Targeted Retreatment of Incompletely Recovered COPD Exacerbations With Ciprofloxacin: A Double-blind, Randomised, Placebo-controlled, Multicentre Phase III Trial

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SEB, LA-M, JPA, BHV, PPW, PMAC, GCD and JAW contributed to the study design, protocol and study materials. AIR, SEB, BHV, LJF, DJW, JPA, LA-M, EB, SLE, PPW and PM contributed to patient recruitment and collection of study data at participating centres. ML designed the statistical plan and performed pre-study power calculations. GCD performed the statistical analysis. AIR and SEB wrote the first draft of the manuscript. All authors contributed to interpretation of the data and revision of the manuscript.

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Abbreviation List

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
CAT	COPD assessment test
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein, serum
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global initiative for chronic obstructive lung disease
GP	General practitioner
HR	Hazard ratio
ICS	Inhaled corticosteroids
IMP	Investigational medicinal product
LABA	Long-acting ß-agonist
MRC	Medical Research Council
NIHR	National Institute of Health Research
RCT	Randomised controlled trial
SGRQ	St George's Respiratory Questionnaire

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Abstract

Rationale

COPD exacerbations are prone to non-recovery but there are no data about the effectiveness of retreatment on these prolonged events. We examined whether further therapy with ciprofloxacin for incompletely resolved COPD exacerbations prolonged the time until the next event.

Methods

This multi-centre randomised double-blind placebo-controlled trial studied retreatment with oral ciprofloxacin 500mg or matched placebo twice daily for 7 days in patients with GOLD stage II – IV COPD with persistent symptoms and/or serum C-reactive protein (CRP) ≥8mg/L initiated 14 (+/- 3) days after an index COPD exacerbation. The primary outcome was the time to the next exacerbation within a 90-day period.

Results

Of 826 patients screened at 4 centres, 144 eligible participants with incomplete recovery were randomised to receive ciprofloxacin (n=72) or placebo (n=72). Within 90 days of randomization, 57% of patients in the ciprofloxacin group and 53% in the placebo group experienced 1 or more exacerbations. The median time to the next exacerbation was 32.5 days (IQR 13-50) in the placebo arm and 34 days (IQR 17-62) in the ciprofloxacin arm, which was not significantly different (adjusted hazard ratio = 1.07, 95% CI 0.68-1.68; p=0.76). No significant differences were seen in quality of life scores or lung function between treatment groups.

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Conclusion

In patients with persistent symptoms and/or raised CRP 14 days following a COPD exacerbation, an additional course of ciprofloxacin resulted in no additional benefit compared to placebo. This suggests that non-recovered exacerbations are not driven by ongoing bacterial infection and may potentially be targeted with anti-inflammatory therapy.

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Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are important events that have significant adverse consequences for patients (1). Frequent exacerbations are associated with accelerated lung function decline (2, 3), impaired quality of life (4) and increased mortality (5). There are also significant healthcare cost implications (6).

Exacerbations associated with sputum purulence or increased sputum volume are treated with antibiotics leading to faster resolution of the exacerbation and a longer time to the next AECOPD (7, 8). Despite antibiotic treatment, however, recovery is often delayed. More than one quarter of patients will experience another event during the following 8 weeks (9), whilst 25% do not recover to baseline by 5 weeks (10) and over one-third by three months (11). These recurrent events are associated with substantially increased mortality (11) and this has led to financial incentives for health care services aimed at avoiding hospital readmission (12, 13).

Previously we have reported that serum C-reactive protein (CRP) measured 14 days after an exacerbation was higher (mean=8.8 mg/dl) in patients experiencing another exacerbation within the next 50 days (recurrent exacerbation) than in those who did not (mean = 3.4 mg/dl) (14). A recent trial has demonstrated the utility of point-of-care measurement of CRP at the onset of an AECOPD to target antibiotic treatment successfully, without negative effects on health status outcomes (15). At present, there are no studies assessing the efficacy of further antibiotic treatment for non-recovery of an AECOPD. We therefore evaluated a novel treatment approach using point-of-care measurement of CRP and/or respiratory symptom review to guide antibiotic retreatment 14 days following an index exacerbation. Our aim was to

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address whether retreatment at day 14 would prolong the time until the next exacerbation and hasten recovery of the index event.

