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Full title of trial:	**Targeted retreatment of incompletely recovered COPD exacerbations with ciprofloxacin: a double-blind, randomised, placebo-controlled, multicentre Phase III trial**
Short title:	**Targeted retreatment of COPD exacerbations**
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Sponsor:	Imperial College London
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ACTIVE IMP(s):	Ciprofloxacin
PLACEBO IMP(s):	Placebo
Phase of trial:	Phase III
Sites(s):	Multi-Site

Chief investigator:

Professor JA Wedzicha
COPD Group
Airway Disease Section
National Heart and Lung Institute (NHLI)
Guy Scadding Building
Dovehouse Street
London
SW3 6LY
+44 (0)207 59 47959

Sponsor Representative:

Ms Tharani Thurairajah

AHSC Joint Research Compliance Office
Imperial College London and
Imperial College Healthcare NHS Trust
510C
Fifth Floor
Lab Block
Charing Cross Hospital
London
W6 8RF
Tel: 020 3311 0213
E-mail: t.thurairajah@imperial.ac.uk

Signatures

The Chief Investigator and the Sponsor have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol.

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator Wisia Wedzicha		
	Signature	Date

Sponsor Representative Tharani Thurairajah		
	Signature	Date

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List of abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
APR	Annual Progress Report
AR	Adverse Reaction
CA	Competent Authority
CFU	Colony Forming Unit
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CLRN	Comprehensive Local Research Network
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	C-reactive protein, serum
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Reports
EC	European Commission
ECG	Electrocardiogram
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
EQ5D	A 5-point standardised measure of health outcome
FEV1	Forced Expiratory Volme in 1 second
FVC	Forced Vital Capacity
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner

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HCU	Health Care Utilisation
HES	Hospital Episode Statistics
IB	Investigator Brochure
ICF	Informed Consent Form
IUD	Intrauterine Device
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised
MA	Marketing Authorisation
Main REC	Main Research Ethics Committee
MHRA	Medicines and Healthcare Products Regulatory Agency
MRC	Medical Research Council
MS	Member State
UK MIA IMP	United Kingdom Manufacturer's Authorisation for Investigational Medicinal Products
N/A	Not Applicable
NIHR	National Institute for Health Research
NHS R&D	National Health Service Research & Development
NIMP	Non Investigational Medicinal Product
PCR	Polymerase Chain Reaction
PCRN	Primary Care Research Network
PCRN-GL	Primary Care Research Network Greater London
Ph Eur	European Pharmacopoeia
PI	Principal Investigator
PIS	Patient Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
RFH	Royal Free Hospital

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SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SD	Standard Deviation
SDV	Source Document Verification
SGRQ	St George's Respiratory Questionnaire
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Trial Coordinator
TB	Tuberculosis
TMG	Trial Management Group
TSC	Trial Steering Committee
WP	Work Package

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1 Trial personnel

Chief Investigator (CI)

Prof Jadwiga Wedzicha
COPD Group
Airway Disease Section
National Heart and Lung Institute (NHLI)
Guy ScaddingBuilding
DovehouseRoad
London
SW3 6LY
+44 (0)207 59 47959

IMPERIAL COLLEGE LONDON
Royal Brompton Hospital

Principal Investigator (PI) in London:

Dr John Hurst
Centre for Respiratory Medicine
UCL Medical School
Royal Free Hospital
Rowland Hill Street
London NW3 2QG
E-mail: j.hurst@ucl.ac.uk
Tel: 020 7472 6260
Fax: 020 7472 6141

Principle Investigator (PI) in Liverpool

Dr Paul Walker
Respiratory Research Department
University Hospital Aintree
Longmoor Lane
Liverpool L9 7AL
Telephone: 0151 529 5886
E-mail: pmacal@liverpool.ac.uk

Sponsor's representative

Ms Tharani Thurairajah

AHSC Joint Research Compliance Office
Imperial College London and
Imperial College Healthcare NHS Trust
510C
Fifth Floor
Lab Block
Charing Cross Hospital
London
W6 8RF
Tel: 020 3311 0213
E-mail: t.thurairajah@imperial.ac.uk

Statisticians

Dr Daniel Jackson Senior statistician)
MRC Biostatistics Unit
Institute of Public Health
University Forvie Site
Robinson Way
Cambridge CB2 0SR
Tel: 01223 330374
Fax: 01223 760729
Email: dan@mrc-bsu.cam.ac.uk

Mr Martin Law
MRC Biostatistics Unit
Institute of Public Health
University Forvie Site
Robinson Way
Cambridge CB2 0SR
Tel: 01223 768257
Fax: 01223 760729
Email: martin.law@mrc-bsu.cam.ac.uk

Routine Local laboratories:

Clinical Research Fellow in Liverpool

Dr Ben Vlies
Respiratory Research Department
University Hospital Aintree
Longmoor Lane
Liverpool L9 7AL

Clinical Research Fellow in London

Dr Simon Brill
COPD Group
Airway Disease Section
National Heart and Lung Institute (NHLI)
Guy Scadding Building
Dovehouse Street
London
SW3 6LY
Tel: 0207 59 47771
Email: s.brill@imperial.ac.uk

Trial Co-ordinator
Miss Luana Alves Moreira
COPD Group
Airway Disease Section
National Heart and Lung Institute (NHLI)
Guy Scadding Building
Dovehouse Street
London
SW3 6LY
Tel: 0207 59 479
Email: l.alves-moreira@imperial.ac.uk

Professor Emma Baker (PI)
Mailpoint J1A
Division of Biomedical Sciences
Jenner Wing, Corridor 10
St George's, University of London
Cranmer Terrace
London SW17 0RE
Tel: 02087255383Email: ebaker@sgul.ac.uk

Mr Michael Tumilty
Respiratory Research Coordinator
St George's University of London
Mailpoint J1A
Jenner Wing, Corridor 10
Cranmer Terrace, London, SW17 0RE
T: 020 8725 5658
Email: mtumilty@sgul.ac.uk

Dr Patrick Mallia (PI)
National Heart & Lung Institute
356 Medical School, St Mary's Campus
T:020 7594 3751
Email: p.mallia@imperial.ac.uk

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2 Summary

Title:	Targeted retreatment of incompletely recovered COPD exacerbations with ciprofloxacin: a double-blind, randomised, placebo-controlled, multicentre Phase III trial
Short title:	Targeted retreatment of COPD exacerbations
Trial medication:	Ciprofloxacin
Phase of trial:	Phase III
Objectives:	The primary outcome will be the time to the next COPD exacerbation following targeted retreatment with the IMP or placebo. Secondary endpoints will include duration of the initial exacerbation, adverse events, changes in lung function and health status, bacterial load and resistance, and hospital readmission.
Type of trial:	Phase III, double-blind, randomised, placebo controlled, multicentre trial.
Trial design and methods:	A 90 day, double-blind, randomised, placebo controlled, multicentre clinical trial investigating the effects of targeted retreatment of COPD exacerbations with antibiotics. Patients who experience an exacerbation of COPD treated with antibiotics will attend, two weeks after the start of initial treatment, for a screening visit. Patients will be eligible for the study if they have not fully recovered at this visit (either persistent symptoms or a raised C-reactive protein [CRP]) and fulfil diagnostic and spirometric criteria for COPD. Eligible participants will be treated with 1 week of ciprofloxacin 500mg BD or placebo. Follow-up will be for a further 3 months, and the primary study endpoint will be the time to the next exacerbation.
Trial duration per participant:	90 days
Estimated total trial duration:	2 years
Planned trial sites:	Multi-Site
Total number of participants planned:	144
Main inclusion/exclusion criteria (summary; see section 6.1 & 6.2):	**Main Inclusion Criteria:** - Diagnosis of COPD confirmed spirometrically at screening - COPD exacerbation with treatment commenced 14 days prior to study enrolment and treated with 5-14 days of a non-quinolone antibiotic. Exacerbation here will be defined as an episode of symptomatic worsening of COPD that was treated by the patient's attending clinician. Confirmation of

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the initial exacerbation diagnosis will be provided from the case notes, referral letter, or directly from the treating clinician, and will be documented in the CRF.

- Age: ≥ 45 years of age at screening.
- Persistent symptoms and/or a CRP≥8mg/L when assessed 2 weeks after exacerbation onset
- Able to complete questionnaires for health status and symptoms and keep written diary cards
- Severity of disease: Patients with a measured FEV1<80% of predicted normal values at 2 weeks post exacerbation
- Able and willing to give signed and dated written informed consent to participate

Main Exclusion Criteria:

- Other clinically predominant chronic respiratory disease.
- Intubated and receiving mechanical ventilation
- Patients with known hypersensitivity to the antibiotic under evaluation, to other quinolones or any excipients of the IMP/placebo.
- Patients with a prior history of tendonopathy or tendon rupture
- Elderly patients taking long term systemic corticosteroids
- Patients on long term antibiotics for other conditions
- Patient too unwell for randomisation, i.e. requiring retreatment in the judgment of the study doctor
- Female patients who are pregnant or planning on becoming pregnant during the study, or are breastfeeding.
- Patient taking clinically significant contraindicated medication as per the SmPC s, such as use of concomitant tizanidine or methotrexate.

Statistical methodology and analysis:

The impact of ciprofloxacin use on the probability of experiencing a recurrent exacerbation will be assessed using survival analysis of time to next exacerbation. A Cox proportional hazards model will be used to adjust for baseline characteristics, including possible centre effects.

