IWT – TBM project

2013 - 2017

Azithromycin for acute COPD exacerbations with hospitalization

the BACE trial

For this study, the protocol and subsequent protocol amendments were released as follows:

- **Original Protocol**, Version 2, dated 17 April 2014
- **Amendment 1**
  forming integrated protocol Version 3, dated 27 May 2014
- **Amendment 2**
  forming integrated protocol Version 4, dated 23 June 2014
- **Amendment 3**
  forming integrated protocol Version 5, dated 12 November 2014
- **Amendment 4**
  forming integrated protocol Version 6, dated 07 August 2015
- **Amendment 5**
  forming integrated protocol Version 7, dated 12 October 2016

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Project Fiche

Title of the project: Azithromycin for acute COPD exacerbations with hospitalization

Recruitment start: April 2014

Steering committee:

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Protocol Signature Page

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I agree to conduct the study in accordance with the protocol described in this document and in compliance with Good Clinical Practice and applicable regulatory requirements.

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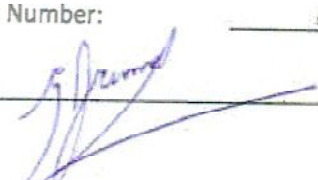Telephone Number: _____

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Protocol Synopsis

Titel of Study:	
	AZITHROMYCIN FOR ACUTE COPD EXACERBATIONS WITH HOSPITALIZATION
Abbreviated Titel:	The BACE trial
Phase:	3
Indication:	Chronic Obstructive Pulonary Disease (COPD)

Study Objectives / Endpoints:	To compare the following endpoints for the azithromycin (intervention) arm with the placebo (control) arm in patients with COPD
	Primary:
	  * Time to clinical failure
	(defined as either death or the referral to intensive care for respiratory reasons, the requirement of additional systemic steroids or new antibiotics for respiratory reasons, or the diagnosis of a new exacerbation after discharge)
	Secondary:
	  * Clinical failures
	  * Time to new exacerbation
	  * Number of new exacerbations
	  * Rate of exacerbations
	  * Days of hospitalization
	  * Days of intensive care
	  * Symptom and quality of life scores (SSQ5, mMRC, EQ5D, CAT)
	  * Pre- and post-bronchodilator FEV1
	  * Total dose of systemic steroids
	  * Total days of steroid use
	  * Total days of antibiotics use
	  * Home physician contacts
	  * Average costs of hospitalization

Study Design:	This is a multicenter, placebo-controlled, randomized, double-blind Phase 3 comparison study evaluating the effectiveness and safety of azithromycin versus placebo in patients with COPD. Patients will be randomly assigned (1:1) to azithromycin (intervention arm) or placebo (control arm).

Study Duration:	Subjects will continue on treatment until at least one of the following occurs:
	  * Death
	  * Unacceptable toxicity
	  * Subject withdraws consent
	  * Treating physician determines discontinuation of treatment is in the subject's best interest
	  * Substantial non-compliance with the protocol

Study Population:	Adult male and female patients (age 18 years or older) with COPD

Main criteria for inclusion:	A patient must meet all of the following inclusion criteria to be eligible for enrollment in this study:
	    1/ Established diagnosis of COPD by medical doctor (based on clinical
	        history or pulmonary function test)
	    2/ Smoking history of at least 10 pack-years
	    3/ Current hospitalization for potential infectious AECOPD treated with standard therapy
	Standard therapy is defined as:
	-Systemic steroids (methylprednisolone) for 5 days, then stop
	 Fixed regimen: 40 mg IV or 32 mg PO (5d)
	 Switch to PO as soon as possible
	-Short-acting bronchodilators via inhalation
	-Antibiotics
	 First choice: fixed regimen of Amoxi-clavulanate 1g IV QID or 2g PO BID for 7d or
	                 alternative regimen of 1 g IV QID or 875/125 mg PO TID for 7 days
	 Alternatives: -Moxifloxacin 400 mg IV or 400 mg PO QD for 5 days
	                 (in case of intolerance or allergy to Amoxi-clavulanate)
	                 (in case of clinical failure on GP initiated Amoxi-clavulanate)
	              -Anti-pseudomonas antibiotics
	               (only in case of bronchiectasis, positive cultures for
	               Pseudomonas in history, high risk of Pseudomonas including
	               failure with GP initiated antibiotics)
	-Oxygen
	-Noninvasive ventilation or mechanical ventilation if needed (only exclusion for randomization if still ongoing at 48-hours post admission)
	    4/ History of at least one exacerbation during the last year for which
	        systemic steroids and/or antibiotics were taken
	    5/ ECG at admission

Main criteria for exclusion:	Exclude a patient from this study if any of the following conditions are observed:
	    1/ Mechanical or non-invasive ventilation at moment of randomization (D1)
	    2/ Long QT interval on ECG (QTc > 450msec for males or > 470msec for
	        females)
	    3/ History of life-threatening arrhythmias
	    4/ Myocardial infarction (NSTEMI or STEMI) less than 6 weeks before start
	        of study drug
	    5/ Unstable angina or acute myocardial infarction (NSTEMI or STEMI) at
	        admission
	    6/ Drugs with high risk for long QT interval and torsade de pointes
	        (amiodarone, flecainide, procainamide, sotalol, droperidol, haldol,
	        citalopram, other macrolides)
	    7/ Documented uncorrected severe hypokalemia ($K^+ < 3.0$ mmol/L) or
	        hypomagnesemia ($Mg^{2+} < 0.5$ mmol/L)
	    8/ Chronic systemic steroids (> 4 mg methylprednisolone /day for ≥ 2
	        months)
	    9/ Actual use of macrolides for at least 2 weeks
	    10/ Allergy to macrolides
	    11/ Active cancer treatment
	    12/ Life expectancy < 3 months
	    13/ Pregnant or breast-feeding subjects. Woman of childbearing potential
	        must have a pregnancy test performed and a negative result must be
	        documented before start of treatment

Identity of Study Medication:	Study medication (azithromycin or placebo) will be provided as tablets. 1 tablet = 250 mg.
Treatment Regimen:	The treatment phase with azithromycin or placebo is 90 days after which the patient will be followed-up for an additional 180 days.
Dose:	**D1-D3** : 500 mg (= 2 tablets) azithromycin or placebo once a day **D4-D90:** 250 mg (= 1 tablet) azithromycin or placebo once every 2 days
Route of Administration:	Oral
Planned Sample Size:	500 patients will be enrolled in the study using a treatment allocation of 1:1 (azithromycin : placebo)
Sample Size Justification:	250 subjects per group (500 subjects in total) will yield 80% power to show a significant difference at a two-sided significance level of 0.05. Sample size calculation is based on a survival analysis using a logrank test with proportional hazards, assuming clinical failure in at least 45% of the placebo arm within 3 months and taking into account a maximal amount of 25% of dropouts.

List of Abbreviations

AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
AMI	Acute Myocardial Infarction
ATS	American Thoracic Society congress
BACE	Belgian trial with Azithromycin during acute COPD Exacerbations
BID	Bis in die; stands for "twice a day"
CAT	COPD Assessment Test
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CTC	Clinical Trial Center
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ERS	European Respiratory Society congress
EUDRACT	European Union Drug Regulating Authorities Clinical Trials
EQ5D	European Quality of Life-5 Dimensions
FAGG	Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten
FEF25-75%	Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
FEV1/FVC	Ratio of Forced Expiratory Volume in 1 second / Forced Vital Capacity
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
HDAC2	Histone Deacetylase-2
ICAM-1	Intercellular Adhesion Molecule-1
ICS	Inhaled Corticosteroids
IDAB	Infectious Disease Advisory Board
IL-(8, 1, 10)	Interleukin-(8, 1 ,10)
IV	Intravenous
LABA	Long Acting $\beta2$ agonist
LAMA	Long Acting anticholinergica
LRD	Leuven Research and Development
MEF	Maximal Expiratory Flow
mMRC	modified Medical Research Counsel
MV	Mechanical Ventilation
NIV	Noninvasive ventilation
(N)STEMI	(non-) ST Elevation Myocardial Infarction
OD	Omne in die; stands for "once a day"
PEF	Peak Expiratory Flow
PO	Per Oral
QID	Quarter in die; stands for " four a day"
SABA	Short Acting $\beta2$ agonist
SAE	Serious Adverse Event
SGRQ	St. George's Respiratory Questionnaire
SSQ5	Social Support Questionnaire 5
TID	Ter in die; stands for "three a day"

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1. Research description

1.1. Rationale

Chronic Obstructive Pulmonary Disease (COPD) is characterized by airflow limitation that is not fully reversible, usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases, often cigarette smoke [1,2]. COPD is currently considered as one of the major health challenges of the next decades. Patients with COPD usually present with progressive dyspnea, but during the course of the disease comorbidities develop and exacerbations occur which critically determine symptoms and prognosis[3]. The majority of exacerbations are caused by viral or bacterial infection and characterized by an acute increase of dyspnea, cough or sputum production requiring treatment with antibiotics or systemic corticosteroids. Because of their huge impact on the natural history of the disease, prevention and appropriate management of exacerbations are one of the prime treatment goals [4]. Although inhalation therapy reduces the frequency of exacerbations by approximately 20% with only a small cumulative effect by combination [5,6], many patients still experience at least one exacerbation a year of which one fourth requires hospitalization. A recent large European audit on COPD exacerbations in hospitalized patients, revealed that these events were associated with 12% mortality and 35% risk of readmission within 3 months [7]. The audit painfully demonstrated that our current drug interventions with systemic steroids and antibiotics are largely insufficient and that new therapies for these acute events are warranted.