Method

Study design

This study was a randomized parallel-group, double-blind placebo-controlled trial performed in 4 academic health centres in the UK. Patients were assessed for incomplete recovery at 14 +/- 3 days following the first day of antibiotic treatment for an AECOPD. Eligible patients were then randomised in a 1:1 ratio to receive oral ciprofloxacin 500mg or matched placebo twice daily for 7 days. Patients were instructed to continue their current COPD inhaled or oral treatment but if further oral corticosteroids or antibiotics other than the investigational medicinal product were clinically indicated at randomisation, then these individuals were excluded. Permuted block randomisation with stratification for site and current smoking status was used via an online portal (Sealed Envelope Ltd, London, UK).

The trial received approval from the National Research Ethics Committee, West Midlands - Edgbaston (13/WM/0364). All patients gave written informed consent. The trial was registered on EudraCT 2012-002198-72 and clinicaltrials.gov NCT 02300220.

Patients

Patients whose exacerbations were treated with antibiotics and/or systemic corticosteroids in accordance with Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidance (16) were screened for participation in this trial. The main inclusion criteria were persistent symptoms and/or a serum CRP $\geq$ 8mg/L on day 14

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following initial treatment. This CRP cut off was selected based on previous work from our group, examining the day 14 CRP in 73 AECOPD (14). Persistent symptoms were defined by any one or more of increased breathlessness, increased sputum volume or increased sputum colour compared to baseline. CRP was measured at the point of care using a Quikread Go CRP analyser (Orion Diagnostica, Helsinki, Finland). Eligible patients had an established diagnosis of GOLD stage II – IV COPD (based on clinical history and spirometry), were 45 years or older, and had a current or past smoking history of ≥10 pack-years. A full list of inclusion and exclusion criteria is provided in the Online Supplement.

Patients were followed for 90 days from randomization and underwent assessment visits on days 7 (visit 2), 28 (visit 3) and 90 (visit 4) after randomisation. Participants were asked to record worsening or new daily respiratory symptoms on diary cards and to self-report and attend for exacerbation visits if necessary (figure 1). New exacerbations during follow-up were assessed by the study physician based on the patient's symptoms and treatment record on the diary card or when seen in clinic. An exacerbation was defined as an increase in respiratory symptoms for two consecutive days, with at least one major symptom (dyspnoea, sputum purulence or sputum volume) plus either another major or a minor symptom (wheeze, cold, sore throat and cough). The first day of these increased symptoms was defined as the day of onset of the exacerbation (10). The full trial protocol is available in the online data supplement.

At clinic visits post-bronchodilator spirometry was measured with a Flow Screen II spirometer (eResearchTechnology GmbH, Estenfeld, Germany) in accordance with ATS/ERS guidance (17). Blood samples were collected for measurement of CRP in

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the hospital laboratory for longitudinal analysis of CRP during the study. Vital signs were recorded and respiratory symptoms assessed using the CAT questionnaire. At randomisation and at day 90, the St George's Respiratory Questionnaire (SGRQ) was completed by the patient. Spontaneous sputum samples were obtained when possible and sent for routine bacterial culture; sputum induction was not performed.

Main efficacy outcomes

The primary outcome was the time from randomisation to the next exacerbation within a 90-day period. Pre-specified secondary outcomes included the duration of the initial exacerbation, change in CRP and health status (assessed by SGRQ and CAT questionnaire).

Sample size

The required sample size was calculated as 72 patients per group, 144 in total, in order to detect a difference in the primary endpoint at a two-sided significance level of 0.05 with 80% power. This is a novel study design, and in the absence of available prior data the power calculation was based on a survival analysis assuming proportional hazards with re-exacerbation within 90 days of 70% in the placebo arm and 45% in the treatment arm (hazard ratio [HR]=0.46). This sample size allowed for a drop-out rate of 5% and recruitment to target within the study centres.

Statistical Analysis

The primary endpoint was assessed using a Cox's proportional hazard model with pre-specified adjustment for patient's self-reported history of exacerbations over the previous year and with stratification for study centre. Survival data was censored at 90 days or at patient withdrawal. Patient demographics are reported as mean

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(standard deviation), median (inter-quartile range) or as percentages. Differences in patient characteristics between sites were compared by ANOVA, Kruskal-Wallis or Chi-squared test as appropriate. Differences in the number of exacerbations during the 90 days of observation were assessed using a negative-binomial regression with adjustment for time under observation. CAT scores were analysed by random effect linear models to accommodate repeated measurements on the same patient. All analyses were performed using STATA 12.1 (STATA Corporation, College Station, TX, USA) and according to the principal of intention-to-treat. All statistical tests were two-sided and a p-value <0.05 considered significant. Apart from the primary outcome all statistical analyses should be considered as exploratory.

