**Procalcitonin-guided treatment regarding antibiotic use for acute COPD exacerbations: a prospective randomised controlled trial**

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PROTOCOL TITLE: Procalcitonin-guided treatment regarding antibiotic use for acute COPD exacerbations: a prospective randomised controlled trial

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| Protocol ID | Xx |
| Short title | PRECISION study |
| EudraCT number | Xx |
| Version | Xx |
| Date | Xx |
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| Subsidising party | |
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| Pharmacy <*if applicable*> | N.A |

**PROTOCOL SIGNATURE SHEET**

| Name | Signature | Date |
|---|---|---|
| **Head of Department:**<br>**Prof. Dr. J.G.J.V. Aerts** | | |
| **[Coordinating Investigator/Project leader/Principal Investigator]:**<br>**Dr. M.M. van der Eerden** | | |

## Synopsis

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|---|---|
| Title | Procalcitonin-guided treatment regarding antibiotic use for acute COPD exacerbations: a prospective randomized controlled trial |
| Short title | PRECISION study |
| Clinical study phase | IV |

## Summary

| | |
|---|---|
| Study objectives | The primary objective of this study is to show that at hospitalization for a severe exacerbation of COPD, PCT-guided treatment regarding antibiotic use is non-inferior to usual care consisting of prednisolone and or antibiotics, in terms of treatment failure at day 30 for patients hospitalized because of an acute exacerbation of COPD (AECOPD). Treatment failure is defined as disease-related mortality, endotracheal intubation, vasopressors, renal failure, lung abcess/empyema, pneumonia development or hospital readmission within 30 days after inclusion of the study.<br><br>The secondary objectives of this study are to assess the following secondary endpoints:<br>• Treatment failure defined as an incomplete resolution of the clinical signs and symptoms associated with the AECOPD at day 30 after inclusion of the study (i.e not reaching the baseline condition prior to the AECOPD) scored using the modified Anthonisen criteria.<br>• Change in Quality of Life on day 1, 10, and after 30 days using the COPD Assessment Test (CAT)<br>• Start of antibiotic therapy after an initial opposite decision (after 48 hours)<br>• Side effects (gastro-intestinal complaints, allergic reactions)<br>• Cumulative antibiotic consumption<br>• Cumulative prednisolone consumption<br>• Length of hospitalization<br>• Time to complete resolution of symptoms according to daily symptom diaries evaluating the modified Anthonisen criteria<br>• Re-exacerbation within 30 days<br>• PROM symptom score: EXACT – Respiratory symptoms scale (at admission, at day 10 and at day 30 after admission)<br>• Non-Invasive ventilation after 72 hours of admission |
| **Test drug**<br>**Name of active ingredient**<br><br>**Dose**<br><br>**Route of administration**<br><br>**Duration of treatment** | Amoxicillin-clavulanic acid or doxycycline (in case of a bètalactam or penicillin allergy) 875/125mg three times a day and 100mg once daily (200 mg on the first day), respectively<br><br>Oral<br><br>5 days |
| | |
| **Indication** | Severe acute exacerbation of COPD (i.e. with hospitalization) |
| **Diagnosis and main criteria for inclusion** | Inclusion criteria<br>- COPD, according to GOLD 2018 definition<br>- Hospitalization because of severe acute exacerbation of COPD<br>- Post-bronchodilator FEV1/FVC < 0,70 and FEV1% < 80%pred. within last 5 years<br>- At least 40 years of age<br>- Smokers or ex-smokers with ≥ 10 packyears |

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| | - Written informed consent<br>- Start of symptoms within 7 days before admission<br>- Presence of at least 2 major symptoms of the modified Anthonisen criteria (acute deterioration in sputum volu11me, sputum purulence and dyspnea) or the presence of 1 major symptom and 1 minor symptom (coughing, wheeze, nasal discharge, sore throat, fever)<br><br><u>Exclusion criteria</u><br>- Indication for ICU and or non-invasive ventilation < 72h of admission<br>- Pneumonia, radiologically confirmed<br>- Infection at another site and/or sepsis according to the SIRS criteria (with tachycardia and tachypnea not being caused by the exacerbation).<br>- COPD before age 40.<br>- Asthma, without presence of COPD.<br>o Patients with COPD , with or without a history of asthma (in childhood or as an adolescent) will NOT be excluded/are allowed to participate.<br>o Patients with Asthma/COPD overlap syndrome (with current asthma AND COPD) will NOT be excluded/are allowed to participate.<br>- Clinically relevant heart failure or myocardial ischemia<br>- Chronic use of immunosuppressants, including prednisolone (prednisone equivalent of 10mg or less is NOT an exclusion criterion).<br>- Known bronchiectasis as a primary diagnosis<br>- Colonisation with *Pseudomonas spp.* or other micro-organisms in recent cultures (last 60 days) not susceptible to amoxicillin-clavulanic acid<br>- Pregnancy<br>- Recent exacerbation (last 28 days) |
| **Study design** | Prospective randomized controlled trial |
| **Methodology** | Hospital based clinical trial |
| **Type of control** | Usual care, in which the physician decides on clinical reasons to prescribe prednisolone and or antibiotics |
| **Number of subjects** | 678 |
| **Primary variabel** | Treatment failure at day 30 |
| **Plan for statistical analysis** | **Primary analysis**<br>The primary endpoint is defined as 30-day treatment failure. The per protocol (PP) population is the main analysis population. The difference and corresponding 95% confidence interval (two-sided) in the incidence of the primary endpoint between the randomly allocated strategies (biomarker-guided antibiotic use minus usual care) will be determined. Non-inferiority will be concluded if the upper limit of this confidence interval does not exceed the prespecified non-inferiority margin of 5%.<br><br>**Secondary analyses**<br>Differences in the incidence of these secondary endpoints between randomly allocated strategies will be analyzed by chi-square tests and logistic regression. |
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## 1. INTRODUCTION AND RATIONALE