Macrolides have strong anti-inflammatory properties that make them exquisite candidates for intervention studies in different chronic respiratory diseases [8,9]. Their potential for preventing COPD exacerbations has been recently confirmed in a large randomized trial showing that chronic azithromycin therapy over 1 year reduced the risk for exacerbations by approximately 30% on top of standard inhalation therapy [10]. However, the long-term use of this class of antibiotics in a large COPD population is not recommended as it is inevitably associated with bacterial resistance and carries the risk for side effects such as hearing loss and life threatening arrhythmias by prolongation of the QT interval [11]. For these reasons, a recent update of the international treatment recommendations for COPD by GOLD did not incorporate azithromycin in the therapeutic arsenal, although they acknowledged its potent effects and its proof of concept [1]. Reducing the dose and time course of azithromycin intervention, as well as restricting the treatment to a subgroup of COPD patients with the highest risk for future exacerbations, may overcome some of these concerns and would therefore be a major step forward to a targeted clinical use [11,12]. Additionally, short courses of macrolides were shown to facilitate the weaning process in ventilator-associated pneumonia and to shorten the time to resolution of pneumonia by approximately 40% [13]. In acute exacerbations of asthma, 10 days of neo-macrolides resulted in significant symptom improvement compared to placebo [14]. In line with these immediate therapeutic benefits for other acute respiratory diseases, azithromycin therapy initiated at the onset of acute COPD exacerbations with hospital admission, may also improve short-term outcomes of hospitalization and prevent early relapse.

Given these proof of concept studies, our consortium will organize a multicenter randomized placebo-controlled intervention trial to establish an appropriate but more restricted use of azithromycin during and immediate after hospital admission for COPD exacerbation to overcome in COPD the highest risk period for treatment failure, relapse and death. If our low dose intervention is proven to be safe and effective, a breakthrough in the acute treatment setting will be obtained and the chronic use of high dose azithromycin in a large and poorly defined group of COPD patients, with inherent dangers and side effects, will be avoided.

1.2. State of the art

A. Burden of COPD exacerbations worldwide, Belgium and Flanders

COPD is presently the 4th leading cause of death, but WHO predicts that it will become the 3rd leading cause of death by 2030 [4]. Whereas mortality due to cardiac diseases and stroke has been decreasing over the period 1970-2002, the mortality due to COPD has doubled over the same time [15]. The course of COPD is aggravated by exacerbations which are currently considered as major risk episodes of the disease. Exacerbations reduce quality of life [16], enhance lung function decline [17], and increase mortality [18]. Although therapy with inhaled corticosteroids, inhaled long-acting B-agonists and inhaled long-acting muscarinic antagonists reduce the frequency of exacerbations, many patients - 20% to 50% depending on the severity stage - still experience at least one exacerbation a year [19]. Approximately 20% to 25% of the exacerbations require hospitalization composing a major burden on our health care system [20]. Studies in the US and Canada have estimated an average direct cost of 9000 US dollars per admission [21;22], but total costs are probably twice as high when taking indirect costs into account.

A recent large European audit included more than 15.000 patients with hospital admission for COPD exacerbations [7]. The audit revealed a mean hospital stay of 8 days, a 6% in hospital mortality and a 12% mortality of any cause at 3 months post admission, which confirmed data of earlier reports[23]. After discharge the risk of readmission within 3 months was 35% of which 80% was directly related to recurrent disease or relapse. When considering the subgroup of 500 Belgian cases, similar outcomes were obtained. Although we have no data on the prevalence of hospital admission in Flanders and Belgium, a French epidemiological survey demonstrated that over the last decade a 40% increase in hospital admissions for exacerbations occurred. According to the French national hospital discharge database in 2007, approximately 18 hospitalizations per 10.000 adults aged above 25 years were primarily related to COPD exacerbation [24]. When extrapolating these data to the Belgian (7.300.000) or Flemish (4.300.000) situation, it would correspond to approximately 13.100 and 7.800 of respective hospital admissions on yearly basis. This is most likely an underestimation as COPD patients often present with uncontrolled comorbidities [25] that might be coded as primary diagnosis at discharge. When taking into account COPD as primary or secondary diagnosis, 27/10000 adults were hospitalized in France [24], which corresponds to 17500 and 11600 admissions in Belgium and Flanders respectively.

Given these epidemic proportions, the bad outcomes and the high economic burden, any treatment which could significantly improve the outcomes of hospitalized exacerbations, will be highly welcomed by patients, the respiratory community and eventually the general population.

B. Azithromycin: effects and side effects

Macrolide antibiotics were discovered over 50 years ago but over the last decade it became apparent that this group of antibiotics also possessed strong anti-inflammatory properties. Several randomized clinical trials have shown clinical benefits of long-term macrolide treatment in a variety of chronic respiratory diseases, particularly diffuse pan-bronchiolitis, cystic fibrosis, bronchiolitis obliterans post-transplantation and bronchiectasis [26 30]. Recent trials also demonstrated that chronic macrolide therapy resulted in an important reduction of exacerbations in COPD and in a subgroup of severe asthma [31]. For COPD in particular, erythromycin (250 mg twice daily for 1 year) evaluated in 115 stable COPD patients resulted in a 35% reduction of exacerbations compared to placebo [9]. A larger trial in 1142 COPD patients with history of exacerbations, demonstrated that daily administration of 250 mg of azithromycin for 1 year reduced exacerbation frequency from 1.83 per patient-year in the placebo group to 1.48 in the intervention arm (hazard ratio 0.73, 0.63-0.84 CI; $P<0.001$) [10]. In this study, the active intervention also resulted in statistical, but not clinically, significant improvements in quality of life monitored by standardized questionnaires (SGRQ). Compared to placebo,

azithromycin therapy also resulted in a lower likelihood of becoming colonized with respiratory pathogens at follow-up visits but no relationship between colonization status and increased incidence of exacerbations could be shown.

At this stage, the mechanisms of action of long-term macrolide treatment in COPD are complex and not entirely resolved. Part of its activity may be explained by its antibacterial effects and reductions in bacterial load, especially in chronic infected or colonized airways. Macrolide therapy also reduces neutrophil accumulation and cytokine production (Il-8, IL-1 and GM-CSF) in the airways and may also switch macrophage activation from M1 to M2 polarized phenotypes producing IL-10. Other potential effects are the induction of antiviral responses by inhibition of ICAM-1 and the restoration of corticoid sensitivity by boosting up HDAC2 [8;32].

Another domain of uncertainty is the appropriate dosage to target therapeutic serum and tissue levels. The dose of azithromycin administered in the study of Albert et al. was 250 mg per day [10]. In earlier pharmacokinetics studies it was found that a dose of 250 mg corresponded with serum peak levels of 0.4 microgram per millimeter with a long half-life of 40-68 hours. However, with repeated administration, lung tissue levels increased to as much as 75 times and persisted even after serum levels declined [33;34]. Therefore several experts believe that 250 mg of azithromycin three times weekly is probably sufficient to obtain all therapeutic benefits, although there are no specific data to support this in COPD [11;35].

Concerns particular with a long-term use of azithromycin, are the adverse effects that include ototoxicity, cardiac toxicity, drug-drug interactions and the induction of antibiotic resistance. Hearing loss was thoroughly examined in the trial by Albert et al. demonstrating a 5% differential in audiogram-confirmed hearing decrement between the azithromycin treatment and placebo group, but with criteria that were probably too stringent as 20% of the placebo group did also report hearing loss or tinnitus [10]. Moreover, the EMBRACE trial did not assess for hearing decrement nor reported any adverse event related to hearing loss over 6 months [27]. We therefore consider potential hearing loss as a mild concern only. Secondly, macrolides are known to prolong the QTc interval by blocking a cardiac potassium channel, which is associated with an increased risk of torsade des pointes, ventricular fibrillation and sudden death [11]. Although the trial by Albert et al. could not detect any signal towards cardiac non-fatal and fatal events with azithromycin use, a recent large retrospective cohort study showed that compared to amoxicillin, a short-term use of 5 days of Azithromycin was associated with a 47 additional deaths from cardiovascular cause per million antibiotic courses[36]. In line with these observations, most experts propose to exclude patients from azithromycin therapy when long QTc interval is present or when unstable cardiac disease is documented. Additionally, the combination with other QT interval prolonging drugs (amiodarone, flecainide, domperidon, and droperidol) should be strictly avoided. Finally, the chronic use of azithromycin unequivocally results in bacterial resistance. In the trial by Albert et al. 81% versus 41% of colonizing pathogens in the placebo arm were resistant to macrolides and similar patterns are also observed in studies of cystic fibrosis. A related concern is the wider spread of macrolide resistance to the general population and the potential risk of losing azithromycin as part of the first-line treatment for non-tuberculous mycobacterial infections [11;37]. Although there are no clear data to support this, it is obvious that restriction of treatment to shorter courses in a subset of individuals may anticipate these rightly concerns.