3 Introduction

3.1 Background

COPD (Chronic Obstructive Pulmonary Disease) is a chronic, ongoing, progressive disease of the lower respiratory tract in the lungs. The hallmark of the disease is difficulty with breathing that slowly gets worse over time. Airway bacteria are present in the lower airways of COPD patients and airway infection is related to airway inflammation, lung function decline (1) and exacerbation frequency (2). COPD is a major cause of mortality and hospital admission with a large unmet need for novel therapeutic approaches. The over-arching aim of this NIHR (National Institute of Health Research) programme is to validate innovative antibiotic strategies to reduce exacerbations, hospital admissions and improve quality of life whilst minimising any bacterial resistance. Bacterial infection is important in COPD pathogenesis in both stable disease and at exacerbation. After understanding how antibiotics are currently used in COPD and developing an optimal regime for treating stable patients, we will evaluate the effect on exacerbations of antibiotic regimes in (i) stable COPD in primary care and (ii) at follow up in high-risk COPD patients to treat non-recovery and prevent recurrence.

This protocol is part of a 6 work programme grant and aims to addresses Aim 4 of programme grant; namely whether optimal antibiotic therapy at exacerbation follow-up speeds exacerbation recovery and prevents recurrent events in COPD.

3.2 Clinical data, Rationale and Risks/Benefits

COPD exacerbations are episodes of increased respiratory symptoms such as increased shortness of breath, increased sputum purulence and increased sputum volume (3). Oral corticosteroids are prescribed if exacerbations are associated with adverse effects on daily activities (4, 5). Antibiotics are normally used to treat COPD exacerbations in the event of associated sputum purulence or increased sputum volume and are associated with faster resolution of the exacerbation and delayed time to the next exacerbation (6).

A recent study has shown that treating a single exacerbation prolongs the time to onset of subsequent exacerbations and reduces mortality (7).

We have shown that following a first exacerbation, 27% of COPD patients will have another exacerbation within 8 weeks (8). In this study we also showed that it is these recurrent exacerbations that drive exacerbation frequency and thus there is a need to prevent their occurrence. The importance of recurrent exacerbations is highlighted by the finding that once a COPD patient is discharged from hospital they are at 34% risk of subsequent exacerbations in the following three months, with significantly increased mortality (9). This indicates an urgent need to validate interventions in this high-risk period after the initial exacerbation to reduce the likelihood of a second exacerbation.

We also reported that a raised serum C-Reactive Protein (CRP) concentration measured 14 days after a first exacerbation is predictive of a second exacerbation within 50 days, suggesting that failure to normalise the inflammatory response may predispose to another (recurrent) exacerbation (10).

Following an exacerbation, patients are often not regularly assessed for non-recovery or recurrence and this may contribute to the high morbidity and readmission rates after exacerbations. At present, there are no studies investigating further treatment for patients after a first exacerbation who have

failed to recover and/or normalise the inflammatory response, and are therefore at heightened risk of a subsequent event. Our aim in this study is to address this question in high-risk patients and test a novel approach to reducing the risk of subsequent exacerbation and speeding recovery.

Patients who suffer an exacerbation of COPD will be treated with antibiotics and/or corticosteroids in the usual way. We shall then closely follow up these patients, randomising them at 14 days to re-treatment or placebo if symptoms have not returned to stable levels and/or the systemic inflammatory response (CRP) has not normalised. The antibiotic to be used for this study is ciprofloxacin (see section 3.4 Rationale /risks benefits).

The formal hypothesis for this study is that re-treatment with ciprofloxacin at day 14 after an exacerbation of COPD, in patients who have not fully recovered (either by persistence of symptoms or inflammation), will lengthen the time to the next exacerbation.

Ciprofloxacin was the IMP of choice for this study based on the following:

- According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the European Respiratory Society guidelines for the management of adult lower respiratory tract infections, and the Canadian guidelines for the management of acute exacerbations of chronic bronchitis, ciprofloxacin is the antibiotic of choice for the treatment of patients with severe exacerbations of COPD (11, 12, 13, 14).
- Based on the findings from WP1, ciprofloxacin, as a second line treatment, was found to be one of 5 most commonly used antibiotics amongst GP practices for the treatment of COPD in the UK
- Ciprofloxacin is non-penicillin, therefore patients who meet the eligibility criteria for the trial but are allergic to penicillin, can also be recruited.

3.3 Preclinical data (as per SmPC)

Non-clinical data reveal no special hazards for humans using ciprofloxacin based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.

Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels.

Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Like other gyrase inhibitors, ciprofloxacin may induce joint damage during the growth phase of juvenile animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

Other preclinical effects were observed only at exposures sufficiently in excess of the maximum human exposure that concern for human safety is negligible with regard to the animal data.

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3.4 Assessment and management of risk

Patients will be treated with ciprofloxacin 500 mg twice daily for 1 week and followed for 90 days post treatment. This dose has been chosen as it is the standard dose when this drug is used for the treatment of lower respiratory tract infections and exacerbations of COPD in clinical practice, and tablets of this strength are routinely available. In all patients, the concomitant medications will be recorded and carefully checked by the study doctor for drug interactions before ciprofloxacin is prescribed. Patients who are taking tizanidine or methotrexate will be excluded from the trial as concomitant use of these is not recommended.

Prior to taking the IMP, patients will be counselled by a suitably qualified member of the study team who is familiar with the drug and the SmPC and has received suitable training in its use. As per the SmPC, specific advice for patients will include:

- Not to take the drug at the same time as dairy products or mineral fortified fruit juice
- Not to take the drug at the same time as iron, zinc, polymeric phosphate binders (eg. sevelamer), sucralfate, antacids or highly buffered pharmaceuticals, containing magnesium, aluminium or calcium. These may reduce the absorption of ciprofloxacin. Ciprofloxacin should be taken 1-2 hours before or four hours after administration of these medications.
- To avoid exposure to extensive sunlight or ultraviolet radiation during the period of treatment, to avoid photosensitive reactions

Certain concomitant medications may be affected by concurrent ciprofloxacin administration, and in these patients extra monitoring, including monitoring of the INR (in the case of warfarin) or serum drug levels, may be initiated according to the study doctor. These medications include theophyllines, cyclosporin, warfarin, glibenclamide, phenytoin, ropinirole and clozapine.

Patients will be asked to complete daily diary cards for changes in symptoms. These will be collected from the patient at the end of the trial. These diaries will note symptoms, any adverse events, adherence to treatment or need for further therapy. Participants will be able to discuss and report symptoms to the study team by telephone and may be asked to attend the hospital or local GP if required.

The table below lists the potential risks associated with all study procedures above standard care:

Intervention	**Potential risk**	**Risk Management**
Spirometry/Lung function testing	Patients report that this can be strenuous. The procedure can cause coughing, and some patients feel slightly faint afterwards	Advise patients not to over-exert themselves during the procedure Allow sufficient time between attempts for full recovery.
Blood tests	Minor bleeding and bruising at the site where the needle is inserted Small risk of superficial skin infections. Slight pain/discomfort during the procedure.	Bruising will be minimised by direct pressure on the site for at least 30 seconds following venepuncture. Infection will be minimised by thorough aseptic technique during the procedure.
Administration of	No excess risk associated with this	N/A

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symptom questionnaires	intervention	
Measurement of observations (BP, pulse, oxygen saturations) and clinical examination	The blood pressure cuff tightens and can be transiently uncomfortable. No other excess risks are associated with this intervention	Inform patient prior to BP measurement.

The table below summarises those risks that are expected to be associated with taking the IMP, and the expected management of these.

Potential risks as per SmPC	**Frequency**	**Risk Management**
Mycotic superinfections	Uncommon	Treat as necessary with antifungal agents Discontinue IMP if necessary
Antibiotic associated colitis	Rare/very rare	Discontinue IMP Review and treat as appropriate
Blood dyscrasias, including eosinophilia,leukopenia, anaemia, neutropenia, leukocytosis, thrombocythaemia, thrombocytopaenia	Rare	Discontinue IMP Review and treat as appropriate
Allergic reaction, including allergic oedema and angioedema	Rare	Discontinue IMP Further management as appropriate
Anaphylactic reaction including life-threatening anaphylactic shock	Very rare	Discontinue IMP Initiate management of anaphylactic shock Immediate transfer to emergency department for further assessment and treatment
Anorexia	Uncommon	Review and treat as appropriate
Hyperglycaemia	Rare	Review and treat as appropriate Discontinue IMP until causality excluded
Psychomotor disturbance, including agitation, confusion, anxiety, abnormal dreams, depression, hallucinations, psychotic reactions	Uncommon – very rare	Review and treat as appropriate Discontinue IMP until causality excluded
Nervous system disorders, including headache, dizziness, sleep disorders, para/dis/hypo-aesthesiae, tremor, seizures, vertigo, gait disturbance, intracranial hypertension, peripheral neuropathy	Uncommon – very rare	Review and treat as appropriate Discontinue IMP until causality excluded
Eye disorders including visual disturbances and colour distortions	Rare - very rare	Review and treat as appropriate Discontinue IMP until causality excluded
Ear and labyrinth disorders including tinnitus and hearing impairment	Rare – very rare	Review and treat as appropriate Discontinue IMP until causality excluded
Tachycardia	Rare	Review and treat as appropriate Discontinue IMP until causality excluded
Life-threatening cardiac arrhythmia including ventricular	Frequency unknown	Discontinue IMP Initiate management of cardiac arrhythmia

arrhythmia and torsades de points		Immediate transfer to emergency department for further assessment and treatment
Vascular disorders including vasodilatation, hypotension, syncope and vasculitis	Rare – very rare	Review and treat as appropriate Discontinue IMP until causality excluded
Dyspnoea	Rare	Review and treat as appropriate Discontinue IMP if causality suspected
Nausea Diarrhoea	Common	Review and treat as appropriate Consider IMP discontinuation if severe
Vomiting Abdominal pain Dyspepsia Flatulence	Uncommon	Review and treat as appropriate Consider IMP discontinuation if severe
Pseudomembranous colitis	Rare	Discontinue IMP Review and treat as appropriate
Pancreatitis	Very rare	Discontinue IMP Review and treat as appropriate
Increase in liver transaminases Increased bilirubin	Uncommon	Review and treat as appropriate Discontinue IMP until causality excluded
Liver impairment, Cholestatic icterus (jaundice) Hepatitis	Rare	Review and treat as appropriate Discontinue IMP until causality excluded
Liver necrosis +/- life-threatening hepatic failure	Very rare	Discontinue IMP Immediate transfer to emergency department for further assessment and treatment
Rash Pruritis Urticaria	Uncommon	Review and treat as appropriate Discontinue IMP until causality excluded
Photosensitivity reactions	Rare	Review and treat as appropriate Discontinue IMP until causality excluded
Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome +/- toxic epidermal necrolysis (may be life-threatening)	Very rare	Discontinue IMP Review and treat as appropriate Immediate transfer to emergency department for further assessment and treatment if indicated
Musculoskeletal pain Arthralgia	Uncommon	Review and treat as appropriate Consider IMP discontinuation if severe
Myalgia Arthritis Increased muscle tone and cramp	Rare	Review and treat as appropriate Discontinue IMP until causality excluded
Muscular weakness Tendinitis Tendon rupture Exacerbation of symptoms of myasthenia gravis	Very rare	Discontinue IMP if suspected Review and treat as appropriate Avoid future quinolone use if diagnosis confirmed
Renal impairment	Rare	Review and treat as appropriate Discontinue IMP until causality excluded
Renal failure Haematuria	Rare	Review and treat as appropriate Discontinue IMP until causality excluded