Chronic obstructive pulmonary disease (COPD) is a prevalent disease, worldwide, and in the Netherlands with approximately 600.000 patients. COPD is currently the 4th leading cause of death worldwide and it is estimated to be the 3rd leading cause in 2020 (1-3). It is also a leading cause of disability-adjusted life years and with increasing prevalence the loss will also increase. The burden on health-care system is therefore impressing: COPD accounts for just over 3% of the total health care budget in the European Union. The majority of these costs are attributed to acute exacerbations of COPD (AECOPD) (4).
Reducing the burden of disease for patients (mortality and disability adjusted life years) and for society (costs) of this leading chronic disease is therefore of paramount importance. Given the contribution of exacerbations both to loss in quality of life and to costs, it is of major importance to improve the current treatment of exacerbations. Treatment of AECOPD generally consists of corticosteroids to reduce airway inflammation and antibiotics to treat bacterial infections, mostly in one-size fits all fashion.

Pulmonary physicians are well aware of overuse of both antibiotics and of prednisolone, but lack the tools to decide which medication to give on in the clinical setting. As a consequence, in the Netherlands 65% of patients hospitalized for COPD receive antibiotics (Landelijk Zorgpad COPD 2018). This overuse is important not only for the costs incurred for giving useless therapy, but there are also major side effects, the more frequent ones being gastrointestinal complaints. Finally, the overuse of antibiotics results in induction of antibiotic resistance, a worldwide grave concern.
Biomarkers may aid towards a more personalized treatment of AECOPD by identifying which patient would benefit from antibiotics. Procalcitonin (PCT) is the precursor of calcitonin and is released in response to a bacterial infection within 6-12 hours by many tissues under stimulation of several cytokines. Procalcitonin levels are minimally raised in viral infections (5), making it a relative specific diagnostic tool for bacterial infections. Several trials have shown a reduction in antibiotic consumption in AECOPD when using a PCT-guided treatment algorithm (6-9). One meta-analysis about the use of PCT to guide antibiotic administration in AECOPD suggested that PCT-based protocols may be superior to standard care in a mixed group of patients and indications (10). In this meta-analysis 7 of the 8 included trials, including trials performed by Stolz et al. (Chest 2007), Verduri et al. (PLoS ONE 2015) and Corti et al. (Int J of COPD 2016) recommended starting antibiotic therapy for procalcitonin levels > 0.25ug/L (or 0.25ng/mL), (6a,b,c) This meta-analysis included the before mentioned study by Schuetz et al. (6). To be able to compare our results to these important international studies we decided to use the same cut-off value. The quality of the data of the meta-analysis was judged low to moderate, necessitating appropriately powered confirmatory trials before recommending introducing such strategies in daily clinical practice (10).
In summary, PCT has not been tested in a clinical setting in a treatment algorithm specifically in COPD with the primary outcome measure being treatment failure.

## 2. OBJECTIVES

We hypothesize that at hospitalization for a severe acute exacerbation for COPD, biomarker-guided treatment based on procalcitonin level to guide antibiotic administration is non-

inferior to usual care consisting of prednisolone and or antibiotics, which is based on a clinical decision, in terms of treatment failure at day 30.
The secondary objectives are to establish that a biomarker-guided decision algorithm results in an improvement in quality of life, a decrease in consumption of antibiotics, and a reduction of important side effects.

## 3. STUDY DESIGN

Study design: prospective randomized controlled trial.

Patients will be randomized to biomarker-guided treatment (based on blood procalcitonin level) or to usual care. In the usual care arm, and in the biomarker guided-arm in case of high procalcitonin, patients will receive amoxicillin-clavulanic acid.
Prednisolone will be given during 5 days and with a dose of 40mg/day in a single dose as recommended by the Dutch National Guideline (16).