C. Study design: primary and secondary endpoints

As COPD exacerbations cluster together with every exacerbation constituting a major risk for a subsequent exacerbation, different experts nowadays accept that a vicious circle of uncontrolled inflammation and recurrent infection drives the event [19;20;38]. Thus, clinical trials evaluating acute treatments that are able to disrupt this negative spiral are most attended [39]. One major problem with many trials in the acute setting of COPD exacerbations, is that short-term endpoints do not provide

data on clinical failure or relapse rate occurring weeks after treatment. Likewise, long-term outcomes such as time to the next exacerbation will not pick–up immediate relief by the intervention [40]. Another concern when studying interventions for acute exacerbations, is the difficulty in differentiating prolonged exacerbations from early relapse as there is no biomarker available which can be used to monitor time course and recovery of the event. To overcome these problems, an international expert panel recently proposed a new primary endpoint for antibiotic trials in acute exacerbations of COPD (AECOPD): clinical failure within 8 weeks after the initiation of antibiotic therapy (with or without systemic steroids) [41]. Clinical failure encompasses the requirement for additional or alternate treatment for the exacerbation within 8 weeks after the initiation of therapy and was used as primary endpoint in the MAESTRAL study[42]. In this study performed in mild COPD exacerbations in primary care, treatment failure for acute exacerbations of COPD was already present in more than 20% of cases.

Almost similar to the MAESTRAL study endpoint, we will use time to clinical failure as primary endpoint in a trial evaluating azithromycin initiated and uploaded at hospital admission for acute exacerbation (500 mg once daily for 3 days) and subsequently administered for a prolonged period of 12 weeks at a lower maintenance dose (250 mg every 2 days). By using this endpoint we will take advantage of the potential short-term benefits of acute macrolide treatment but also of the long-term benefits of prolonged treatment over 3 months. The medical intervention will be evaluated on top of maximal standardized therapy which includes systemic steroids, antibiotics and short-acting bronchodilators. The combined endpoint of clinical failure will be defined as either death, the referral to intensive care or start with ventilation, the requirement of additional systemic steroids or new antibiotics, or the diagnosis of a new exacerbation after discharge. This primary endpoint will be evaluated within the period from randomization to study medication (within 48 hours after admission) until the end of intervention (day 90) in the intention to treat population.

An additional follow-up period of 6 months without study medication will be foreseen to study relapse rate after study drug withdrawal. This period may offer insight in potentially long-lasting effects once the vicious inflammatory cycle has been abrogated. Interestingly, survival curves on exacerbation free interval in the large recent trials in COPD and bronchiectasis, indicate that a major part of the reduction in exacerbations is already obtained within 90 days after treatment onset [10;27]. Thereafter survival curves may still diverge, whereas after 6 months of treatment a more steady and equal decline for both the placebo and intervention arm are reached. Remarkably, in the study of Wong et al. in which azithromycin was stopped after 6 months treatment, benefits persisted for another six months of follow-up [27]. It indicates that azithromycin withdrawal after prolonged intake of 3 to 6 months is fair to consider. Indeed, restricting the course of macrolide therapy to a limited period of 3 months might be sufficient for interrupting the circle of inflammation, infection and relapse. On the other hand, it will prevent continuous and long-term treatment for patients without strong indication and with an unfavorable balance to side effects.

Secondary endpoints of the study will include number of treatment failures, time to new exacerbation, number of exacerbations, total days of hospitalization, total days of intensive care, total days of antibiotics, total dose of systemic steroids but also FEV1 and self-administered symptom or quality of life scores (questionnaires: EQ5D, SSQ5, mMRC, CAT) at discharge, 3 and 9 months. In a subgroup of the intervention study, physical activity levels will also be addressed with portable validated activity monitors at discharge, 3 and 9 months. Physical activity is strongly reduced with exacerbations and failure to increase physical activity is associated with relapse[43]. Physical inactivity is known to be associated with cardiovascular and metabolic morbidity[44] and is one of the strongest predictors of mortality in COPD [45]. Apart from potential direct effects of the intervention on treatment failure and symptoms, positive effects on physical activity may offer considerable benefits in the long run [46-48].

Finally, when ignoring its potential unfavorable side effects, the widespread and chronic use of azithromycin for the prevention of exacerbations is probably a cost-saving strategy in Belgium [49]. Our multicenter randomized trial executed in one country will provide an excellent tool for more precise health economic assessments. In a first approach rough estimates on savings of direct costs will be made by taking into account the Flemish average costs for a single hospitalization day at a respiratory ward, for a day at intensive care, for an emergency visit, for a home physician contact and for an antibiotic-steroid course. A more detailed cost-effectiveness and cost–utility analysis will be performed only in case significant clinical benefits are found in favor of the active treatment. For this purpose medical resource use data will be collected and linked to EQ5D scores in patients enrolled in the centers that are signing in for this sub-study.

D. Safety

As side effects and risks with long-term macrolide treatment currently outweigh the benefits, reducing the dose and restricting the treatment period should counter this concern. Safety evaluations will be performed by repeated electrocardiogram (ECG) recordings, and bacterial cultures for assessing antibiotic resistance on spontaneous sputum samples provided at baseline, 3 and 9 months visits. As a recent retrospective cohort study has shown that a short course of azithromycin is associated with a small increased risk of cardiovascular death compared to control antibiotics, careful attention will be attributed to cardiovascular safety [36]. Although we assume that the reported excess mortality of 47 cases on 1 million azithromycin courses, will not be detected in a trial studying 500 individuals (0,024 extra deaths), the higher risk profile and the prolongation of the drug over 3 months (at lower dose), warrants some precautions. First, patients at risk for long QT interval because of medication, a history of life-threatening arrhythmias, recent or current myocardial infarction (NSTEMI or STEMI), or unstable angina pectoris at admission will be excluded. Second, ECG recordings will be checked at baseline, discharge and control visits and in case long QT is detected, study medication will be stopped. Finally, an independent safety committee will be appointed to adjudicate mortality and cardiovascular safety during and at the end of the trial.

1.3. Objectives

The large multicenter randomized controlled trial has two main scientific objectives:

(1) The first objective is to prove the effectiveness of azithromycin on top of standard therapy in the acute treatment of COPD exacerbations which require hospitalization.

(2) A second objective is to prove and improve safety without losing effectiveness by reducing dose and duration of a current everlasting treatment.

The innovation of the study is to develop a new treatment strategy for acute hospitalized exacerbations which are currently lacking effective interventions. The treatment approach we propose will not only deal with short-term in hospital outcomes but also with relapse rate during 3 months after discharge, a period known to have the highest risk for deterioration.

The overall aim of this project is to offer a time-limited indication for a low dose of azithromycin therapy with important restriction to a subgroup of patients with the most unmet needs. If proven safe and effective, we may kill two birds with one stone. 1/ the presented approach may be incorporated in the GOLD guidelines for acute treatment. 2/ the ongoing uncontrolled, long-lasting and preventive use of azithromycin in real life, with inherent dangers and side effects, might be abandoned.

1.4. Study organization

The present study is sponsored by the KULEUVEN and UZGENT with funding obtained from the Institute for Science and Technology of Flanders (IWT-TBM program). The main sponsor is the KULEUVEN with UZLEUVEN functioning as central ethics committee. The principal investigator of the study, prof Wim Janssens (KUL), is chair of the steering committee which is composed by promoter prof Wim Janssens (Chair), co-promoter prof Guy Brusselle, prof Geert Verleden (COPD expert, KUL) and 4 other experts including prof Kris Bogaerts (statistician, KUL), prof Thierry Troosters (physical activity, KUL), prof Guy Joos (COPD expert, UGent) and prof Vincent Ninane (COPD expert, ULB). The steering committee is part of the scientific board of the trial in which each participating hospital (subcontractor) is represented by one respiratory physician, with exception of the centers of Leuven and Gent.

Intellectual property related to the foreground of BACE (i.e. the development of the study) belongs to the steering committee that will decide on all publications and output related to the study. In case no consensus can be found, the chair will have final decision. All members of scientific board will have co-authorship on all publications related to study. We do not expect patents or industrial interest to spin off from the project as azithromycin is registered and off patent since many years. The steering committee will meet at regular time intervals and report to the scientific board of the study joining at least 1 time a year. Meetings will be organized centrally in Brussels at the Belgian Thoracic society who will provide logistic support.

All data will be gathered in a central web-based database. Two appointed data managers will be responsible for correct input of data in the database which will remain closed (password protected) for analysis, unless decided differently by the steering committee and with exception of an independent safety committee appointed to adjudicate mortality and cardiovascular safety after 300 finalized inclusions. Statistical analysis of the final data set will be performed by statisticians in close collaboration with steering committee. Each center will be provided with its respective center data but publications on these data are only possible with agreement of the steering committee.