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Crystalluria Tubulo-interstitial nephritis		
Fever	Rare	Review and treat as appropriate Consider discontinuation of IMP if causality suspected
Oedema Hyperhidrosis/excess sweating	Very rare	Review and treat as appropriate Consider discontinuation of IMP if causality suspected
Increased serum alkaline phosphatise Abnormal prothrombin level Increased amylse.	Rare	Review and treat as appropriate Consider discontinuation of IMP if causality suspected

The trial risk based approach has been assessed and classified this trial as a **Type B trial**, on the basis that this is a phase III trial using an IMP that is licensed in human use with a good safety profile but not currently used for this indication in this patient population.

4 Objectives

4.1 Primary objective

To assess the effect of antibiotic retreatment by comparing the use of ciprofloxacin to a placebo, on the time to onset of the next exacerbation (from the start of retreatment with the IMP and up to a maximum follow-up period of 90 days). Exacerbation is fully defined in section 12.1.1 ('Primary Outcome').

4.2 Secondary objectives

Secondary objectives will include:

- Duration of (first) exacerbation recovery (from point of retreatment V1) based on diary card symptoms
- Treatment-related adverse events
- Exacerbation frequency (rate) during follow-up
- Total number of antibiotic courses received during 90 day follow-up
- (Re)admission/re-attendance to hospital during 90 day follow-up
- Changes in respiratory healthcare status, assessed using SGRQ and CAT
- Change in lung function from study entry to 90 days
- Change in CRP from study entry to 90 days
- Changes in bacterial resistance to ciprofloxacin as assessed by standard culture and sensitivity methods at trial beginning and end (in those patients in whom sputum is spontaneously expectorated)
- Change in bacterial load from trial beginning to end (in those patients in whom sputum is spontaneously expectorated)
- To collect further data on cost-effectiveness which will be analysed in a future study (Work Package 5 of the NIHR grant programme)

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5 Trial design

This is a Phase III, randomised, placebo controlled, double-blind trial. Patients and investigators will be blinded to treatment group by over- encapsulating the active IMP and placebo.

5.1 Overall Design

This is a Phase III, randomised, placebo controlled, double-blind trial. Patients and investigators will be blinded to treatment group by over- encapsulating the active IMP and placebo.

5.2 Justification of trial design, participants and follow up

The three months following an exacerbation has been identified as a high-risk period in patients with COPD, with high rates of re-exacerbation. This trial is designed to assess whether the intervention prevents further exacerbations in these patients within this time frame. Participants will therefore have COPD and have had a recent exacerbation, and will be followed up for 90 days. The intervention is targeted at those patients who have not fully recovered, and in order to provide adequate retreatment a further full course of antibiotics will be given (one week, which is a standard length, at a standard dose of 500mg twice daily).

A schematic diagram of the overall trial design can be found in section 22 ‘Schedule of Study Visits’

6 Selection of Subjects

6.1 Inclusion criteria

Patients eligible for enrolment in the study must meet all the following criteria:

- Pre-existing diagnosis of COPD confirmed by post-bronchodilator FEV1/FVC ratio of <0.7 at screening
- Severity of disease: Patients with a measured FEV1<80% of predicted normal values
- Evidence of COPD exacerbation treated 14 days prior to study enrolment (as defined by an episode of treated symptomatic worsening of COPD which is documented in the case notes or referral letter and/or confirmed with the treating clinician) with 5-14 days of non-quinolone antibiotics
- Age: ≥ 45 years of age at screening.
- Measured CRP (C-reactive protein) ≥8mg/L AND/OR persistence of one or more major symptom at the screening visit as assessed using a standardised short questionnaire. The individual ‘major symptoms’ are dyspnoea, increased sputum purulence and increased sputum volume.
- Able to complete questionnaires for health status and symptoms and to keep written diary cards
- Patients must be able to give consent to participate in writing

6.2 Exclusion criteria

Patients meeting any of the following criteria must not be enrolled in this study:

- Patients with other clinically predominant chronic respiratory disease. Patients with other respiratory diagnoses may be enrolled if COPD is the predominant condition (in the judgment of

the study doctor) and if the additional diagnosis will not affect the safety of the patient or validity of their results.

- Intubated patients receiving invasive positive-pressure ventilation. Patients receiving non-invasive ventilation and/or oxygen therapy may be included if they otherwise fulfil the inclusion and exclusion criteria.
- Patients with known hypersensitivity to ciprofloxacin, to other quinolones or any of the excipients used in its manufacture or that of the placebo.
- Patients with prior history of tendinopathy or tendon rupture.
- Elderly patients (≥80 years) on long-term (>6 weeks) systemic corticosteroids at a dose of ≥5mg/day prednisolone or equivalent.
- Patients on long term antibiotics for other conditions
- Patients already retreated with antibiotics for the current exacerbation (i.e. between day -14 and the screening visit)
- Patients who at the screening visit are too unwell for randomisation and/or fulfil one or more of the following criteria:
  - SaO2 <88% on air (OR ≥5% less than their usual known baseline saturation level on their usual oxygen dose if using long-term oxygen therapy)
  - Systolic blood pressure <90mmHg or >200 mmHg
  - Resting tachypnoea >28 breaths/minute
  - Resting tachycardia >120 beats/minute
  - Drowsy or confused
  - Clinical examination suggesting pneumonia or complications (e.g. parapneumonic effusion/empyema)
  - Further antibiotic treatment required in the judgment of the study doctor and therefore would be at risk if randomised to the placebo arm
- Female patients who are pregnant or planning on becoming pregnant during the study, or are breastfeeding.
- Clinically relevant abnormal laboratory values available at the screening assessment that could interfere with the objectives of the trial or safety of the volunteer.
- Patient taking clinically significant contraindicated medication, as per the SmPCs, in particular tizanidine and methotrexate.
- Patients who are actively enrolled in another interventional clinical trial (i.e. taking another IMP). Patients enrolled in observational COPD research (e.g. the London COPD Cohort Study [a recruitment source for this study] or COPDMAP) may continue as long as a) this study does not adversely impact on the scientific validity of the other study, and b) simultaneous participation is not unduly onerous for the patient. See section 8.8.
- Patients with glucose-6-phosphate dehydrogenase deficiency
- Patients with any other condition precluding enrolment in the trial, according to the assessment of the study doctor. This will be documented at screening.

Females of childbearing potential must be willing to use an effective method of contraception from the time consent is signed until (6 weeks) after treatment discontinuation. These include:

- Complete abstinence from screening to final visit
- Male partner is sterile (vasectomy with documentation of azoospermia) prior to female subject entry into the study, and this male partner is the sole partner for the subject

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- Implants of levonorgestral inserted for at least 1 month prior to the study medication administration but not beyond the third successive year following insertion
- Injectable progestogen administered for at least 1 month prior to study medication administration
- Oral contraception (combined or progestogen only) administrated for at least one monthly cycle prior to study medication administration.
- Double barrier methods: condoms or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/get/film/cream/suppository)
- An intrauterine device (IUD), inserted by a qualified physician, with published data showing that the highest expected failure rate is less than 1% per year
- Estrogenic vaginal ring
- Percutaneous contraceptive patches.

Females of childbearing potential must have a negative pregnancy test within 7 days prior to being registered for trial treatment.

NOTE: Subjects are considered not of childbearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal.

7 Recruitment

Study recruitment, in both sites, will take place by any of the following means:

- Hospital recruitment via:
  - Inpatients admitted with COPD exacerbation
  - Outpatient clinics if patients have COPD and/or have recently suffered an exacerbation
  - Patients identified as suitable by their treating clinician will be asked if they are happy to speak to the study team and will be contacted directly if they agree.
- Recruitment from the London COPD cohort, a research cohort of over 200 COPD patients who are under close longitudinal follow-up at the ROYAL BROMPTON and Harefield NHS Foundation Trustin London and who attend with exacerbations
- Community recruitment via:
  - Community COPD services in the local and surrounding areas (any suitable patients known to the community team, particularly those with recent treated exacerbations)
  - British Lung Foundation or other charity support groups. Representatives of our research group frequently attend meetings of patient groups such as these, and patients may express interest in participating in research. These patients may be contacted directly by the study team once they have given their permission and contact details. If they subsequently experience an exacerbation they may be recruited in the normal way.
  - Pulmonary rehabilitation services – patients identified by letter or directly (for example patients experiencing exacerbations during their rehabilitation course)
  - Advertisements containing information about the study placed in local journals/newspapers for patients to contact the research team. Posters may also be placed in GP practices.
  - GP surgeries, for example when patients attend for treatment of a COPD exacerbation.
  - Via community pharmacies who agree to act as PICs. Trial information packs containing an invitation letter and PIS will be included with COPD-specific medication (e.g. prescriptions of Tiotropium [Spiriva] or Seretide) and a week's course of steroids and antibiotics

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dispensed to patients ≥ 45 years of age. Patients expressing an interest in the study will be invited to reply directly to the study team.