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|---|---|---|
| **Usual care** | **Physician's choice** | **Prednisolone ± antibiotics** |
| **PCT level guided care** | **PCT ≤ 0.25ug/L** | **Prednisolone** |
| | **PCT > 0.25ug/L** | **Prednisolone + amoxicillin-clavulanic acid** |

The procalcitonin will be measured in both groups but will only be reported for the patients randomised to the PCT group and not for patients in the usual care group during the study period. The measurement will be performed in the usual care group but this will be blinded until the study is completed.

## 4. STUDY POPULATION

### 4.1 Population (base)

Patients with a severe exacerbation of COPD, defined according to the GOLD criteria (3) and modified Anthonisen criteria (13,14), for which they need to be hospitalized.

### 4.2 Inclusion criteria

- COPD, according to GOLD 2018 definition
- Indication for hospitalization because of acute severe exacerbation of COPD, as defined by GOLD 2018 and modified Anthonisen criteria (13,14)
- Presence of at least 2 major symptoms of the modified Anthonisen criteria (acute deterioration in sputum volume, sputum purulence and dyspnea) or the presence of 1 major symptom and 1 minor symptom (coughing, wheeze, nasal discharge, sore throat, fever)
- Post-bronchodilator FEV1/FVC < 0,70 and FEV1% < 80%pred. within last 5 years
- At least 40 years
- Smokers or ex-smokers with $\geq$ 10 packyears
- Written informed consent
- Start of symptoms no more than 7 days before admission

**4.3 Exclusion criteria**

- Indication for ICU and or non-invasive ventilation < 72h of admission
- Pneumonia, radiologically confirmed
- Infection at another site and/or sepsis according to the SIRS criteria (with tachycardia and tachypnea not being caused by the exacerbation).
- COPD before age 40.
- Asthma, without presence of COPD.
    - Patients with COPD , with or without a history of asthma (in childhood or as an adolescent) will NOT be excluded/are allowed to participate.
    - Patients with Asthma/COPD overlap syndrome (with current asthma AND COPD) will NOT be excluded/are allowed to participate.
- Clinically relevant heart failure or myocardial ischemia
- Chronic use of immunosuppressants, including prednisolone (a prednisone equivalent of 10mg or less is allowed/is NOT an exclusion criterion)
- Known bronchiectasis as a primary diagnosis
- Colonisation with Pseudomonas spp. or other micro-organisms in recent cultures (last 60 days) not susceptible to amoxicillin-clavulanic acid
- Pregnancy
- Recent exacerbation (last 28 days)

**4.4 Sample size calculation**

In international literature there is scarce information about the percentages of treatment failure in patients admitted with an AECOPD receiving usual care. Therefore, we have performed a further search on PCT studies with a primary outcome of 30-day treatment failure. In the study by Schuetz et al. (JAMA 2009), who studied patients with lower respiratory tract infection, 30-day treatment failure was observed in 15.5% of the patients randomised to biomarker-based treatment, as compared to 18.9% in those randomised to usual care. This implies a relative risk of 0.82 in favour of the biomarker-based strategy. The study by Schuetz et al. was designed as a non-inferiority study, using a non-inferiority boundary of 7.5%. In view of these data we decided to design our study as a non-inferior study, whereas we choose a non-inferiority boundary of 5.0%. We based the primary outcome on the study of Huang et al. (NEJM 2018) (15). The incidence of the primary outcome was 20.4%. Using the relative risk of 0.82 in favour of the PCT-guided treatment group we expect the incidence of the primary outcome to be 16.7% in the PCT-guided treatment group. Then a total sample size of 626 is required (313 per treatment arm) to demonstrate non-inferiority with a power of 80%, and applying a one-sided alpha error of 0.025. We aim to enroll a total of 690 patients, accounting for a 10% drop-out rate. Because of an interim-analysis this number of patients will increase to 693 (as detailed below in section 10.4).

**5. TREATMENT OF SUBJECTS**

Patients will be randomized into:

- biomarker-guided treatment based on blood procalcitonin level to receive amoxicillin-clavulanic acid 875/125 mg three times a day for 5 days or no antibiotic treatment depending on the serum PCT-level

*or alternatively to*

- usual care depending on the clinical decision of the physician to start or to withhold antibiotic treatment consisting of amoxicillin-clavulanic acid three times a day 875/125mg. The duration of treatment will also be by physician's choice.

*In case of a bètalactam or penicillin allergy:*

- *doxycycline 100mg (200 mg on the first day) once daily for 5 days*

All patients will receive prednisolone 40mg once a day during 5 days, following the Dutch national guideline (16).
Next to antibiotics and prednisolone allocation as detailed above, all patients will additionally receive all standard care according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 guidelines and the Dutch guideline for care for patients with an acute exacerbation of COPD (16).