2. Detailed research protocol

2.1. General study design

The study is designed to be embedded in a real-life hospitalization setting. All screening tests to assess eligibility are part of the routine assessment on emergencies when hospitalized for exacerbations. Randomization should be finished within 48 hours post-admission.

The currently recommended treatment of systemic steroids and antibiotics is fixed to a standard regimen which is needed to observe changes in treatment (or treatment failure) during and after hospitalization. In line with recent literature on the dose of systemic steroids during acute exacerbations, we decided to use a fixed regimen of 5 days of systemic corticosteroids (40 mg methylprednisolone IV or 32 mg methylprednisolone PO for 5 days with no taper) [1;50-52]. As half of the acute exacerbations may be triggered by virus infections which often precede a bacterial infection, all patients entering the study will be treated with antibiotics to ascertain a uniform standard treatment. This use of a single course of antibiotics is in line with the IDAB Belgian guidelines for antibiotic use in acute COPD exacerbations with hospitalization.

The day of hospital discharge is not fixed and left at the local investigators discretion because many other factors including age, social circumstances, insurance, week-ends etc. are important determinants for discharge which cannot be affected by the intervention. Length of hospitalization is not part of the primary endpoint but will be assessed as a secondary endpoint.

The primary endpoint, which is time to treatment failure, is evaluated after 3 months, which is also the day all study medication will be stopped. However, patients will be further monitored in the study for 6 additional months to evaluate the effect of study drug withdrawal.
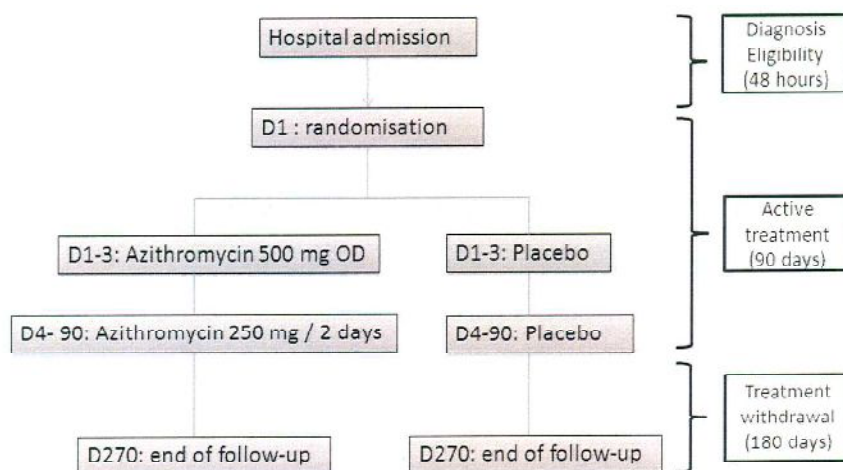
2.2. Inclusion and exclusion criteria

Inclusion criteria:

1/ Established diagnosis of COPD by medical doctor (based on clinical history OR pulmonary function test)

2/ Smoking history of at least 10 pack-years (10 pack-years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years, etc.)

3/ Current hospitalization for potential infectious AECOPD treated with standard therapy (standard therapy is defined under *2.3 Details study visits and required study assessments, D0 Hospital admission*)

4/ History of at least one exacerbation during the last year (prior to the current hospital admission) for which systemic steroids and/or antibiotics were taken

5/ ECG at admission

Exclusion criteria:

1/ Mechanical or non-invasive ventilation at moment of randomization (D1)

2/ Long QT interval on ECG (QTc > 450msec for males or > 470msec for females)

3/ History of life-threatening arrhythmias

4/ Myocardial infarction (NSTEMI or STEMI) less than 6 weeks before start of study drug

5/ Unstable angina pectoris or acute myocardial infarction (NSTEMI or STEMI) at admission

6/ Drugs with high risk for long QT interval and torsade de pointes
(amiodarone, flecainide, procainamide, sotalol, droperidol, haldol, citalopram, other macrolides)

7/ Documented uncorrected severe hypokalemia (K^+ < 3.0 mmol/L) or hypomagnesemia
(Mg^{2+} < 0.5 mmol/L)

8/ Chronic systemic steroids (> 4 mg methylprednisolone /day for ≥ 2 months)

9/ Actual use of macrolides for at least 2 weeks

10/ Allergy to macrolides

11/ Active cancer treatment

12/ Life expectancy < 3 months

13/ Pregnant or breast-feeding subjects. Woman of childbearing potential must have a pregnancy test performed and a negative result must be documented before start of treatment

2.3. Details study visits and required study assessments
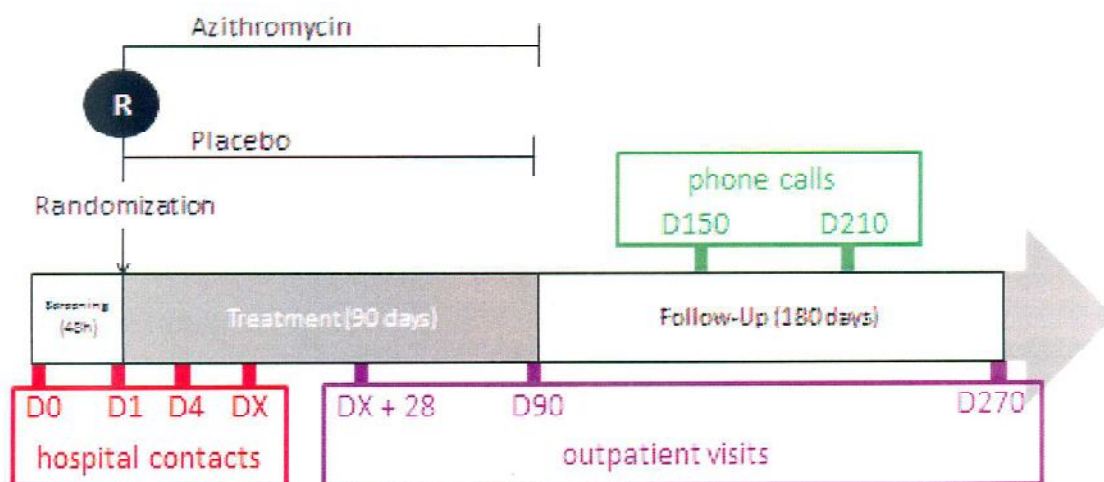
D0: hospital admission for AECOPD

1/ Standard diagnostic exploration:

- Vital parameters (including: heart rate, blood pressure, breathing frequency, oxygen saturation, Glasgow Coma Scale)
- Laboratory (including but not limited to: Hemoglobin, Hematocrit, Total WBC count and Differentiation, Platelets, Creatinine, Ureum, Na^+, K^+, Cl^-, $HCO3^-$, Mg^{2+}, AST, ALT, LDH, Glucose, CRP, Ths-troponine)
- ECG
- RX thorax
- Arterial blood gas (pH, pCO_2, pO_2, HCO_3^-)
- Sputum sample
  (only if available – bacterial culture and antibiogram including macrolides)

2/ Start standard treatment:

- Systemic steroids (methylprednisolone) for 5 days, then STOP
  > Fixed regimen: 40 mg IV or 32 mg PO (5d) (switch IV to PO as soon as possible)
- Short-acting bronchodilators via inhalation
- Antibiotics (AB):
  > First choice: fixed regimen of Amoxi-clavulanate 1g IV QID or 2g PO BID for 7 days or alternative regimen of 1 g IV QID or 875/125 mg PO TID for 7 days

  > Alternatives:
  > Moxifloxacin 400 mg IV or 400 mg PO OD for 5 days
  > (in case of intolerance or allergy to Amoxi-clavulanate)
  > (in case of clinical failure on GP initiated Amoxi-clavulanate treatment)
  > Anti-pseudomonas antibiotics
  > (only in case of bronchiectasis, positive cultures for Pseudomonas in history, high risk of Pseudomonas including failure with GP initiated antibiotics)
- Oxygen
- Non-invasive ventilation (NIV) or mechanical ventilation (MV) if needed (only exclusion for randomization if still ongoing at 48-hours post admission).