- Any other patient interested in the study and who has given agreement for the study team to contact them.

Where applicable, patients' details will only be passed on to the study team once patients have given their permission to their treating clinician.

Recruitment will take place to ensure the required patient sample size is achievable within the estimated recruitment period of 18 months. Any patient with COPD exacerbation will be approached by the research team after they have given permission via their treating clinician. Participants will be given or sent a patient information sheet (PIS) describing the study in detail. Patients expressing an interest in participation will be contacted by the study team and invited to a screening appointment (V1) at the hospital 14 days after the onset of treatment for their exacerbation (henceforth defined as day zero).

Patient recruitment at each site will only be done when each trial site has been initiated by the sponsor or delegate and issued with an 'Open to Recruitment letter.

8 Study procedures and schedule of assessments

8.1 Informed consent procedure

All individuals working on the trial will have to review the protocol and the **PROTOCOL TRAINING LOG.**

The Informed consent discussion will take place at the approved sites. The delegated individuals (as documented in the delegation log at sites) will be GCP trained, suitably qualified and experienced.

When patients present with an exacerbation and are treated with standard antibiotics, the patient's treating clinician will briefly discuss the study with the patient and obtain the patient's permission for the study team to approach them. This will be documented in the patient's medical records or source document. The study team will then contact the patient, discuss the study in more detail, give or send the patient a PIS and ensure they have a minimum of 24 hours to consider this information before agreeing to take part. Patients expressing an interest in participation will be offered a screening appointment at the hospital 2 weeks after the start of treatment for the initial exacerbation

Prior to obtaining written consent at the screening visit, the delegated research staff will explain of the aims, methods, anticipated benefits and potential hazards of the study and give the patient opportunity to ask questions. It will also be explained to the patient that they are under no obligation to enter the trial and that they can withdraw at any time from the trial, without having to give a reason and without impact upon their usual clinical care.

Written informed consent will include consent for all trial related procedures, access to all written and electronic medical records and databases, and contact with the patient's usual medical team and general practitioner. A copy of the signed informed consent will be given to the participant. The original signed form will be retained at the study sites and placed in the TMF/SMF; a third copy will be kept with the paper CRF.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated as necessary and subjects will be re-consented as appropriate.

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No clinical screening or trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into trial. All patients screened will be recorded on the screening log, along with a screening number. Those patients who are enrolled into the trial will be allocated a formal trial identifier at the point of randomisation, and this will be the study number used to identify them for all subsequent study procedures.

8.2 Randomisation procedures

- Randomisation will take place according to the trial specific randomisation SOP.
- Sealed Envelope™ (www.sealedenvelope.com) will be responsible for the randomisation process including production of the randomisation list. The randomisation list will be held by Sealed Envelope™ until data lock.
- Randomisation of patients will be conducted by delegated member of the research team at the sites using an internet randomisation service provided by Sealed Envelope, at visit 1 (screening visit) (if patient is eligible for the study following assessment of results), and after the patient has provided informed consent and baseline data (Class A method of randomisation).
- Patients will be randomised equally into the treatment (ciprofloxacin) or control (placebo) group (1:1 randomisation) using a computer-generated permuted block system of variable sizes, stratified by site and presence or absence of symptoms (as defined by any one or more of persisting breathlessness, increased sputum volume, increased sputum colour. This will be assessed by the standardised symptom questionnaire detailed in section 8.4).
- Subjects who cease taking their randomised treatment (non-compliers) will continue to be followed up at the end of study visit (day 90). They will not be "replaced" with a further randomised patient (i.e. intention to treat analysis).
- Upon randomisation, patients will be allocated a trial number and will be given a study specific patient card, which will have the study title, IMP details, patient trial number and the contact details of the PI/CI/research team and out of hours contact details in cases of emergency.
- Randomisation details will also be entered on to the trial subject log held in the site file.
- Following the randomisation process and the generation of a randomisation number, pharmacy at the research sites will be notified by an automatic email. The research fellow will give the study medication to the patient at the screening visit.

8.3 Unblinding Procedures

- Unblinding will take place through a web based service provided by Sealed Envelope.
- An authorised member of the research team at each site will have administrative rights to the unblinding system and a nominated individual will be available 24 hours a day.
- Unblinding will only take place when the patient's health is compromised or an SAE has occurred that requires unblinding for treatment to be delivered.
- In the event that unblinding is required a formal request will be made by the Investigator or treating health care professional to an authorised individual.
- If the person requiring the unblinding is not the CI/PI then that health care professional will notify the Investigating team (via the 24 hour number telephone number on the patient contact card) that unblinding is required for a trial subject and prompt unblinding will be carried out, in consultation with the clinical and research teams where possible.

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- Authorised individuals will break the blind by providing the unique randomisation number, via number or other identifier used for the trial medication, and will be immediately notified of the unblinded treatment allocation.
- On receipt of the treatment allocation details the CI/PI or treating health care professional will treat the participant's medical emergency as appropriate.
- The CI/PI will document the code break and the reasons for doing so on the CRF, in the site file and medical notes. All code breaks will be included in the final study report and/or statistical report.
- The CI/Investigating team will notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break.
- Trial Committees, where required within their charters will also be notified.
- Subject always to clinical need, and where possible, other members of the research team will remain blinded.
- The written information will be disseminated to the Data Safety Monitoring Committee for review in accordance with the DMC Charter.
- The following procedure will be used to unblind for the submission of a SUSAR report to the regulatory agencies:
  - An authorised member of the sponsor's office will unblind in the event of a SUSAR report and will therefore, hold administration rights to the unblinding system
  - The Sponsor will follow the procedures described in the SOP.
  - The Sponsor will provide the unblinded information on the e-SUSAR website
  - Unblinded information in SUSAR reports will not be forwarded to the trial team and shall be kept in the sponsor files
  - SUSAR reports will be disseminated to Investigators at sites, but the report will remain blinded.

8.4 Screening Assessment (Visit 1)

This visit will take place 14 +/- 3 days after the start of treatment for the initial exacerbation. This will be defined as day zero, with the date of treatment onset for the initial exacerbation thereafter defined as day -14. The following procedures will take place:

- Informed consent
- A screening medical history will be taken, including:
  - Previous medical and surgical history including number of COPD exacerbations suffered in previous year and details of COPD diagnosis and treatment
  - Smoking history of cigarettes and any other recreational drug use
  - Concomitant medications
- Assessment of medication sensitivities, particularly to antibiotics or the excipients of the IMP and placebo
- A full physical examination, including:
  - height and weight,
  - blood pressure, pulse rate, respiratory rate, oxygen saturations, and
  - chest examination
- A post-bronchodilator spirometry assessment (3 readings) Urine pregnancy test (females of childbearing potential).

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- Standardised screening trial-specific questionnaire as described in section 8.12.
- Blood test for CRP (see section 8.13)
- Confirmation of Eligibility Criteria and enrollment to the trial. **If the patient is too unwell for randomisation (as defined in the exclusion criteria) then further investigation and/or treatment may be started at this point according to the judgment of the study doctor. The patient will not be enrolled into the trial.**
- EQ5D, SGRQ (assessing symptoms over the previous 4-week time frame) and CAT questionnaires (to be done before after eligibility has been confirmed and before the IMP is dispensed).
- treatment allocation and issue of patient trial number
- Study prescription.
- A blood sample will be collected for laboratory CRP levels as described in section 8.13. (results do not need to be available before the patient commences treatment);
- Serum sample for future laboratory analysis (See section 8.13).
- Where patients are able to spontaneously expectorate sputum, a sample will be taken (see section 8.13)
- The patient will be given diary cards for the duration of the study period, along with a symptom code card, and asked to record their symptoms daily (see section 8.12).
- The patient will also be given a trial contact card and will be asked to show this to any other healthcare professionals they may see during the study period, and request those healthcare professionals to contact us with any queries regarding the study. The patient will also be asked to contact us if they have any worsening respiratory symptoms, suspected side effects, or other medical problems during the study period, so that these can be recorded and discussed.
- IMP dispensing and and patient instructed on precautions and how to take the study medication.
- An appointment will be made for 7 days after the screening visit. If the patient provided a sputum sample at screening then a sputum pot will be given to the patient in case they are able to expectorate and bring a sample on the morning of the appointment. Patients will also be asked to bring any unused medication with them to this visit.

8.5 Treatment procedures

- Ciprofloxacin: 500 mg, twice daily for 1 week (oral)
- Placebo: one capsule, twice daily for 1 week.

Patients will commence the study medication on the day of screening (visit 1)

8.6 Follow-up visits (V2 & V3)

Patients will return to the hospital at 7 (+3) days (V2) and 28 (+/-3) days (V3) after V1 for follow up appointments. The following procedures will be carried out:

- The occurrence of AE/SAE and exacerbations will be checked and recorded.
- Diary cards will be checked and the patients reminded/re-educated on how to fill these in correctly (see section 8.12).
- Changes to concomitant medications will be recorded including start and stop dates of any modified treatments.

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- Blood sample for CRP analysis (see section 8.13)
- Serum sample for future laboratory analysis (see section 8.13)
- Spirometry (see 8.12).
- Where spontaneously expectorated, sputum will be collected and subsequently analysed for bacterial load and antibiotic resistance
- CAT symptom questionnaire.
- At V2 (at 7 days) a pill count will be performed and any unused medication collected to check adherence to the IMP.
- Further investigation and treatment may be organised if indicated in the opinion of the study doctor. This will fall outside the usual study procedures but will be fully documented in the CRF.