**5.1 Investigational product/treatment**
Patients will receive amoxicillin-clavulanic acid or no antibiotic therapy

**5.2 Use of co-intervention (if applicable)**
N.A.

**5.3 Escape medication (if applicable)**
**5.3.1** N.A.

## 6. INVESTIGATIONAL PRODUCT

### 6.1 Name and description of investigational product(s)
N.A.

### 6.2 Summary of findings from non-clinical studies
N.A.

### 6.3 Summary of findings from clinical studies
N.A.

### 6.4 Summary of known and potential risks and benefits
N.A.

### 6.5 Description and justification of route of administration and dosage
N.A.

### 6.6 Dosages, dosage modifications and method of administration
N.A.

### 6.7 Preparation and labelling of Investigational Medicinal Product
N.A.

### 6.8 Drug accountability
N.A.

## 7. NON-INVESTIGATIONAL PRODUCT

### 7.1 Name and description of non-investigational product(s)

Not applicable: it is standard of care in all guidelines to administer prednisolone and antibiotics in the majority of patients. Our drugs and dosing are within registration label and adhere to the Dutch guideline for in-hospital treatment of COPD exacerbations (16) (in line with GOLD 2018).

### 7.2 Summary of findings from non-clinical studies

These are not presented here: it is standard of care in all guidelines to administer prednisolone and antibiotics in the majority of patients. Our drugs and dosing are within registration label and adhere to the Dutch guideline for in-hospital treatment of COPD exacerbations (16) (in line with GOLD 2018).

### 7.3 Summary of findings from clinical studies

Appendix 1

### 7.4 Summary of known and potential risks and benefits

Appendix 1

### 7.5 Description and justification of route of administration and dosage

Appendix 1

### 7.6 Dosages, dosage modifications and method of administration

Appendix 1

### 7.7 Preparation and labelling of Non Investigational Medicinal Product

Appendix 1

### 7.8 Drug accountability

N.A.

## 8. METHODS

### 8.1 Study parameters/endpoints

#### 8.1.1 Main study parameter/endpoint

The primary objective of this study is to show that at hospitalization for a severe exacerbation of COPD, PCT-guided treatment regarding antibiotic use is non-inferior to usual care consisting of prednisolone and or antibiotics, in terms of treatment failure at day 30 for patients hospitalized because of an acute exacerbation of COPD (AECOPD). Treatment failure is defined as disease-related mortality, need for endotracheal intubation or vasopressors, renal failure*, lung abcess/empyema, development of pneumonia or rehospitalization within 30 days after inclusion.

*renal failure is defined as Kidney Disease: Improving Global Outcomes (KDIGO) stage 3 – new renal replacement therapy, tripling of baseline creatinine, or serum creatinine ≥ 350 umol/L.

#### 8.1.2 Secondary study parameters/endpoints

The secondary objectives of this study are to assess the following secondary endpoints:-

The key secondary objective is:
- Treatment failure defined as an incomplete resolution of the clinical signs and symptoms associated with the AECOPD at day 30 after inclusion of the study (i.e not reaching the baseline condition prior to the AECOPD) scored using the modified Anthonisen criteria.

The other secondary objectives are:

- Change in Quality of Life on day 1, 10, and after 30 days using the COPD Assessment Test (CAT)
- Decision to start antibiotic therapy after an initial opposite decision (after 48 hours)
- Side effects (gastro-intestinal complaints, allergic reactions)
- Cumulative antibiotic consumption
- Cumulative prednisolone consumption
- Length of hospitalization
- Time to complete resolution of symptoms according to daily symptom diaries evaluating the modified Anthonisen criteria
- Re-exacerbation within 30 days
- PROM symptom score: EXACT – Respiratory symptoms scale (at admission, at day 10 and at day 30 after admission)
- Non-Invasive ventilation after 72 hours of admission

#### 8.1.3 Other study parameters (if applicable)

Demographics
Vital signs
Sputum for routine bacterial cultures
Serum sample for storage at -80 degrees Celsius
Sputum sample for storage at -80 degrees Celsius
Charlson Comorbidity Index

Cost-effectiveness analysis (CEA):

- General considerations

Alongside the clinical trial, an economic evaluation will be performed conform the guidelines of the Health Care Institute Netherlands (17). This evaluation will be conducted from a societal and payer's perspective. When adopting the societal perspective, costs will include 30-day inpatient and outpatient (emergency room, specialist visits) hospital costs, primary care costs (visits to GP and nurse practitioner), medication costs, ambulance costs, productivity costs, informal care costs and travel costs.