3/ Check eligibility criteria based on initial assessment

If patient is eligible for inclusion and the standard treatment has been initiated, the final enrollment with informed consent and subsequent randomization should be performed as soon as possible to remain within the time interval of **48 hours post admission on emergency.**

D1: randomisation (within 48h post admission) and uploading

1/ Informed consent

2/ Registration of medical history

- Date of COPD diagnosis
- Smoking history (pack years, quit date, day last cigarette)

- Current co-morbidities (Charlson index, COPD comorbidity index, hearing problems)
- History of exacerbations (number, hospitalization)
- Respiratory therapy at admission
  (ICS, LABA, LAMA, SABA, theophylline, steroids, vitamin D supplements; pulmonary rehabilitation)

3/ Current admission:

- Viral symptoms
  (fever, sore throat, rhinitis – start date)
- Lower respiratory symptoms
  (cough, sputum volume, sputum purulence, dyspnea, other – start date)
- Intervention by GP (steroids, AB, inhalation therapy – start date)

4/ Baseline characteristics and vital parameters

- Age, gender, length and weight
- Heart rate, blood pressure, breathing frequency, oxygen saturation, oxygen need, Glasgow Coma Scale
  (at admission and at randomization)

5/ Questionnaires

- modified Medical Research Councel dyspnea score (mMRC)
- COPD assessment test (CAT)
- SSQ 5 (hearing loss)
- EQ5D

6/ Randomization to placebo or azithromycin

- Randomization within 48 hours post hour of emergency or hospital admission
- Day 1 – Day 3: 500 mg (= 2 tablets of 250 mg) Azithromycin or placebo OD
  Day 4 – Day 90: 250 mg (= 1 tablet of 250 mg) Azithromycin or placebo / 2 days
- Hour and date of first intake of study drug

D4: start maintenance therapy

Day 4 (D4) is considered as the first day post loading dose of azithromycin when normal maintenance dose of 250 mg of azithromycin every second day is started. All the actions of D4 (with exception of starting the maintenance dose) may be carried forward to D5 or D6 (maximal time interval of 72 hours) to deal with weekends during hospital admission. Primary and secondary endpoints will be evaluated on a continuing time scale.

1/ Check status primary endpoint

- Death (Y/N, date, reason: respiratory, cardiovascular, other)
- Referral to intensive care (Y/N, date, reason: respiratory, cardiovascular, other)
- Additional dose of methylprednisolone ($\geq$ 40 mg IV or $\geq$ 32 mg PO or equivalent)
  (Y/N, date, reason: respiratory, cardiovascular, other)
- Upgrade antibiotics for clinical failure

(Y/N, date, reason: respiratory failure, respiratory focus, pneumonia, non-respiratory focus)

2/ Registration of vital parameters

- Heart rate, blood pressure, breathing frequency, oxygen saturation, oxygen need

3/ Perform new laboratory

- Total WBC count and differentiation, Na^+, K^+, Cl^-, $HCO3^-$, Mg^{2+}, CRP, Ths-troponine, 25-hydroxyvitamin D, total IgE, RAST Aspergillus, IgG Aspergillus

4/ Check adverse events, serious adverse events (SAE) (at D4)

- New diagnosis of infarction, stroke, acute heart failure, syncope (Y/N, date)
- Check hearing loss (Y/N, increased or decreased)
- Gastrointestinal complaints (diarrhea Y/N, nausea Y/N, anorexia Y/N)
- Other (open text)

5/ Perform new ECG

- Check ECG for long QTc (QTc > 450 msec for men, QTc > 470 msec for women)
- New arrhythmia's
- New repolarization disturbances
- New conductance disturbances

6/ Questionnaires

- mMRC, CAT

7/ Check study drug intake and start maintenance dose azithromycin or placebo 250mg
(start on day 4, further every 2 days).

DX: day of discharge (at investigators discretion)

1/ Check status primary endpoint (at DX)

- Death (Y/N, date, reason: respiratory, cardiovascular, other)
- Referral to intensive care (Y/N, date, reason: respiratory, cardiovascular, other)
- Additional dose of methylprednisolone (≥ 40 mg IV or ≥ 32 mg PO or equivalent)
  (Y/N, date, reason: respiratory, cardiovascular, other)
- Prolongation of steroid administration to > 8 days
- Upgrade antibiotics for clinical failure
  (Y/N, date, reason: respiratory failure, respiratory focus, pneumonia, fever, non-respiratory focus)

2/ Registration of vital parameters (at DX)

- Heart rate, blood pressure, breathing frequency, oxygen saturation, oxygen need

3/ Registration of respiratory therapy (at DX)

   (ICS, LABA, LAMA, SABA, theophylline, steroids, vitamin D supplements)

4/ Questionnaires (at DX)

   - mMRC, CAT, EQ5D, SSQ5 – (PROactive : only in subgroup)

5/ Check adverse events, serious adverse events (at DX)

   - New diagnosis of infarction, stroke, acute heart failure, syncope (Y/N, date)
   - Hearing loss (Y/N, SSQ5)
   - Gastrointestinal complaints (diarrhea Y/N, nausea Y/N, anorexia Y/N)
   - Other (open text)

6/ Spirometry*

   - Pre- and post-bronchodilator spirometry
     (FVC, FEV1, FEV1/FVC ratio, PEF, MEF, FEF25-75%)

7/ Sputum sample*

   - If available
   - Routine bacterial and fungal culture – antibiogram including macrolides

8/ Instruction of diary*

   - Diary with weekly questionnaires for symptom evaluation, medication changes and
     detection of new exacerbation, hospitalization or GP visits
   - Diary containing information for GP for appropriate disease management.
   - Diary registration of all GP visits

9/ Confirmation of diagnosis of AECOPD (Y/N)*

(* all these actions may be executed from D5 but should remain within 96 hours before discharge)

After discharge with standard therapy, different follow-up visits are planned as embedded in routine clinical practice: a first outpatient visit 4 weeks after discharge (DX + 28) and a second follow-up visit planned at day 90 after randomization (D90). To cover this 3 months period, patients are instructed with a diary to document any doctor visit or any treatment change by their general practitioner (GP), or specialist in case of readmission. During this 3 months study treatment period, all treatments are allowed with exception of a maintenance treatment with macrolides (azithromycin, clarithromycin, roxithromycin or erythromycin for more than 10 days).

DX + 28: study outpatient visit 1 *

1/ Check status primary endpoint (at DX+28)

   - Prolonged course of methylprednisolone during and after admission (> 8 days in total)
     (Y/N, duration)
   - Additional dose of methylprednisolone (≥ 40 mg IV or ≥ 32 mg PO or equivalent)

(Y/N, date, reason: respiratory, cardiovascular, other)
- New course of AB and/or steroids for respiratory reasons
  (Y/N, start date – stop date, reason: bronchitis, AECOPD, pneumonia, other)
- New hospitalization for respiratory reasons
  (Y/N, start date – stop date, reason: bronchitis, AECOPD, pneumonia, other)
- Death
  (Y/N, date, reason: respiratory, cardiovascular, other)

2/ Check therapy adherence, diary compliance

3/ Check adverse events, serious adverse events

- New diagnosis of infarction, stroke, acute heart failure, syncope (Y/N, date)
- Hospitalization (Y/N, reason: respiratory, cardiovascular, other)
- Hearing loss (Y/N, increased, decreased)
- Gastrointestinal complaints (diarrhea Y/N, nausea Y/N, anorexia Y/N)
- Other (open text)

4/ Obtain ECG

- Check ECG for long QTc (QTc > 450 msec for men, QTc > 470 msec for women)
- New arrhythmia's
- New repolarization disturbances
- New conductance disturbances
- Life threatening changes

5/ Questionnaire

- CAT, mMRC

*Control visit 1 (DX +28) is planned 4 weeks after discharge with a time interval of 2 weeks (between 4 and 6 weeks after discharge). Control visit 1 is standard in most hospitals and is important to check endpoints, cardiovascular safety and study compliance (diary and drug intake). The final follow-up plan with primary endpoint visit (control visit 2) is also fixed at visit 1. In case the patient is being hospitalized for more than 60 days, the study visit 1 is cancelled and all tests are postponed to study visit 2 which is at Day 90 of study medication intake (with a window of 20 days). In case the patient is still hospitalized, the study visit at Day 90 should be organized in the hospital.

D90: end of treatment - study outpatient visit 2*

1/ Check status primary endpoint

- New course of AB and/or steroids for respiratory reasons
  (Y/N, start date – stop date, reason: bronchitis, AECOPD, pneumonia, other)
  New hospitalization for respiratory reasons
  (Y/N, start date – stop date, reason: bronchitis, AECOPD, pneumonia, other)
- Death
  (Y/N, date, reason: respiratory, cardiovascular, other)

2/ Check therapy adherence, diary

- Collection of remaining capsules and blister
- Stop study drug intake

3/ Registration of vital parameters, smoking history, inhalation therapy

- Heart rate, blood pressure, breathing frequency, oxygen saturation, oxygen need
- Respiratory therapy
  (ICS, LABA, LAMA, SABA, theophylline, steroids, vitamin D supplements)
- Smoking history (current, ex or never smoker?)

4/ Questionnaires

- mMRC, CAT, EQ5D, SSQ5 – (PROactive : only in subgroup)

5/ Spirometry

- Pre- and post-bronchodilator spirometry
  (FVC, FEV1, FEV1/FVC ratio, PEF, MEF, FEF25-75%)

6/ Obtain ECG

- Check ECG for long QTc (QTc > 450 msec for men, QTc > 470 msec for women)
- New arrhythmia's
- New repolarization disturbances
- New conductance disturbances
- Life threatening changes

7/ Check adverse events, serious adverse events

- New diagnosis of infarction, stroke, acute heart failure, syncope (Y/N, date)
- Hearing loss (Y/N, SSQ5)
- Hospitalization (Y/N, date, reason: respiratory, cardiovascular, other)
- Gastrointestinal complaints (diarrhea Y/N, nausea Y/N, anorexia Y/N)
- Other (open text)

7/ Sputum sample

- If available of the same day (morning sample)
- Routine bacterial and fungal culture – antibiogram including macrolides

8/ Control of diary

- Registration of number of GP visits (DX – D90)
- Registration of hospitalization days (DX – D90)

*The 3 months visit 90 days post randomization should be planned as close as possible to day 90 but with a 20 day interval from day 86 till day 105 to allow the practical organization. The study medication will be stopped at the 3 month study visit, on day 104 at latest. After the 3 months visit, patients will be instructed and managed according to standard care guidelines and closely monitored with diary and 2 follow-up telephone calls by the central or local study-nurse. During this study treatment withdrawal phase, all treatments are allowed with exception of more than 10 days of

azithromycin, clarithromycin, roxithromycin or erythromycin which are reason for drop-out of the secondary analysis.