8.7 Follow-up telephone call

The patient will be contacted by telephone between days 50-60 for a telephone review. The following will be carried out and documented in the CRF:

- Telephone consultation and assessment for AE/SAE and any exacerbations
- Reminder to fill in diary cards
- General discussion and identification of any problems

8.8 Ongoing study monitoring

Patients who are participating in other observational research studies (for example the London COPD Cohort, COPDMAP or the ECLIPSE legacy study) may continue their usual monitoring procedures during this study. Patients enrolled in other interventional research studies (i.e. receiving another IMP) will not be recruited to the current study.

8.9 Exacerbation visits (if applicable)

Patients will be asked to contact the study team by telephone if they develop worsening respiratory symptoms at any point during the study period. If the patient is able to they will be asked to attend to see the study team on the same day. Where the patient is hospitalised on site, and well enough to carry out study procedures, the study team may visit the patient in hospital for this. If the patient is too unwell or unwilling to attend for a study visit then they will seek treatment for the exacerbation in their usual way. They will still be asked to inform the study team and this will be recorded in the CRF.

The following will be carried out:

- Review of symptoms and diary cards to confirm exacerbation
- Clinical examination and recording of pulse, oximetry, blood pressure, heart rate and respiratory rate
- Spirometry to assess FEV1 and FVC (see 8.12)
- CAT symptom questionnaire
- A blood sample for CRP analysis (see section 8.13)
- serum sample (see section 8.13)

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- Sputum sample will be collected if spontaneously expectorated. (see section 8.13)
- Treatment for the exacerbation will be dispensed as needed via the hospital pharmacy and recorded as concomitant medication.
- Further investigation (e.g. chest radiograph) and treatment may be organised if indicated in the opinion of the study doctor. This will fall outside the usual study procedures but will be fully documented in the CRF.

8.10 End of Study Visit (V4)

Patients will return to the hospital 90 (+/- 3) days after IMP issue, and the following assessments will be made:

- The occurrence of AE/SAE or exacerbations will be checked and recorded.
- Spirometry will be performed to assess FEV1 and FVC (see section 8.12).
- Diary cards will be collected by the investigator.
- SGRQ (4 week version) and CAT questionnaires.
- EQ5D.
- A sputum sample will be taken from the patient (See section 8.13).
- Any changes to the concomitant medications will be recorded including start and stop dates of any modified treatments.
- A blood sample will be collected for CRP analysis (See section 8.13).
- Serum sample for future work (see section 8.13.
- Further investigations (e.g. chest radiograph) and treatment may be organised if indicated in the opinion of the study doctor. This will fall outside the usual study procedures but will be fully documented in the CRF. If the patient requires ongoing clinical follow-up this will be organised via local NHS services and the patient's general practitioner.

8.11 Flowchart of study assessments

This can be found in section 22.

8.12 Clinical Procedures and Data collection

- **Post-bronchodilator Spirometry**: to assess FEV1 and FVC. A minimum of three spirometry readings will be taken to assess FEV1 and FVC. The highest individual FEV1 and FVC readings will be used to calculate the FEV1/FVC ratio and for comparison with the predicted normal value. The spirometry will be considered post-bronchodilator if the patient has taken their usual long-acting bronchodilator medication OR if they have had a short-acting bronchodilator administered in clinic 10-15 minutes prior to spirometry testing. Spirometry will be performed according to the standardised ATS/ERS Consensus statement [Miller et al., ERJ, 2005].
- **Diary Cards**: These cards will be used to measure changes in symptoms/side effects, as well as in defining exacerbations for the primary endpoint, and therefore will be carefully explained to the patient at this time.
- **Basic physiological measurements and clinical examination**: These include blood pressure, oxygen saturations, pulse oximetry, respiratory rate, pulse rate, height and weight. These will all be performed in the usual manner.

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- **Questionnaires (study specific symptom questionnaire, EQ5D, CAT, SGRQ)** will be given to the patient to complete while in the clinic room. The study doctor will be on hand to answer any questions and give any necessary assistance.
- **Blood sampling** will be carried out in the usual manner. Laboratory procedures are detailed below.

8.13 Laboratory Procedures

Samples will be collected by delegated research staff at sites.

- **CRP Blood samples:** will be analysed from study visits via the routine NHS biochemistry laboratory for CRP levels using a point-of-care testing CRP analyser.
- **Serum Samples**: will be processed according to a standardised SOP and stored at -80C or future analysis of inflammatory markers.
- **Sputum samples**: will be collected from patients and processed as clinical samples in the hospital Microbiology laboratories for:
  - Analysis for bacterial numbers by quantitative culture methods.
  - Evaluation of any bacterial resistance by susceptibility testing +/- gene sequencing.

Sputum samples will be processed according to a standard SOP and stored at -80C at sites and will be transferred in batches to the main laboratory at ROYAL BROMPTON and Harefield NHS Foundation Trust for storage and further analysis. Quantitative PCR bacterial detection will subsequently be carried out according to the relevant protocol/SOP.

All Stored Sample tubes will be labelled with the unique subject number and date of collection and logged at the study site and receiving laboratory. Consent for the collection and storage for future studies will be obtained at study entry, and all storage and sample and analysis will take place in appropriately equipped and licensed facilities either in the Dept of Medical Microbiology at the RFH London or at the COPD Unit at the NHLI . If data from the analysis is to be transferred outside of the EU, consent for this will be obtained separately.

8.14 Definition of end of trial

The end of the trial will be defined as the date of the last hospital visit by the last study participant.

8.15 Discontinuation/withdrawal of participants and 'stopping rules'

Patients will be discontinued from the study when one or more of the following takes place:

- When patients drop out of the study, with reasons recorded wherever possible.
- SUSAR
- AE/SAE of any type which prevents continued participation in the study, with reasons recorded.
- Patient commenced on medication that is contraindicated with the IMP (e.g. tizanidine). In this case the IMP will be discontinued and the patient will continue study procedures as per intention-to-treat protocol.

In all cases, when patients are discontinued from study medication, the following minimum information will be recorded in the CRF by the research fellow:

- Date of discontinuation

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- Date last study medication taken
- Pill count/drug count
- A sputum sample taken if possible
- Any SAE/AE

Subjects who cease taking their randomised treatment (non-compliers) will continue to be followed up at the end of study visit (day 90). They will not be "replaced" with a further randomised patient (i.e. intention to treat analysis).

It is thought unlikely that the trial will be stopped prematurely as the study IMP is routinely used for a similar duration to that here. However If a number of SAEs occur that in the opinion of the TSC are deemed unacceptable (if IMP behaving outside the normal safety profile) then the trial will be prematurely stopped.

9 Investigational Medicinal Product

9.1 Name and description of investigational medicinal product(s)

Ciprofloxacin is a fluoroquinolone antibacterial agent. Its bactericidal action results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

Placebo is a tablet containing lactose and other pharmacologically inactive substances.

Ciprofloxacin and placebo will be over-encapsulated to ensure that blinding is maintained for both the study team and the patient.

9.2 Name and description of each NIMP

There are no Non Investigation Medicinal Products routinely prescribed for this study.

9.3 Concomitant medication

Patients will continue with their existing concomitant medications. New medication may be prescribed for exacerbations or other medical conditions that require treatment during the study period, according to the clinical judgment of the study doctor. All medication prescribed will be documented in the 'concomitant medications' section of the CRF and details of the consultation leading to the prescription will be documented in the relevant section (for exacerbation) or in the notes section.

Oral corticosteroids will be permitted as treatment for the index exacerbation.

Where the patient is already taking medication that is contraindicated as per the SPC (e.g. tizanidine, methotrexate) the patient will not be entered into the trial. If the patient needs to start a contraindicated medication during the seven day IMP course, the IMP will be discontinued but the patient followed up as per intention-to-treat analysis. See section 8.15.

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9.4 Description and justification of route of administration and dosage

- Oral Capsules; this is the standard route of antibiotic therapy for COPD exacerbations unless very unwell and requiring hospital admission.
- Ciprofloxacin: oral dose of 500 mg, twice daily for 1 week or Placebo: one oral capsule twice daily for 1 week. There are no dose modifications for this trial.
- Capsules are to be swallowed un-chewed with fluids. They can be taken independent of mealtimes however should not be taken with dairy products or mineral-fortified fruit juice.

9.5 Preparation and labelling of Investigational Medicinal Product

Ciprofloxacin is a UK marketed product which will be over encapsulated by a MIA IMP holder in UK. Placebo capsules using the same backfill of the active IMP will also be manufactured, under the same conditions. Preparation and labelling of the investigational medicinal products (active and placebo) will be carried out by the Manufacturing Unit at the Royal Free hospital. The labels will not disclose the active or placebo content to preserve the Blind. The labels will meet Annex 13 of GMP requirements and will be approved by the sponsor and regulatory authority

9.6 Drug accountability

RFH manufacturing pharmacy will be responsible for QP release of all IMPs and shipping the IMPs to sites via a courier service. IMP shipping arrangement instructions for site pharmacy will be in the Summary of Drug Arrangements. Usual procedures for monitoring of temperature and transport conditions of the IMP will apply and will be documented on the IMP shipping form. Upon receipt of the IMP, the site pharmacy will confirm receipt of the IMPs by posting/faxing back the accompanying shipping form to RFH manufacturing pharmacy and copies retained at trial sites. In cases where the IMP was damaged or not stored correctly this will warrant an urgent notification to the RFH manufacturing pharmacy and a replacement will be arranged. RFH manufacturing Pharmacy will be responsible for dispatching replacement IMPs to pharmacy sites. Site pharmacy will be responsible for logging receipt of the IMPs on the site accountability log within the hospital pharmacy file. Full IMP accountability will be conducted during the trial, all IMP will be dispensed and logged in the local pharmacy site file.

All used/unused IMPs will be collected from the patients by delegated research staff at both sites, to be then forwarded onto the corresponding research site Pharmacy for updating the drug accountability log in the hospital pharmacy file in each site. Drug destruction will be conducted, once agreed with the sponsor and in accordance to local pharmacy practice, and this will be documented in the drug destruction log in the hospital pharmacy file in each site.