- Cost analysis

The resource utilization underlying these costs will be obtained from a combination of sources, including case report forms, hospital administrative systems and a patient's self-reported questionnaire, which is based on an adapted version of the iMTA Medical Consumption Questionnaire (iMCQ) (18). When adopting the payer's perspective only the costs covered by the Health Insurance Act will be included. Unit costs will be based on reference prices obtained from the costing manual (19). In a sensitivity analysis we will adjust the unit cost of a hospital day to reflect ward-specific and hospitalization-day-specific costs instead of average costs based on all patients in a hospital. Productivity costs will be based on the Friction Cost method (20).
Savings in health care costs are expected to result from a reduction in antibiotics use, a reduced length of stay and a reduction in the incidence of side-effects from antibiotics. These savings will be compared to the additional costs of adopting the procalcitonin-guided treatment, including the costs of additional lab tests.

- Patient outcome analysis

The difference in total costs between the two groups will be related to the difference in the following outcomes: QALYs, treatment failures and CAT (COPD Assessment Test). This will result in the following incremental cost-effectiveness ratios (ICER): costs per QALY, costs per treatment failure avoided and costs per additional patient with at least one MCID improvement in CAT. The utilities to calculate QALYs will be measured with the EQ-5D-5L with and without the respiratory bolt-on (21). The ICER's will be estimated using a decision tree model that synthesizes the evidence collected during the clinical trial. The uncertainty around the ICER will be estimated in probabilistic sensitivity analysis, the results of which will be graphically shown in a CE-plane and Cost-Effectiveness Acceptability Curve.

Budget impact analysis (BIA):

- General considerations

A budget impact model to estimate the impact of large-scale implementation of the intervention will be developed. This model will be a transparent cost calculator that includes nation-wide estimates of the size of the COPD population that is hospitalized for exacerbations, scenarios on the proportion and speed of uptake of the procalcitonin-guided AECOPD treatment, and changes in costs as a result of this.

o Cost analysis
These analyses will be conducted in accordance with the ISPOR and Dutch guidelines of ZONMW, for time horizons between 1 and 5 years (22, 23).

**8.2 Randomisation, blinding and treatment allocation**
Upon presentation at the emergency department, patients will be clinically judged for in- and exclusion criteria, among which indication for hospitalization. When eligible the patient will be notified about the study. When the patient is interested in participating, the patient information form will be discussed by the treating physician. The participation being voluntarily and the opportunity to discontinue participation will be made clear by the treating physician. Informed consent will be requested with at least two hours of time to decide. Randomisation will occur by a computer-based program. We will use a block-randomisation with randomly alternating blocks of 4 or 6 patients (random permuted block randomisation) and with stratification by center and with stratification by pre-treatment with antibiotics. The patient will not be blinded for the treatment received (prednisolone with or without antibiotic therapy) but the patient will be blinded for the treatment strategy (usual care or PCT-guided treatment). The participating centers will appoint two physicians that will be outcome assessors. The outcome assessors will be blinded for the treatment strategy.

**8.3 Study procedures**
***Study period:***
All the assessments will be done at baseline, at day 10 and day 30.
Patients diary cards will be reviewed at each visit for symptoms and exacerbations

| | Day 1 | Day 3 | Day 5 | Day 10 | Day 30 |
|---|---|---|---|---|---|
| **Initiation procedures** | | | | | |
| Informed consent | X | | | | |
| Medication history | X | | | | |
| Vital signs | X | | | | |
| Check for eligibility | X | | | | |
| Sputum collection | X | | | | |
| Blood sampling, including procalcitonin* | X | | | | |
| Blood sampling CRP, eosinophils | x | | | | |
| Serum for storage | X | | | | |
| Sputum for storage | X | | | | |
| Modified Anthonisen criteria | X | X | X | X | X |
| Clinical assessment for treatment failure | | X | X | X | X |
| CAT | X | | | X | X |
| E-RS | X | | | X | X |
| EQ-5D-5L | X | | | X | X |
| iMCQ | | | | | X |
| Randomization | X | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Antibiotic consumption | X | X | X | X | X |
| Diary cards according to modified Anthonisen criteria** | X | X | X | X | X |
| Assessment of adverse effects | x | X | X | X | X |

* (PCT will only be reported for the randomised PCT group and not for the usual care group during the study period. The measurement will be performed in the usual care group but this will be blinded until the study ends.)
** This symptom card will be evaluated on the given days by the patient

**8.4 Withdrawal of individual subjects**
After signing the informed consent, patients still are allowed to withdraw from the study. Every attempt will be made to collect the primary end-point. Withdrawal by the investigator will mainly be because of safety reasons and mostly constitute a treatment failure.

**8.4.1. Specific criteria for withdrawal (if applicable)**
**N/A**

**8.5 Replacement of individual subject after withdrawal**
No subjects will be replaced in the study as soon as the quotum is reached of randomised subjects.

**8.6 Follow-up of subjects withdrawn from treatment**
Patients who are withdrawn from the study will be invited for a follow up visit as detailed above, and otherwise it will be attempted to collect data on the primary end-points as long as this is within the agreement of the informed consent.