1/ Check diary for secondary endpoint

- Course of AB and/or steroids for respiratory reasons
  (Y/N, start date – stop date, reason: bronchitis, AECOPD, pneumonia, other)
- Hospitalization for respiratory reasons
  (Y/N, start date – stop date, reason: bronchitis, AECOPD, pneumonia, other)
- Death
  (Y/N, date, reason: respiratory, cardiovascular, other)

2/ Check study adherence

- No use of macrolides (azithromycin, clarithromycin, roxithromycin or erythromycin)
  for > 10 days
- Diary adherence

3/ Check adverse events, serious adverse events

- New diagnosis of infarction, stroke, acute heart failure, syncope (Y/N, date)
- Hearing loss (Y/N, increased, decreased)
- Hospitalization (Y/N, date, reason: respiratory, cardiovascular, other)
- Gastrointestinal complaints (diarrhea Y/N, nausea Y/N, anorexia Y/N)
- Other (open text)

4/ Questionnaires

- mMRC, CAT

1/ Check diary for secondary endpoint

- Course of AB and/or steroids for respiratory reasons
  (Y/N, start date – stop date, reason: bronchitis, AECOPD, pneumonia, other)
- Hospitalization for respiratory reasons
  (Y/N, start date – stop date, reason: bronchitis, AECOPD, pneumonia, other)
- Death
  (Y/N, date, reason: respiratory, cardiovascular, other)

2/ Check study adherence

- No use of macrolides (azithromycin, clarithromycin, roxithromycin or erythromycin)
  for > 10 days
- Diary adherence

3/ Check adverse events, serious adverse events

- New diagnosis of infarction, stroke, acute heart failure, syncope (Y/N, date)
- Hearing loss (Y/N, increased or decreased)
- Hospitalization (Y/N, date, reason: respiratory, cardiovascular, other)
- Gastrointestinal complaints (diarrhea Y/N, nausea Y/N, anorexia Y/N)
- Other (open text)

4/ Questionnaires

- mMRC, CAT

A central or local study nurse will contact the patient at D150 and D210 to check and advice the patient at home. In case there is any doubt on treatment change or endpoint, the general practitioner will be contacted for further details.

D270: safety follow-up - outpatient visit

1/ Check status secondary endpoint

- Course of AB and/or steroids for respiratory reasons
  (Y/N, start date – stop date, reason: bronchitis, AECOPD, pneumonia, other)
- Hospitalization for respiratory reasons
  (Y/N, start date – stop date, reason: bronchitis, AECOPD, pneumonia, other)
- Death
  (Y/N, date, reason: respiratory, cardiovascular, other)

2/ Registration of vital parameters, smoking history, inhalation therapy

- Heart rate, blood pressure, breathing frequency, oxygen saturation, oxygen need
- Respiratory therapy
  (ICS, LABA, LAMA, SABA, theophylline, steroids, vitamin D supplements)
- smoking history (current, ex)

3/ Questionnaires

- mMRC, CAT, EQ5D, SSQ5 – (PROactive: only in subgroup)

4/ Spirometry

- Pre- and post-bronchodilator spirometry
  (FVC, FEV1, FEV1/FVC ratio, PEF, MEF, FEF25-75%)

5/ Obtain a ECG (only in case ECG at D90 had severe disturbances)

- Check ECG for long QTc (QTc > 450 msec for men, QTc > 470 msec for women)
- New arrhythmia's
- New repolarization disturbances
- New conductance disturbances
- Life threatening changes

6/ Check adverse events, serious adverse events

- New diagnosis of infarction, stroke, acute heart failure, syncope (Y/N, date)
- Hearing loss (Y/N, SSQ5)
- Hospitalization (Y/N, reason: respiratory, cardiovascular, other)
- Gastrointestinal complaints (diarrhea Y/N, nausea Y/N, anorexia Y/N)
- Other (open text)

7/ Check study adherence

- No use of macrolides (azithromycin, clarithromycin, roxithromycin or erythromycin) for > 10 days
- Diary adherence

8/ Sputum sample

- If available of the same day (morning sample)
- Routine bacterial and fungal culture – antibiogram including macrolides

9/ Collection of diaries

- Registration of number of GP visits (D90 – D270)
- Registration of hospitalization days (D90 – D270)

10/ End of study - plan further clinical follow-up.

2.4. Study duration

Safety monitoring will begin at the time Informed Consent Form is signed and continue for 180 days after the last dose of study medication.

During the active intervention phase, patients will continue on treatment (from day 1 up to and including day 90) until at least one of the following occurs:
* Death
* Patient withdraws consent, irrespective of reason
* Unacceptable toxicity
* Treating physician determines discontinuation of treatment is in the patient's best interest
* Substantial non-compliance with the protocol.
    With regards to the intake of the study medication, no more than 5 consecutive intakes may be missed.

If one of the specified conditions would occur, the patient will be considered a drop-out. All attempts should be made to schedule an end of treatment and safety follow-up visit (for the tests, please refer to the D90 and D270 visit respectively), with the focus on primary endpoint collection.

During this study treatment withdrawal phase, all treatments are allowed with exception of more than 10 days of azithromycin, clarithromycin, roxithromycin or erythromycin which are reason for drop-out of the secondary analysis.

2.5. Primary and secondary endpoints

Primary endpoint: Time to clinical failure.

Clinical failure is a composite endpoint as multiple clinical interventions may indicate that an initiated therapy is failing. **Clinical failure is defined as either death or the referral to intensive care for respiratory reasons, the requirement of additional systemic steroids or new antibiotics for respiratory reasons, or the diagnosis of a new exacerbation after discharge.** The additional use of systemic steroids is defined as an additional administration of more than 40 mg methylprednisolone (or its equivalent) on top of the standard regimen, or the prolongation of the steroid therapy of 5 days to more than 8 days. Change or narrowing of the initial antibiotics based on proven bacterial cultures is not considered as treatment failure but as good clinical practice. Change of antibiotics for respiratory clinical failure is considered as a primary endpoint. The diagnosis of a new exacerbation after discharge is based on the increase of dyspnea for which the general practitioner initiates new antibiotics and/or systemic steroids. Clinical failure will be assessed between day 1 (from 1 hour after first drug intake) till day 90 (24 hours after last study drug intake). The primary endpoint will be evaluated in the intention-to-treat population (including drop-outs) and as a secondary analysis also in the per-protocol population. In case the primary endpoint is reached, the study drug is still continued until day 90.

Secondary endpoints:

Main secondary endpoints assessed at D90 and D270 include: clinical failures, time to new exacerbation*, number of new exacerbations*, rate of exacerbations*, days of hospitalization, days of intensive care, symptom and quality of life scores (EQ5D, CAT), pre- and post-bronchodilator FEV_1, total dose of systemic steroids, total days of steroid use, total days of antibiotics use, home physician contacts, average costs of hospitalization.

Other analyses include: primary and main secondary endpoints in subgroups of smokers-ex end nonsmokers, age > 65 or ≤ 65, GOLD stage A, B, C or D. Subgroup analysis of physical activity (total steps, time spent in moderate to vigorous physical activity, daily physical activity level) over 90 days, Cost-effectiveness and cost-utility analysis in subgroup over 90 and 270 days.

*: definition of COPD exacerbations:

Moderate exacerbations are defined as episodes of increasing symptoms of dyspnea beyond normal day-by-day variation, lasting for at least 24 hours, and for which treatment with antibiotics and/or systemic steroids (≥ 3days) are prescribed or taken. Severe COPD exacerbations are exacerbations requiring hospital admission.

Safety analysis:

We will address cardiovascular safety including: total mortality, cardiovascular events (AMI, sudden death, stroke, acute heart failure), unexplained syncope, arrhythmias, long QT, repolarization disturbances, conduction disturbances. We will also evaluate bacterial presence and macrolide resistance in sputum samples. We will monitor hearing decrement with questionnaires. Any serious adverse event (SAE) should be reported via the eCRF within 2 days of occurrence.

In case of unexplained syncopes, long QT, life-threatening arrhythmias or life-threatening conduction disturbances are observed, the patient should be excluded from further study drug continuation but

still followed and monitored till the end of the study. Bacterial resistance or reported hearing decrement as well as other serious adverse events are no reason for study drug discontinuation.