9.7 Source of IMPs including placebo

Oral ciprofloxacin tablets will be sourced through pharmacy at the RFH and will be over encapsulated by the Manufacturing Unit that holds a valid UK MIA IMP licence. Placebo capsules will be manufactured using the same backfill of the Active will also be manufactured under the same conditions of the Active. It will then be shipped to site pharmacies. The sourcing arrangements are detailed in the Summary of Drug arrangements.

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9.8 Assessment of compliance

9.8.1 Compliance to the IMP

- Patients will be asked to complete a daily diary card for the whole period of the trial (i.e. 90 days) to record daily symptoms, patient status, and the need for further therapy. This will also include documentation of IMP compliance, and any missed doses of study medication, during the week of IMP therapy.
- Patients will be advised to complete the daily diary cards in the morning prior to taking any study medication.
- Pill counts will be taken at visit V2
- Compliance to the IMP will be documented in the source data (Case Report Form)
- As this is an intention to treat analysis, there will be no minimum level of compliance to the IMP and therefore non-compliance will not result in the withdrawal of the patient.

9.8.2 Compliance to the Protocol

Noncompliance to the protocol study procedures will be documented in the Case Report Form and on the protocol deviation log by the investigator and reported to the Sponsor as agreed. As this is an intention to treat analysis, persistent noncompliance to study procedures by the patient will not result in withdrawal from the study and they will continue to be followed up as per protocol requirements.

9.9 Post-trial IMP arrangements

Trial IMPs will not be available after the end of trial and patients will revert to standard best practice of care post-trial. This will clearly be stated in the patient information sheet.

10 Recording and reporting of adverse events and reactions

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which **is related** to any dose administered to that subject. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: - results in death,

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adverse reaction	- is life-threatening, - requires hospitalisation or prolongation of existing hospitalisation, - results in persistent or significant disability or incapacity, or - consists of a congenital anomaly or birth defect.
Important Medical Event	These events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorization, in the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
SUSAR	Suspected Unexpected Serious Adverse Reaction

10.2 Recording adverse events

Reported symptoms and illnesses will be reviewed by the study doctor and discussed with the PI as to causality and expectedness of the event, and a decision made as to whether this qualifies as an SAE or SUSAR. Reporting of SAEs and SUSARs will follow established sponsor SOPs and to the competent authority and research ethics committee (REC), if applicable. An independent data monitoring committee will assess safety data during the course of the trial.

All adverse events will be recorded in the paper CRF (which is the source data), whether believed to be related or unrelated to the treatment.

All SERIOUS adverse events must be recorded in the CRF and AE log.

If the investigator suspects that the disease has progressed faster due to the administration of the IMP, then she/he will report this as an unexpected adverse event to the sponsor.

Clinically significant abnormalities in the results of objective tests (e.g. ECG) may also be recorded as adverse events. If the results are not expected as part of disease or IMP, these will also be recorded as unexpected.

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

All adverse events will be reportable to the Sponsor up to 30 days after the last IMP administration.

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10.3 Assessments of Adverse Events

Each adverse event will be assessed for the following criteria:

10.3.1 Severity

Category	Definition
Mild	The adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

10.3.2 Causality

The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

10.3.3 Expectedness

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Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with the information about the IMP listed in the SPC **or clearly defined in this protocol.**
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with the information about the IMP listed in the SPC

The reference document to be used to assess expectedness against the IMP will be the SPC appended to the simplified IMPD used by the manufacturer to source and over encapsulate Ciprofloxacin for this trial. The protocol will be used as the reference document to assess disease related and/or procedural expected events as described in section 10.4 Procedures for recording and reporting Serious Adverse Events.

10.3.4 Seriousness

Seriousness is defined for an SAE above.

Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be completed according to the sponsor's SOP

10.4 Procedures for recording and reporting Serious Adverse Events

- All serious adverse events will be recorded in the paper CRF, and the sponsor's AE log by the delegated research staff at site. The AE log will be reported to the sponsor at least once or twice per year.
- All serious adverse events will be reported to the sponsor on a SAE form within 24 hours, **with the exception of COPD exacerbations requiring hospital admission and without other complication**. Up to 30% of patients discharged from hospital following a treated exacerbation of COPD will be readmitted within 90 days and therefore this SAE is likely to occur often; it is also an expected end-point of the study. Complicated exacerbations (e.g. pneumonia, requiring ventilatory support or other procedures including chest drainage) will be reported to the Sponsor. Where there is uncertainty as to whether the admission is complicated or should be classified as serious, this will be discussed with the Sponsor within 24 hours of the site becoming aware of the event.

  The Research Fellow will complete the sponsor's serious adverse event form and the form will be faxed or emailed to the sponsor [Fax: 0203 311 0203, Email: Nabila.Youssouf@imperial.ac.ukinsert fax/email details], within 24 hours of his / her becoming aware of the event. The event will be discussed with the Chief or Principal Investigator and any SAE queries raised by the sponsor will be responded to as soon as possible.
- All SUSARs must be notified to the sponsor immediately (or within 24 hours) according to the sponsor's written SOP.

Exceptions to SAE reporting requirements:

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Symptoms of COPD exacerbations requiring hospital admission and without other complication, such as:

- Breathlessness and reduced exercise tolerance
- Increased sputum volume
- Increased sputum purulence
- Upper airway viral symptoms (e.g. runny nose)
- Wheeze or tight chest
- Sore throat
- Increased cough
- Fever

Example: As the IMPs used in this trial are licensed in the UK and used within their marketing authorization, EXPECTED SARs (as outlined in the SPCs appended to the simplified IMPD for this trial) and listed below will be RECORDED in the CRF. However, SAE forms will not be completed and sent to the sponsor.

The most commonly reported adverse drug reactions with ciprofloxacin are nausea and diarrhoea. As these events are very common with well-established safety data profile, for this protocol, these will not be reportable.

10.5 Managing serious adverse events in a multi-centre trial

The PI of each site will send the report to the CI and the Sponsor concurrently .The PI at each site will review the report first before sending to the CI and the Sponsor as soon as received and within 24 hours. The CI will review the SAE and this will be discussed at the TMG meeting. All SUSARs will be reported simultaneously to the sponsor and to other sites.

Sites reporting to the sponsor and CI will be complete the SAE report as per sponsor's SOP and using IMPERIAL COLLEGE LONDON SAE form.

10.6 Notification of deaths

All deaths will be reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event. Notification of death will take place within 1 day.

10.7 Reporting SUSARs

The sponsor will notify the main REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them.

The procedure for unblinding in the event of a SUSAR is described in section 6.3 of this protocol.

10.8 Development Safety Update Reports

The sponsor will provide the main REC and the MHRA with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team and the Sponsor's office. The report

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will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

This will be done in accordance with the sponsor's SOP

10.9 Annual progress reports

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

The chief investigator will supervise the preparation of the APR.

10.10 Pregnancy (If applicable)

- Female participants in this study are unlikely to be of child-bearing age because of the nature of the disease investigated and the minimum age cut-off. However, in the event of a pregnancy occurring during the study, this must be reported using a clinical trial pregnancy form.
- To ensure subject's safety, each pregnancy must be reported to sponsor within 24 hours of learning of its occurrence. The pregnancy must be followed to determine outcome (including premature termination) and status of mother and child.
- Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortion must be reported as an SAE to the CI and Sponsor within 24 hours of learning of its occurrence.
- Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to sponsor.

10.11 Overdose:

Overdoses of greater than three tablets in a single dose reported by patients will be recorded and notified to the sponsor (this information should be placed on the deviation log). As an intention to treat (ITT) analysis is planned, patients who overdose will still be included in the final analysis and attend for further study procedures where possible.

If an AE/SAE is associated with the overdose the overdose will be fully described in the AE/SAE report form.

10.12 Reporting Urgent Safety Measures

If any urgent safety measures are taken the PI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

Please refer to the following website for details on clinical trials safety reporting:
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

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10.13 The type and duration of the follow-up of subjects after adverse events

All AEs and SAEs must be followed until resolution, until the condition stabilises, until the event is otherwise explained, or the subject is lost to follow-up. The investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information should be recorded on the originally completed SAE CRF with all changes signed and dated by the investigator.

Any SUSAR related to the IMP will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

10.14 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor's SOP on the will be followed.

11 Data management and quality assurance

11.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and trial identification number, will be used for identification.'

11.2 Data collection tools and source document identification

The final version will be approved by the sponsor. All data will be entered legibly in black ink with a ball-point pen. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialled and dated by the person making the alteration. Overwriting or use of correction fluid will not be permitted.

There will also be an electronic version of the CRF, and all data contained in the paper CRF and any other source documentation will be transcribed into this.

The data collection methods for this study will comprise the following:

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- Patient and study-specific data (e.g. medical history, clinical examination) will be collected and directly transcribed onto the paper CRF by the research fellow. This will form the main source document.
- Symptom and quality of life indices (questionnaires) will be completed by the patients onto standard template forms.
- Data will be entered from both sites onto a password protected web based electronic case report form collection system (Sealed Envelope) and this will be the trial database.

The following Source Documents will be collected:	**Type**
Paper Case Report Form	Stand alone document
Consent form from patient	Stand alone document
Date and cause of death (where appropriate)	Death certificate
SGRQ EQ5D CAT	Stand alone questionnaires (completed by patient)
Daily Diary cards	Stand alone document (completed by patient)
CRP result – point-of-care testing	Printed label and/or hand transcribed into paper CRF
Lab results- blood Sputum analysis data	Hospital data base
Pregnancy test result	Hospital data base.
Master Patient List	Stand alone document
Record of Initial Contact telephone call and patient details	Stand alone document
Hospital discharge summary or other information regarding the initial exacerbation (**where available only**)	Stand alone document

NOTE: Blood, sputum and pregnancy test results will be transcribed into the paper CRF. Any print out hard copies of results will be kept with the paper CRF.