**8.7 Premature termination of the study**
N/A

## 9. SAFETY REPORTING

### 9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except in so far as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

### 9.2 AEs, SAEs and SUSARs

#### 9.2.1 Adverse events (AEs)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavourable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in

the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In the following differentiation between medical history and AEs, the term 'condition' may include abnormal e.g. physical examination findings, symptoms, diseases, laboratory, pulmonary function test (PFT).

All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Common expected adverse events are:
- Diarrhoea
- Gastric complaints

### 9.2.2 Serious adverse events (SAEs)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a-f):

a) Results in death;
b) In life-threatening:
   The term 'life-threatening' in the definition refers to an event in which the subject was at risk of death at the time of the event, it does not refer to an event, which hypothetically might have caused death if it were more severe
c) Requires inpatient hospitalization or prolongation of existing hospitalization
   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exception is met:
   - The admission results in a hospital stay of less than 12 hours
   - The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study);
   - The admission is not associated with an AE (e.g., social hospitalization for purposes of respite care).

   However, it should be noted that invasive treatment during a hospitalization may fulfil the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.
d) Results in persistent or significant disability / incapacity
   Disability means a substantial disruption of a person's ability to conduct normal life's functions
e) Is a congenital anomaly / birth defect;
f) Is another medically important serious advent as judged by the investigator

When a SAE is reported spontaneously by the subject or observed by the principal investigator or his staff it will be reported to the coordinating investigator in the ErasmusMC.
The coordinating investigator will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reaction.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

### 9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:

a) Summary of Product Characteristics (SPC) for an authorised medicinal product;
b) Investigator's Brochure for an unauthorised medicinal product.

The coordinating investigator in the ErasmusMC will report expedited the following SUSARs through the web portal ToetsingOnline to the METC:
- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The coordinating investigator will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

## 9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the coordinating investigator will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;

- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

### 9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

### 9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

An interim analysis will be performed at 50% of patient accrual, analysing the primary outcome and safety data. The safety data consists of observed adverse events and SAE. A DSMB will assess this interim analysis. The members of the DSMB will be dr. Gert-Jan Braunstahl (pulmonologist Franciscus Gasthuis & Vlietland), dr. Mireille van Westreenen (medical microbiologist Erasmus Medical Center) and prof. dr. ir. Eric (H.) Boersma (Professor of Clinical Epidemiology of Cardiovascular Diseases Erasmus Medical Center).
The advice(s) of the DSMB will only be sent to the principal investigator of the study. Should the principal investigator decide not to fully implement the advice of the DSMB, the principal investigator will send the advice to the reviewing Ethical Committee (in Dutch: METC), including a note to substantiate why (part of) the advice of the DSMB will not be followed.

Criteria on which the DSMB may decide to terminate the trial prematurely are:
1. Any serious adverse event related to the treatment under investigation has occurred.
2. A significant evidence of benefit

## 10. STATISTICAL ANALYSIS

There will be two analysis populations for this study:

1. The Intention-to-Treat (ITT) population is defined as all randomised patients who took at least one dose of study drug.

2. The Per-Protocol (PP) population is defined as a subset of ITT population constituted by those patients who: a) met all inclusion/exclusion criteria, b) attained a sufficient compliance to the treatment received, treatment with prednisolone and/or antibiotics, when prescribed on admission for at least 5 days, and c) did not present serious deviations from the protocol.

The analysis of all the efficacy variables will be performed on both the ITT and the PP populations in order to assess the robustness of the findings from the ITT population.
All the demographic and baseline patients' characteristics and safety outcomes will be analysed using the ITT population.
All efficacy variables will be analysed for ITT and the PPS, and the PP population will be considered the primary population for assessing efficacy.

### 10.1 Primary study parameter(s)

The primary objective of this study is to show that at hospitalization for a severe exacerbation of COPD, PCT-guided treatment regarding antibiotic use is non-inferior to usual care consisting of prednisolone and or antibiotics, in terms of treatment failure at day 30 for patients hospitalized because of an acute exacerbation of COPD (AECOPD). Treatment failure is defined as disease-related mortality, need for endotracheal intubation or vasopressors, renal failure*, lung abcess/empyema, development of pneumonia or rehospitalization within 30 days after inclusion.

*renal failure is defined as Kidney Disease: Improving Global Outcomes (KDIGO) stage 3 – new renal replacement therapy, tripling of baseline creatinine, or serum creatinine ≥ 350 umol/L.

### 10.2 Secondary study parameter(s)

Key secondary outcome:
- Treatment failure defined as an incomplete resolution of the clinical signs and symptoms associated with the AECOPD at day 30 after inclusion of the study (i.e not reaching the baseline condition prior to the AECOPD) scored using the modified Anthonisen criteria.