2.6. Power analysis - sample size calculation

Sample size calculation is based on a survival analysis using a logrank test with proportional hazards, assuming clinical failure in at least 45% of the placebo arm within 3 months *(based on 35% readmissions in the Belgian COPD population in the European COPD audit, a proportion of 50% with a new exacerbation within 4 months after randomization in our vitamin D trial enrolling similar but stable patients [53], and a 20% treatment failure within 8 weeks in the MAESTRAL study looking at mild exacerbations[42])*, anticipating a 35 % relative improvement with azithromycin intervention (HR = 0.65) *(HR 0.73 in NEJM for time to first exacerbation [10], HR of 0,5 for time to resolution of ventilator associated pneumonia[13])* and taking into account a maximal amount of 25% of dropouts. 250 subjects per group (500 subjects in total) will yield 80% power to show a significant difference at a two-sided significance level of 0.05. Sample size calculation was done using EAST version 5.4 by prof. Kris Bogaerts (Center for Biostatistics, KUL)

2.7. Subgroup studies

A/ BACE trial: PROactive Sub-study: In a subgroup of the intervention study, physical activity levels will be addressed with portable validated activity monitors in patients recruited in the University Hospitals of Leuven, but all other participating centers that have interest will be welcomed and trained for the application. Randomized patients that are willing to participate in the sub-study will be monitored for activity by validated and easy-to-wear portable devices (Dynaport®). This activity monitor was recently thoroughly validated for use in COPD by the Pro-Active consortium and will be used at the baseline, 3 months and 9 months visit [54;55]. We hypothesize that with a positive medical intervention, differences in recovery of physical activity will be appreciated when measuring 30 subjects in each arm. International Expertise on physical activity monitoring is readily available with prof Thierry Troosters (FABER, KUL) being part of our steering committee and chairing the Pro-active consortium (www.proactivecopd.com).

Patients will follow the standard protocol but will also wear an activity monitor for 7 days post discharge, at day 90 and at day 270. This device is not only registering physical activity for 7 days but is also coupled to a standardized and patient-validated questionnaire on physical activities which needs to be filled out at day 8 to cover a recall period of 7 (monitored) days. The activity monitor and the questionnaire will be sent back by post-package 1 week after discharge, 1 week after day 90 and 1 week after day 270.

The use of the PROactive tool to monitor physical activity will be used in the centers that wish to participate in the substudy. In these centers, a different informed consent will be provided which describes the additional measures related to the activity sub-study. However, individual patients can still opting out for these tests and only participate in the medical intervention study.

B/ BACE trial: FarmEc Sub-study: Another sub-analysis will include a detailed cost-effectiveness study. First, a rough estimation on savings in the entire study cohort will be made by an evaluation of average costs in Flanders for a single hospitalization day, for a day on intensive care, for an emergency visit and a home physician contact. In hospitals that are willing to participate in the cost-effectiveness subgroup study, medical resource use data will be collected retrospectively via hospital invoices (direct costs including drugs, physician visits, laboratory tests, technical exams, medical

imaging, hospital stay) but also prospectively via patient diaries to cover direct and indirect costs during the entire outpatient period. In collaboration with prof. Steven Simoens (Pharmaco-Economics, KUL), cost-utility analyses and cost-effectiveness will be performed to get profound insight in the potential benefits of 3 months azithromycin therapy at 3 and 9 months interval.

Hospitals that are willing to participate in the cost-effectiveness study will provide all invoices of the study participants during the entire study period (D1-D90) and (D90-D270).

Patient will have to give informed consent that additional to the clinical evaluation, invoices will be collected in these centers. Again, a different informed consent will be provided which describes the additional measures of the cost-effectiveness study. However, individual patients can still opting out for these analyses and only participate in the medical intervention study.

2.8. Report Form (CRF)

A web-based Case Report Form (CRF) application will be developed by a professional IT specialist (Jurgen Silence - SiBeTec). The developer has more than 10 years of experience with application development and has a degree of doctor in biomedical sciences. Former collaboration with SiBeTec within the framework of the Belgian Pulmonary Function study was very satisfactory. SiBeTec, assigned as subcontractor, will take care of hosting, development of the front -end interface and various back-end follow-up tools, database architecture and back-up services. Throughout the entire study, SiBeTec will actively participate in the process of data management and export, and will also handle the maintenance, updating and expansion of the web application and server. The electronic CRF will be accessible at all sites with password protection. It will encompass anonymous data of screenings and randomized subjects including demographic characteristics, medical history, clinical data (lung function measurements, radiographic assessments, sputum cultures, questionnaires etc.), detailed data on systemic steroids and antibiotic use, days of hospitalization and intensive care, and safety data (ECG). Patient diaries will be developed by the consortium to monitor patients at home for GP and hospital visits and changes in symptoms and therapy. All data of diaries will be transferred by the central study coordinators to the electronic CRF.

2.9. Randomization and blinding

Eligible patients will be randomly assigned to one of the two treatment groups. The randomization schedule will be computer generated by the hospital pharmacy of the University Hospital of Ghent, which will also perform the randomization of all eligible patients of the other participating hospitals. Randomization will be stratified by hospital centre in block sizes of 10 patients to avoid large differential assignment to active treatment or placebo within an individual hospital. Randomization codes will be obtained from a secured web-based program in Ghent to allocate blocks of 10 packages (5 placebo – 5 active treatment) to the pharmacies of all sites with codes in sealed opaque envelopes. The local pharmacist of every participating hospital will be responsible for the delivery of the appointed drugs to the individual patient by study number. At all time, randomization codes are kept strictly confidential during the study, with exception of an ad hoc independent safety committee adjudicating cardiovascular side effects and mortality after 300 patients. Nevertheless, code breaks will be available at the site and un-blinding may occur in the case of an emergency (SAE) which will require knowledge of the treatment assignment.

The identity of study medication will be concealed by the use of a format that is identical in packaging, labelling, schedule of administration and appearance. As most hospital pharmacies in Belgium (including university hospital pharmacies) have no longer authorization for the production of

placebo, the production of active treatment, placebo comparator and its packaging will be outsourced to a specialized company which has all European licenses for production and sales (Apotheek Haagse Ziekenhuizen, NL and Laboratoria Wolfs NV, BE – large cost). Randomization and distribution in Belgium will be carried out by the hospital pharmacy of the University Hospital of Ghent.

2.10.   Ethics Committee and Insurance

The protocol and an informed consent form (in Dutch, French and German) as approved by the steering committee, will be submitted to the central ethics committee of Leuven, who will coordinate and collect advice of all ethics committees from the different hospitals involved. A "no fault" indemnity insurance will be foreseen by the University Hospitals of Leuven in case the study has received ethics committee and contract approval. At the same time, the clinical trial centre of Leuven (CTC-Leuven) in collaboration with Leuven research and development (LRD- Leuven) will make a contract form between the hosting University of Leuven, the University hospital of Ghent and the different participating hospitals, defined as subcontractors.

2.11.   Registration

In agreement with the CONSORT guidelines, a detailed protocol with statistical plan will be registered at an international study registry (www.ClinicalTrials.gov) prior to the first inclusion. In agreement with Belgian law, a medicinal intervention trial will first be registered and approved on the EUDRACT website. The trial will also be registered at the FAGG which will include submission of the investigational medicine product document of the study medication

2.12.   Timelines

Under close supervision of promoter and co-promoters, two study coordinators will be implemented in the complex administration and registration prior to the execution of this multi-centre randomized controlled trial. The headquarters of the consortium will be housed in Leuven but one study coordinator will operate from Ghent, the other from Leuven which will provide large advantages for work package 2. We anticipate that the start of the project will be in October 2013 and that a first patient enrolment will only be feasible from April 2014.

3. Data collection of the BACE trial

3.1. Enrollment

Patient screening and randomization will be performed in 20 different hospitals and will be competitive. Large hospitals will recruit faster and more than the smaller hospitals although we have experienced that in previous studies all of the current centers had an excellent participation. To support the operating clinicians, two trained study coordinators will be fully engaged in the data collection and data transfer to the electronic CRF (mm CRA).

Once the patient has been randomized, a site specific study number will be appointed in the electronic CRF. This number will be noticed by a central study coordinator who will plan phone call visits on fixed moments and visit the local site for assisting with the data management. The study coordinator operating from Ghent will be responsible for most of the hospitals in Flanders with exception of Brabant and Limburg which will be assisted by the coordinator of Leuven, together with the hospitals of Brussels and Wallonia.

With the support of two 'flying' central study coordinators who operate alongside and together with local dedicated study nurses and investigators, we think to relieve an important part of the administrative burden and to enhance enrolment. To cover remaining costs and efforts inherent to the clinical trial, local investigators will obtain a fixed budget on per-patient basis (subcontractors).

3.2. Data monitoring

Data will be collected by the local investigators, their dedicated local study nurses and the central flying study coordinators of the trial. By bimonthly visits, the central study coordinators are responsible for correct and complete input of data in the electronic CRF which will need approval of the local clinical investigator. The electronic CRF will be monitored by the clinical trial centre of the University Hospitals of Leuven in all participating hospitals. This will include a 2 person-month task during 2 consecutive years (person-month CTC).