As a minimum, the following will be recorded directly on to the paper CRF (Case Report Form) which will then be transcribed into the electronic CRF:

- Dated statement that the subject has entered the clinical study and that written consent was taken prior to the subject's entry into the study
- A medical history at the screening visit.
- Details of the index exacerbation, including date of treatment onset (day -14) and (if applicable) the date that the patient says symptoms returned to normal
- Physical examination findings
- Spirometry
- Inclusion/exclusion criteria
- Confirmation of diagnosis of the disease being treated (COPD)
- Eligibility of patient for the study

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- Initials, sex and date of birth
- Demographic data
- Smoking history
- Exacerbation frequency in previous year (patient recall)
- Randomisation number
- Treatment kit number
- AE/SAEs
- Pill count
- Concomitant medication
- Off study (date off study/last study medication taken, reason off study)
- Subsequent visit dates (including unscheduled visits)
- Start and stop dates of study medication

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database. Patients who have not returned their study questionnaires or missed a scheduled visit will also be telephoned to reschedule a visit or request them to post the questionnaire to ensure completion of data.

11.3 Data handling and analysis

A data management SOP will be followed. A web-based database will be programmed by Sealed Envelope. The software is Sealed Envelope's own software application with an underlying MySQL database for storage. It has been used successfully in other trials over the last five years.

The web-based database will include the following:

- All information recorded in the paper CRF
- Randomisation records
- EQ-5D, CAT and SGRQ questionnaires
- Diary card

The system will also have the following attributes:

- Password protected user accounts for Delegated staff at each site.
- Single data entry with validation checks and source data verification against the data in the database.
- Have the ability to edit data and view history of edits. Only authorised delegated members of staff at each site will be able to edit the data from that site.
- Have the ability to add queries to CRFs to assist with follow-up of missing data or other issues.
- Full audit log of all changes to data
- The delegated research staff at both sites and the statisticians in Cambridge will have read-only access to the electronic data set (back end access) to download whenever required for data

cleaning and/or analysis purposes. Queries can be raised and will be addressed by the authorised delegated members of staff at site.

- An audit trail will be maintained of any change or correction to the case report form or the electronic database. Data will be generated, recorded and reported in compliance with the protocol and with Good Clinical Practice. Free text variables will also be allowed to describe, for example, deviations from the protocol. These will also be recorded on the protocol deviation log.
- The CRFs are designed for ease of use and to minimise cross-validation errors. Nevertheless, data cleaning and monitoring will be conducted by the trial manager and statistician during and at the end of the trial. It will be possible to check patient notes with any queries that arise.
- Data will not be double entered.
- Data entries will be checked to ensure they fall within the normal parameters at the time of entry- data will also be reviewed by the statistician and members of the steering committee for other queries.
- The Authorised delegated members of staff at both sites will complete data entry in the paper CRF at the time of seeing the patient. This data will then be entered onto the online database. Site staff may insert new records and browse records they have previously entered, but will not be able to access records of patients from the other trial site.
- Data entered via the website will not contain personal identifiers.
- Each patient will be given a unique number, which will be linked to a paper record of the participants' names and addresses. This will only be accessible by trial personnel seeing patients at the study site. Any patient-identifiable data will be stored securely and separately from anonymised documents at each site, and will not be entered onto the electronic database.
- The database will also be accessed centrally by the study statistician and the steering committee (on a read only basis) and analysed to assess recruitment and retention levels and for data cleaning according to specified SOPs developed by the research team.
- Data analysis for the trial will be done by the trial Statistician who is independent to the person entering the data on to the database.
- All data collected will be in adherence to Data Protection Act 1998 , as well as IMPERIAL COLLEGE LONDON Information Security Policy and Trust Information Governance Polices. The data will be stored in a highly secure data centre owned and operated by Rackspace in the UK (www.rackspace.co.uk). The data centre is audited annually under the SAS70 accreditation system. Backup is daily to tape on-site (2 week retention) and hourly offsite to a failover server with full disk encryption held at Sealed Envelope's offices. In the event of disaster at the main data centre online operations can be switched to the failover server.

11.4 Record keeping and archiving

Archiving will be authorised by the Sponsor following submission of the end of study report.

- Site Files and Consent Forms will be securely stored with access restricted to trial authorised persons only at participating sites.
- CRF will be securely stored with access restricted to trial authorised persons only at participating sites as a hard (paper) copy.

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- All essential documents held at sites (e.g. CRF, Site Files and Consent forms) will be archived at site according to local trust policy. These documents will be archived for a minimum of 5 years after completion of the trial.
- The electronic trial database, which includes an electronic version of the CRF, will be stored electronically on the server of Sealed Envelope™. Authorised staff at the Dept of Respiratory Medicine at the ROYAL BROMPTON and Harefield NHS Foundation Trust, Dept of Clinical Sciences, as well as to the study statisticians (Dr Daniel Jackson and Mr Martin Law) at the MRC Biostatistics Unit, Cambridge, will be able to access this data as needed. At the end of the analysis, the database will be securely transferred electronically (based on the secure processes Sealed Envelope have in place and the arrangements will be detailed in the data management SOP) to the Dept of Respiratory Medicine at the ROYAL BROMPTON and Harefield NHS Foundation Trust. Only Trial authorised persons will have access to the database.
- Chief Investigator is responsible for the secure archiving of essential trial documents within the TMF for the trial and the trial database as per their trust policy. All essential documents will be archived for a minimum of 5 years after completion of the trial.

Destruction of essential documents will require authorisation from the Sponsor.

12 Statistical Considerations

Dr Daniel Jackson and Mr Martin Law are the trial statisticians who will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

12.1 Outcomes

12.1.1 Primary outcome

The primary outcome will be the time in days to the first day of the next exacerbation following IMP start (at day 0, 14 days after the initial exacerbation), up to a maximum of 90 days. Exacerbation is defined fully below. Patients who do not suffer a recurrent exacerbation will be censored at the end of follow-up / time of drop-out.

The onset of the next (recurrent) exacerbation will be defined as **either**:

1) The first day of treatment with antibiotics and/or steroids for an exacerbation of COPD (HCU definition), **or**
2) The first of two or more consecutive days of increased respiratory symptoms recorded on the daily diary cards, either:
    a. Two ‘major’ symptoms (increased dyspnoea, increased sputum volume, or increased sputum purulence), or
    b. One ‘major’ and one ‘minor’ symptom (cold, wheeze/chest tightness, sore throat, cough or fever).

A recurrent exacerbation will only be diagnosed based on diary cards if there are a minimum of five symptom-free days after the end of the previous exacerbation.
The end of the first exacerbation will be defined as the first day of two consecutive symptom-free days.

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12.1.2 Secondary outcomes

- Duration of the initial exacerbation (from point of retreatment V0) based on diary card symptoms. The exacerbation will be considered to have ended on the first of two consecutive symptom-free days.
- Treatment-related adverse events
- Exacerbation frequency (rate) during follow-up.
- Total number of antibiotic courses received during follow-up
- Rates of (re)admission/re-attendance to hospital during follow-up
- Changes in respiratory healthcare status, during follow-up, assessed using SGRQ and CAT. Changes in lung function during follow-up.
- Change in CRP during follow-up.
- Changes in bacterial resistance to ciprofloxacin as assessed by standard culture and sensitivity methods at trial beginning and end (in those patients in whom sputum is spontaneously expectorated)
- Change in bacterial load from trial beginning to end (in those patients in whom sputum is spontaneously expectorated)
- Cost-effectiveness will be assessed as part of a future study (WP5)

12.2 Sample size and recruitment

12.2.1 Sample size calculation

Over the two centres, based on HES data, we anticipate that a total of 218 hospital admission or ambulatory exacerbations will be identified over the 18-month recruitment period (http://www.hscic.gov.uk/hes). Based on data from the London COPD Cohort, 33% of exacerbating patients have a CRP of 8 or above at 2 weeks. Furthermore, our pilot data suggest that of patients with CRP >8mg/L, at least 60% of patients report symptoms at day 14. Thus, assuming that 90% of eligible patients will agree to take part in the study, we expect 218/3 ≈ 73 patients eligible due to CRP level, 0.6(218-73) = 87 eligible due to symptoms at day 14, and to randomise 0.9(73+87)=144 patients in total.

Pilot data from our group suggests that at a level of CRP>10mg/l at 14 days, there will be 36% recurrent exacerbations within 50 days. Assuming a constant hazard of exacerbation this translates to around a 55% recurrent exacerbation rate at 90 days. A similar proportion of recurrent exacerbations are seen in the London COPD cohort (for both CRP>10 and CRP<10). An observational database study by Roede et al. (2008) reported a hazard ratio of 0.62 when antibiotics were given in addition to usual treatment. Allowing for a 5% dropout, we will therefore have 80% power at a 5% two-sided significance level to detect a 22% absolute reduction in the proportion of exacerbations seen at 90 days (from 55% to 32%), using time-to-event (survival) methods. This is equivalent to detecting a hazard ratio of 0.48 over the follow-up period.

The recruitment period for this trial is estimated to be 18 months, requiring approximately 8 patients per month to be randomised across both sites.