Other secondary outcomes:

- Change in Quality of Life on day 1, 10, and after 30 days using the COPD Assessment Test (CAT)Start of antibiotic therapy after an initial opposite decision (after 48 hours)
- Side effects (gastro-intestinal complaints, allergic reactions)
- Cumulative antibiotic consumption
- Cumulative prednisolone consumption
- Length of hospitalization
- Time to complete resolution of symptoms according to daily symptom diaries evaluating the modified Anthonisen criteria
- Re-exacerbation within 30 days
- PROM symptom score: EXACT – Respiratory symptoms scale (at admission, at day 10 and at day 30 after admission)
- ICU admission after 72 hours of admission
- Non-Invasive ventilation after 72 hours of admission

### 10.3 Other study parameters

Demographics
Vital signs
Sputum for routine bacterial cultures
Serum sample for storage at -80 degrees Celsius
Sputum sample for storage at -80 degrees Celsius
Charlson comorbidity index
Cost effectiveness analysis, as detailed above in section 8.1.3

**Statistical and analytical plans**

**Primary analysis**

The primary endpoint is defined as 30-day treatment failure. The per protocol (PP) population is the main analysis population. An analysis will be performed for the randomly

allocated antibiotic strategy (i.e. usual care versus antibiotics in patients with PCT >0.25 µg/L). The difference and corresponding 95% confidence interval (two-sided) in the incidence of the primary endpoint between the randomly allocated strategies (biomarker-guided drug use minus drug-in-all) will be determined. Non-inferiority will be concluded if the upper limit of the 95% confidence interval does not exceed the prespecified non-inferiority margin of 5%.

**Secondary analyses**

The minimal clinically important difference (MCID) of the COPD Assessment Test (CAT) is considered to be a decrease of 2 to 3 points (after rehabilitation) and a decrease of 2 points according to Kon et al. who conducted 3 trials, in patients who underwent rehabilitation, paients who were admitted to the hospital because of an exacerbation and outpatient who were stable (24, 25). We will consider a decrease of 2 points as a minimal clinically important difference. The definition of symptomatic improvement of the E-RS is RS-total ≥ -2.0 (scale range 0-40) (26). Adverse events will be compared by total number of adverse events, of serious adverse events, and separately for gastro-intestinal complaints. Differences in the incidence of these secondary endpoints between randomly allocated strategies will be analyzed by chi-square tests and logistic regression. Secondary endpoints consisting of continuous variables will be analyzed either using the unpaired t-test (for variables with normal distribution) or the Man-Whitney-U test (for variables with a skewed distribution). The distribution will be analyzed when the results are complete.

### 10.4 Interim analysis (if applicable)

An interim analysis will be performed after 50% of the participants needed has been accrued/included. The analysis will focus on the primary outcome and on safety. The non-inferiority design of the study means that a clear disadvantage of the PCT-guided treatment arm or in other words a clear benefit of the usual care arm will lead to discontinuation of the trial. The p-value at the interim analysis will be 0.0054 according to the O'Brien-Fleming method, and the p-value at final analysis will be 0.0492 (27). The safety data consists of observed adverse events and SAE. The change of the p-value at final analysis will lead to an increase of 2 patients per treatment arm. The number of patients per treatment arm will be 315. Using a 10% drop-out rate this will lead to a total number of patients of 693.

## 11. ETHICAL CONSIDERATIONS

### 11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (59th WMA General Assembly, Seoul, Korea, October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

### 11.2 Recruitment and consent

This study will include 693 patients during a 48-month period. Annually, there are around 23,000 hospital admissions for AECOPD in the Netherlands (28). Nine centers will participate in the study: Amphia hospital (Breda), Erasmus MC (Rotterdam) Groene Hart (Gouda), Isala clinics (Zwolle), North West Hospital Group (Alkmaar), OLVG Oost (Amsterdam), the Sint Franciscus Gasthuis (Rotterdam), Zuyderland (Heerlen), Bravis Hospital (Bergen op Zoom/Roosendaal) , MST (Enschede) and Catharina hospital (Eindhoven).

Informed consent forms will be presented before start of the study. Only patients that signed the informed consent will be entered in the study. Subject's written informed consent will be obtained prior to any study-related procedures. At any time patients have the right to withdraw from the study without any consequences for their ongoing treatment. For further details, see 8.4.

### 11.3 Objection by minors or incapacitated subjects (if applicable)

**N/A**

### 11.4 Benefits and risks assessment, group relatedness

Benefits: The main problem is the worldwide overuse of antibiotics contributing to the induction of global antibiotic resistance. We expect that a biomarker-based intervention using PCT to guide antibiotic treatment next to being non-inferior regarding treatment failure, will decrease the number of adverse effects and improve quality of life.

Risks assessments: Common side effects of antibiotics are diarrhoea and other gastro-intestinal complaints.

