performed on severe (50% had exacerbation in the previous year) COPD patients(22). We aim to determine how long-term azithromycin treatment alters airway inflammation and the respiratory microbiota, and whether Azithromycin can reduce exacerbation rates in COPD patients in risk class C/D.

We recognize the importance of understanding individual differences in clinical response, biological information, and microbiota changes in response to combined medication. We hope to provide an in-depth understanding of key biological and physiological mechanisms that lead to AECOPD with this study. With a better understanding of the interplay between microbiota changes and therapeutic influences on this by ICS and azithromycin, the treatment of COPD symptoms can be continuously reevaluated and adapted to each patient. Since study participants will not be exposed to irresponsible risks and can greatly benefit from the study's results and participation in the study, we believe that the study is scientifically and ethically sound.

The research project will be carried out according to the Helsinki Declaration, the Personal Data Act and the Health Act. The study will be registered in the US Clinical Trials database (www.clinicaltrials.gov), which is based on guidelines defined by The Food and Drug Administration.

11. Informed Consent

Participation in the trial is voluntary, and participants will not receive any form of financial compensation for participation. Informed is obtained from the participants of the trial in accordance

[1] 20% of COPD patients in class C/D have blood eosinophil counts ≥ 300 cells/μL

with the Executive Order no. 1149 from September 30th, 2013, on information and consent to participation in health science research projects and the report and supervision of health science research projects. Participants are protected under the Personal Data Processing Act, and the study is reported to the Regional Science Ethics Committee (VEK), the Danish Medicines Agency (Lægemiddelstyrelsen), and the Danish Data Protection Agency (Videnscenter for Dataanmeldelser).

12. Compensation and Reimbursement Schemes

The trial is covered by the patient compensation scheme. Participants can apply for compensation in accordance with Statutory Order No. 1113 of 7 November 2011 on the right of appeal and compensation in the healthcare system if participants experience unexpected damage during the trial or at inclusion.

13. References

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