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12.3 Statistical analysis plan

12.3.1 Summary of baseline data and flow of patients

A CONSORT diagram will be produced to illustrate recruitment and flow of patients through the study. (http://www.consort-statement.org/)

The variables to be collected at day zero are:

- Bacterial load: If spontaneously expectorated, sputum samples will be collected and analysed to measure bacterial load in the lung. Concentrations will be log transformed and expressed as log10 CFU (colony forming units)/ml. Collection of sputum is not a requirement for study entry and this will therefore form a subgroup analysis.
- CRP: Blood samples will be collected and analysed for CRP levels to measure presence of inflammation in the body. This is measured in milligrams per litre of blood (mg/L)
- Spirometry: A test used to measure lung function. Specifically the measurement of volume and flow of air inhaled and exhaled. The parameters measured will be the Forced vital capacity (FVC) and Forced expiratory volume (FEV) at 1 second. The FEV1/FVC ratio and FEV1 as a percentage of Predicted Normal value will be computed.
- SGRQ: This is a standardized self-completed questionnaire for measuring impaired health and perceived well-being ('quality of life') in airways disease. It has been designed to allow comparative measurements of health between patient populations and quantify changes in health following therapy.
- EQ5D: This is a standardised instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status. Health outcome at treatment end will be compared to baseline data to assess change in health status.
- CAT: This is a standardised self-completed symptom questionnaire
- Age and Gender
- Smoking status
- Self-reported exacerbation frequency in the previous year

Summary statistics for all baseline variables will be presented (mean, standard deviation, median, interquartile range for continuous variables, percentages for categorical variables), stratified by treatment group, site and presence of symptoms to assess baseline comparability. No formal statistical tests of these baseline comparisons will be made.

The flow of patients through the trial will be summarised in a CONSORT diagram, showing all exclusions including reasons for non-randomisation and drop-outs / lost to follow-up statistics. The CONSORT diagram will be stratified by randomised group.

12.3.2 Primary outcome analysis

The primary outcome is the time to the next exacerbation within the 90-day study period. This will analysed using Cox proportional hazards regression and the estimated hazard ratio between the groups will be reported, along with its standard error. A log-rank test will be used to test the primary hypothesis. A Kaplan-Meier plot will be produced. Patients who do not suffer a recurrent exacerbation during follow-up will be treated as censored observations at their end of follow-up time. As analysis is intention to treat, non-compliers will be treated as belonging to the treatment group originally randomised to. Where patients withdraw from follow up, every effort will be made

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to ascertain their primary outcome (i.e. date of next exacerbation OR exacerbation-free survival to 90 days) by telephone.
Analysis will be adjusted for a number of important baseline covariates including; sex, exacerbation phenotype, level of symptoms (CAT), levels of CRP, disease severity (FEV), baseline exacerbation frequency in previous year, hospital admission at initial exacerbation.

12.3.3 Secondary outcome analysis

Summary measures of the secondary endpoints will be presented (mean, standard deviation, median, interquartile range for continuous variables, percentages for categorical variables) by treatment group and for both baseline and end of trial follow-up visits. The percentage of missing data will be summarised.

- Time until resolution of first exacerbation will be compared between the active treatment and placebo groups, using a log-rank test. Cox regression analysis will also be conducted adjusting for important baseline covariates.
- The number of treatment-related adverse events will be analysed by using (over dispersed) Poisson regression or a suitable zero-inflated model and adjusted for treatment group and important baseline covariates.
- Exacerbation frequency: The rate of exacerbations experienced during the study period will be analysed by using (over dispersed) Poisson regression or a suitable zero-inflated model and adjusted for treatment group and important baseline covariates and with length of follow-up as an offset.
- Frequency of antibiotic courses: The rate of antibiotic courses received for patients in the active treatment and placebo groups will be compared using using (over dispersed) Poisson regression or a suitable zero-inflated model adjusting for treatment group and important baseline covariates.
- The rate of hospital attendances during the study period will be analysed by using (over-dispersed) Poisson regression or a suitable zero-inflated model and adjusted for treatment group and important baseline covariates.
- Changes in respiratory healthcare status, assessed using SGRQ and CAT. SGRQ (score between 0 and 100) and CAT (score between 0 and 40) from baseline to day 90 will be modelled as a normally distributed random variable by using a suitable transformation (e.g. a Box-Cox like transformation to remove skewness and possible boundary effects). Any analysis will be adjusted for baseline scores, treatment, and other important baseline covariates. Repeated measures analysis will be used to assess treatment effects over time during the follow-up period.
- Lung function: Changes in FEV1, FEV1 as % predicted, and FEV1/FVC ratio and FVC at day 90 from day 0 will be modelled separately as continuous outcomes and assumed to be normally distributed (an appropriate transformation will be applied before analysis if required). Analyses will be adjusted for baseline values, treatment, and other important baseline covariates. Repeated measures analysis will be used to assess treatment effects over time during the follow-up period.
- Change in CRP from study entry to 90 days will be modelled as a normally distributed random variable by using a suitable transformation (e.g. a Box-Cox like transformation to remove skewness and possible boundary effects). Any analysis will be adjusted for baseline CRP, treatment, and other important baseline covariates. Repeated measures analysis will be used to assess treatment effects over time during the follow-up period.

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- Resistance patterns (not resistant, resistant) will be analysed using logistic regression and adjusting for treatment group, baseline values and other important baseline covariates.
- The change in bacterial load from trial beginning to end will be analysed using multiple tobit regression and adjusting for baseline values and other relevant baseline covariates. Values below limits of detection will be treated as left censored observations in the tobit regression analysis.
- Adherence as assessed by pill counts. The number of pills taken over total number dispensed will be modelled using logistic regression (Binomial distribution with logit link). The difference in percent adherence will be assessed between treatment groups.
- Cost-effectiveness will be assessed as part of a future study (WP5)

This study is not powered to test these secondary outcomes – only the primary outcome. As such, analyses of the secondary outcomes will be hypothesis generating only.

12.4 Randomisation methods

Randomisation will be conducted by the research fellow contacting a central randomisation service (Sealed Envelope™) after the patient has provided informed consent and baseline data (Class A method of randomisation).

Patients will be randomised using a 1:1 ratio from a computer-generated permuted block system of variable sizes. Stratification will take place by site and each patient will be randomised to one of the two treatment groups on an individual basis.
Randomisation will further be stratified according to the type of inclusion criteria (persistent symptoms or raised CRP).

12.5 Interim analysis

An interim analysis will not be required on the primary end point. The IMP has a well-established safety record and is being administered for a short course only; all treatment-related adverse events will be reviewed with the PI and trial steering committee during the trial. If there is suspicion that the IMP is acting outside its normal safety profile then further analysis will be undertaken.

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, the procedure for an early termination or temporary halt will be arranged after consultation by all involved parties. This will be recorded in the CRF and documented in the final report. Unblinding at this point is unlikely to be necessary.

The sponsor will submit a written notification to the Regulatory Authority concerned and Ethics Committee/Institutional Review Board providing the justification of premature ending or of the temporary halt.

12.6 Other statistical considerations

Any deviations from the statistical plan will be discouraged. However, any unforeseen changes will be described and justified in the final report, as appropriate. The sponsor, CI, TSC and or DMC will be notified of these deviations. Where required the sponsor and Chief Investigator will notify REC, Regulatory Authorities and the funder.

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13 Name of Committees involved in trial

Trial Steering Group (TSC)
Data Monitoring Committee (DMC)

Each of the above committees will have terms of references described in charters which will be kept within the TMF.

14 Direct Access to Source Data/Documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

15 Ethics and regulatory requirements

The sponsor will ensure that the trial protocol, patient information sheet, consent form, and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and a main research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, as assessed by the sponsor, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before the site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee must apply for NHS permission from their Trust Research & Development (R&D) and be granted written permission. It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval from their Trust Research & Development (R&D). This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 10.12 for reporting urgent safety measures).

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the MHRA and main REC within 1 year after the end of the trial.

16 Monitoring requirement for the trial

A trial-specific monitoring plan will be established for this study. The trial will be monitored with the agreed plan.

17 Finance

Funds for this trial have been secured from the NIHR.

18 Insurance

Imperial College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove

that Imperial College London has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. Imperial College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of Imperial College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

19 Publication policy

All proposed publications will be discussed with the Sponsor prior to publishing other than those presented at scientific forums/meetings. Please refer to Imperial College London publication policy.

The Funder (NIHR) will review publications and poster presentations prior to presentation and, where possible, prior to submission.

Published data will be fully anonymised and none of the patients involved in the trial will be identified in any report or publication.

The study design and the results will be published on Clinicaltrials.Gov

20 Statement of compliance

The trial will be conducted in compliance with the approved protocol, the UK Regulations, EU GCP and the applicable regulatory requirement(s).

21 References

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22 Schedule of Study Visits

	Pre-Screening	Screening visit	First follow up	Second follow up	Telephone call	Exacerbation visit	End of study visit
Day:	-14	0 (±3)	7 (+3)	28 (±3)	50-60 (±3)	As needed	Day 90 (±3)
Visit name:		**V1**	**V2**	**V3**	**Tel1**	**EX**	**V4**
Clinical events:							
Patient identified by treating clinician and referred to study team	**X**						
Patient experiences COPD exacerbation	**X**					**X**	
Patient commences treatment for exacerbation (NIMP, as needed)	**X**					**X**	
Study procedures:							
Informed Consent Form		**X**					
Inclusion/Exclusion criteria applied		**X**					
Medical History		**X**					
Vitals (Blood pressure, Pulse rate, respiratory rate, O2 sat)		**X**				**X**	
Spirometry (FEV1/FVC)		**X**	**X**	**X**		**X**	**X**
Full clinical examination (including Chest exam)		**X**				**X**	
IMP Issue		**X**					
Pill Count			**X**				
Diary Cards/reminder to fill in		**X**	**X**	**X**	**X**	**X**	**X**
Concomitant medication assessment		**X**	**X**	**X**		**X**	**X**
Collect final data for study endpoints							**X**
Assess, record SAE/AE/exacerbations			**X**	**X**	**X**	**X**	**X**
Laboratory Investigations:							
Blood CRP level		**X**	**X**	**X**		**X**	**X**
Store serum inflammatory markers		**X**	**X**	**X**		**X**	**X**
Sputum (analysis/storage), if applicable		**X**	**X**	**X**		**X**	**X**
Pregnancy test if applicable		**X**					
Questionnaires/healthcare indices:							
Screening trial-specific questionnaire to assess presence of symptoms		**X**					
SGRQ		**X**					**X**
CAT		**X**	**X**	**X**		**X**	**X**
EQ5D		**X**					**X**