### 11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

### 11.6 Incentives (if applicable)

**N.A.**

## 12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

### 12.1 Handling and storage of data and documents

Data will be handled and collected in compliance with ICH-GCP (Good Clinical Practice) and in accordance with prevailing national and international regulations, principles and guidelines such as VSNU code, NFU, WGBO and WMO and Erasmus MC policy on clinical trials ("Richtlijn wetenschappelijke integriteit Erasmus MC", "Erasmus MC Onderzoeksbeleid")

**Database**

For randomization, clinical data collection and central data management, Castor® will be used. Castor® is a web-based software tool designed to capture clinical study data. Castor® is hosted by an external party (Castor EDC), which is validated for conducting clinical trials in the Erasmus MC and meets all requirements to be ICH-GCP compliant.

The standard way to capture data in clinical studies is via e-CRFs which are specifically designed to collect study data in a structured format. Castor® allows sponsors (or their delegates) to design, manage and complete study specific e-CRFs. The e-CRFs can be completed for all participating subjects and can be reached from various locations in the world, allowing Castor® to be used for multicenter studies.

**CRF design**
The sponsor of the study will design CRFs that accurately represent the protocol of the clinical study. The study specific CRFs will be designed in such a way that they accurately capture the required data for addressing the study objectives as outlined in the protocol of the clinical study. They should be parsimoniously (i.e. only collect what is needed to know, not what is nice to know) while at the same time being complete (i.e. no critical omissions leading to incomplete data).

**Audit trail and data back-up**
One of Castor®'s prime features is that it keeps an audit trail, i.e. provides documentary evidence of the sequence of activities by user that have affected at any time a specific operation, procedure, or event. Data cannot be permanently deleted, ensuring proper backing-up of data. With regard to data entry, each change after submission will need to be accompanied by a reason for change.

**Data entry**
Data entry will be done according to Standard Operating Procedures. Besides, study specific data entry guidelines will be provided to local datamanagers, promoting a uniform and standardized way of data entry and providing ways of working in case of exceptions (i.e. missings, unknowns etc). The local datamanagers will be trained in using the eCRF system Castor® prior to data entry start. All trainings will be documented conform GCP requirements.

### 12.2 Monitoring and Quality Assurance
A study specific monitoring plan, compliant with NFU guidelines and the Erasmus MC requirements for the METC approved monitoring risk (i.e. minimal, medium or high, will be written. This study specific monitoring plan will focus both on quality assurance and cost efficiency.
Throughout the trial, a trained, qualified and independent monitor will periodically visit each participating site in order to, among other things, randomly check compliance with the protocol, compliance with in- and exclusion criteria, proper implementation and conduct of Informed Consent procedures, Source Data Verification (i.e. cross-check data in Castor® with patient dossier and vice versa) and SAE reporting.
Findings will be discussed with the Local Investigator and reported in a standard monitor report that will be shared with and filed by the Sponsor. The monitor will also feed any relevant findings back to the person(s) responsible for data validation (central data management).

**Data validation/ Central Data management**
For critical data, i.e. data prone to errors, front-end validation checks (i.e. error messages) may be applied, preventing users from incorrect or illogical data entry.
Advanced back-end data consistency checks, focusing on missings, inconsistencies and outliers will be applied as batch cleanings to filter affected records. Affected records (i.e. missings, outliers) will be dealt with appropriately. That is, data queries will be generated and sent to the respective participating site. The participating site will have to address these queries until they are resolved satisfactory.
Timely data entry will be monitored throughout and reminders will be sent in case of delays.

A comprehensive study specific data management, detailing which data should be handled when, how, and by whom until they are deemed validated for data analyses, will be written prior to study commencement and reviewed/edited throughout the trial if so needed.

### 12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.
< *Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation*.>

### 12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

### 12.5 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 180 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

### 12.6 Public disclosure and publication policy

This study is an investigator-initiated study. Therefore, arrangements concerning the public disclosure and publication between the sponsor and the investigator are not applicable. Results of this study will be disclosed to the public without any restrictions.

## 13. STRUCTURED RISK ANALYSIS

### 13.1 Potential issues of concern

Patients in both groups will either receive amoxicillin-clavulanic acid 875/125mg three times a day during five days or no antibiotic therapy. Common expected adverse events are: diarrhoea and other gastro-intestinal complaints. Patients will receive diary cards, these diary cards will be reviewed at each visits for symptoms, adverse events and exacerbations. In case of an adverse event measures will be taken to treat the existing adverse event.

### 13.2 Synthesis

It is standard of care in all guidelines to administer prednisolone and antibiotics in the majority of COPD patients. Our drugs and dosing are within registration label and adhere to the Dutch guideline for treatment of COPD exacerbations in the hospital (15) (in line with GOLD 2018). We expect that risks of experiencing adverse events are acceptable for the subjects participating in the study.

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