3.3. Cardiac safety

One major concern is cardiac safety. Although an important number of exclusion criteria will reduce cardiovascular risk, ECG recordings will be taken at every study visit and QTc intervals (obtained with automated calculator) will be registered in electronic CRF. In case prolonged QTc interval or life threatening arrhythmias or conduction disturbances occur, patients will be withdrawn from study medication but monitored until the end of the study (discontinuation due to severe adverse event). Life threatening arrhythmia's or conduction disturbances include runs of ventricular tachycardia, torsade de pointes, ventricular fibrillation, 2nd and 3th degree AV block or unexplained syncope.

All other Adverse and Serious Adverse Events will be also recorded which include particular attention to cardiovascular events. For this reason all cardiovascular events (AMI, sudden death, stroke, acute heart failure, syncope) will be questioned every study visit. These events will be recorded but won't be reason for immediate study drug withdrawal. Any serious adverse event (SAE) should be reported via the e-CRF within 2 days of occurrence.

After completion of 300 patients with the 90 day post randomization visit (intention to treat), an ad hoc safety committee will be appointed in Leuven to adjudicate cardiovascular safety with insight in the randomization code. This independent safety committee will consist of a clinician and statistician who are both not involved in the trial.

<u>In case of QTc prolongation documented during study participation</u>:

Treatment with study medication should be discontinued if:

- QTc value is ≥500 ms on at least 2 separate ECGs   <u>OR</u>
- QTc value shows > 60 ms change from baseline

An evaluation by a cardiologist must be performed and adequate patient management and follow up must be put in place immediately after observation of the QTc prolongation.

3.4. Concomitant medication

As the trial evaluates a medical intervention on top of standard practice, most drugs can be started during the trial and changes in the ongoing therapy are allowed. However, during the first 3 months of the trial drugs with high risk for long QT interval and subsequent torsades de pointes (amiodarone, flecainide, procainamide, sotalol, droperidol, haldol, citalopram) are prohibited. Short courses of macrolides for antibiotic purposes (maximal 10 days) should be avoided but are allowed if there is no antibiotic alternative for that specific indication. Longer courses of macrolides (> 10 days) during the entire study period (9 months) are considered as protocol violations and study drop-outs.

3.5. Timelines

On average, 27 patients per hospital need to be enrolled to reach the final sample size of 500 subjects. We assume that two third of the admissions for acute exacerbation might be eligible and that one on five eligible patients will be finally enrolled. It means that in an average hospital 200 admissions for acute exacerbations are needed over the entire recruitment phase of the study. This is much lower than the actual number of hospitalizations in a large hospital (for instance, in Leuven we have more than 500 admissions/year for COPD) but may correspond to the recruitment in smaller hospitals. As COPD exacerbations are more frequent in winter period, we have foreseen a maximal recruitment phase of 2 years. By including two winter periods in the recruitment phase of the trial we will guarantee sufficient enrollment to reach our target number. The study will start in April 2014, recruitment will be possible until April 2016. With study duration of 9 months, the last patient visit will be planned in December 2016, which is the end of work package 2.

4. Data analysis and dissemination of results

4.1. Data analysis

After the last patient has finished the D270 follow-up visit, the entire data set will be checked for outliers who will be linked to the original on site documents for revision via queries to the investigators. After database lock, the randomization code will be broken. A statistical analysis will be performed according to a comprehensive statistical plan which defines primary, secondary, safety and subgroup analyses and which has been submitted to clinicaltrials.gov prior to the first enrollment. Because of the potential impact of the study, statistical expertise will be hired (Kris Bogaerts, Center for Bio-statistics, KUL) to perform all analyses in close collaboration with the steering committee. Depending on the results, post-hoc and subgroup analyses will be initiated if approved by the steering committee.

4.2. Study report and publication

The results of the BACE trial will be first discussed at the steering committee and then presented to the scientific board. Results will be presented as abstract form at the annual major congresses of respiratory medicine, including the American Thoracic Society (ATS) congress and the European Respiratory Society (ERS) congress. The study will be published in a peer-reviewed international scientific journal with high impact factor to increase visibility.

4.3. Dissemination of the BACE trial

After publication, results will be disseminated at different levels. If the trial shows clear benefits for azithromycin treatment in the acute setting, it will be a breakthrough in the acute management of COPD exacerbations. All channels will then be used for maximal visibility. Apart from a high impact publication and its communication at international scientific meetings, the current consortium houses most key opinion leaders on COPD in Flanders and Belgium. With the help of the Belgian Thoracic Society and the communication services of both hosting institutes, communication to a lay audience, to the medical press and to local health authorities will be organized. Moreover, by the participation of many peripheral hospital centres our new treatment approach will be rapidly incorporated in daily practice in Flanders.

Additionally, the co-promoter occupies a key position on the international guideline office (G. Brusselle, Guideline director of European Respiratory Society). Whether 3 months of azithromycin therapy in the acute severe exacerbation setting will eventually be incorporated in the guidelines, is dependent on the trial results. But once that step would be accomplished, a broad international application will follow.

4.4. Timelines

The database lock will follow after all queries are completed and answers are revised. This will take 3 months. The statistical analysis and interpretation will be done in the next 2 months, the writing-submission-revision of the manuscript will take a minimal period of 4 months. It is only after the publication in a peer reviewed high impact journal (October 2017) that further dissemination of study results will be carried out.

Timelines:
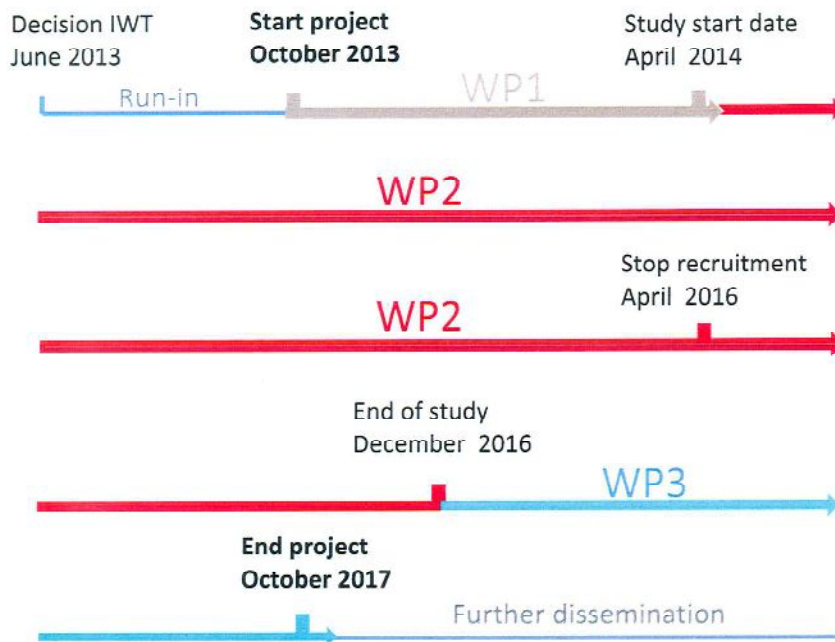
Summary of person-months (pm) during the project:

	Research group 1 (Respiratory Medicine UZLeuven) (44mm)				Research group 2 (Respiratory Medicine UZGent) (40 mm)			
	J1	J2	J3	J4	J1	J2	J3	J4
Workpackage 1	6 pm (CRA)				3pm (CRA)			
Workpackage 2	6 pm (CRA)	12 pm (CRA) 2 pm (CTC)	12 pm (CRA) 2 pm (CTC)	2 pm (CRA)	6pm (CRA)	12 pm (CRA)	12 pm (CRA)	2 pm (CRA)
Workpackage 3				1 pm (CRA)				
TOTAL	**12**	**14**	**14**	**6**	**12**	**12**	**12**	**2**

Flow Chart:

Test	Screening (48 hours)	Randomisation (D1)	Maintenance (D4)	Day of discharge (DX)	Control visit 1 (DX + 28)	Control visit 2 (D90)	Telephone 1 (D150)	Telephone 2 (D210)	Control visit 3 (D270)
RX thorax	X								
ECG*	X		X		X	X			(X)
Arterial Blood Gas	X								
Laboratory	X		X						
Sputum sample	X			X		X			X
spirometry	X			X		X			X
Eligibility + informed consent	X								
anamnesis + medical history		X							
Current respiratory medication		X		X		X			X
vital parameters		X	X	X		X			X
mMRC + CAT		X	X	X	X	X	X	X	X
EQ5D		X		X	X	X			X
SSQb		X		X	X	X			X
Pro-Active*				(X)		(X)			(X)
Administer study medication		X							
check therapy adherence			X	X	X	X	X	X	X
Check prim/sec endpoint			X	X	X	X	X	X	X
Record AE and SAE			X	X	X	X	X	X	X
Diary instruction + overview				X	X	X	X	X	X
		Study drug intake					Study drug withdrawel		

(ECG* only performed at D270 if flow QT, severe arrhythmia's or severe conductance disturbances were present on ECG at D90)
(Proactive* only in 6 university centres)
[test additional to routine clinical follow-up]

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