The full study protocol and pre-specified statistical analysis plan are included in the online supplement.

Results

Patients

Between July 2014 and November 2017, 826 patients with an AECOPD attending an emergency department or respiratory outpatient clinics were identified at the 4 hospitals. A total of 224 of these patients were screened at 14 days and 144 randomized to either ciprofloxacin (n=72) or placebo (n=72) (figure 2). The most common reason for screening failure was recovery in symptoms of the index exacerbation (n=38 [17%]; see figure 2). Demographic and clinical characteristics of randomised subjects were well balanced across treatment arms (Table 1). There were no significant differences in adherence between groups; the median number of

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treatment doses taken by patients was 14 (IQR 14-14) in the ciprofloxacin and 14 (IQR 14-14) in the placebo arm (chi squared test, p=0.945).

Clinical presentation

Of the 144 participants, 119 reported continuing symptoms of which there were 22 type I, 34 type II and 63 type III Anthonisen criteria exacerbations based on symptom questionnaires recorded at randomisation (table 1). There was good balance between treatment arms. In addition to the 22 type I exacerbations, there were 19 patients with persistent sputum purulence. 64 participants randomised had a positive CRP. Overall the mean CRP for included particpants was 15.3mg/L (SD 9.23). 73 patients had ongoing sputum purulence and/or Anthonisen type 1 and/or a raised CRP.

Primary endpoint

At 90 days after commencing retreatment, 41 (56.9%) patients in the ciprofloxacin and 38 (52.8%) in the placebo group had experienced 1 or more exacerbations. The median time to the first exacerbation in the ciprofloxacin group was 34 days (IQR 17-62) and 32 days (IQR 13-50) in the placebo group. There was no significant difference between treatment arms in a pre-specified Cox proportional hazard model analysis that adjusted for the number of exacerbations in the previous year and stratified by centre (HR = 1.071, 95%CI 0.684-1.676, p=0.764; Figure 3). Patients with a prior history of more exacerbations in the previous year were at greater risk of another event (HR = 1.18, 95%CI 1.060-1.319; p=0.003).

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Subgroup analyses

The primary outcome findings were unchanged if only those exacerbations included for reasons of persistent respiratory symptoms were examined, or only those with a raised CRP at 14 days (see table 2).

There was a significant difference between the two major recruitment sites (Royal Brompton, London (n=106) and Aintree, Liverpool (n=25), with a greater risk of a subsequent exacerbation at Aintree (hazard ratio=2.14; p=0.006).

Secondary endpoints

Duration of symptoms post-randomisation

Data was available on 113 patients (78%); 25 participants failed to adequately complete diary cards and 6 participants continually recorded chronic symptoms. The median number of days symptoms persisted after retreatment was 3 days (IQR 0-8, n=56) for ciprofloxacin, and 4 days (0-9, n=57) for placebo; Mann-Whitney p=0.703).

Exacerbation rate during follow up

Over 90 days, there were slightly more exacerbations (median 1 (IQR 0-1); mean = 0.86 (SD 0.91) in the ciprofloxacin group compared to (median 1 (IQR 0-1); mean = 0.74 (SD 0.90) in the placebo group. In an unadjusted analysis, there was no difference in the exacerbation rate between the two arms, with an incident rate ratio for ciprofloxacin compared to placebo of 1.14 (95% CI: 0.78-1.66; p=0.498).

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Lung function changes

There were no significant between-group differences in the change in FEV_1, FVC or FEV_1/FVC ratio at any time point (figure 4 and supplementary table 2). Once data collected post-second exacerbation (occurring in the 90 day study period) were excluded, significant improvements were seen in FEV_1 and FVC, but not FEV_1/FVC ratio, in both treatment groups following the index exacerbation (supplementary figure 4). However, there were no significant differences between treatment groups in this analysis.

Quality of life questionnaire assessments

Comparing treatment arms, there was no difference in change in total or component SGRQ scores between randomisation and day 90. (Table 3). The CAT scores also did not differ comparing ciprofloxacin and placebo (0.77 higher for ciprofloxacin versus placebo 95% CI: -1.71 to 3.27; p=0.540) (figure 5).

C-reactive protein

CRP was significantly lower at V2 and V3 than at randomisation but there were no differences between treatment groups. All 144 exacerbations were treated with antibiotics; 117 were also treated with oral prednisolone and 27 with antibiotics alone. The prednisolone-treated exacerbations had a CRP of 8 mg/dL (IQR 3-20; n=26) compared to 7.8 mg/dl (IQR 3-9.9, n=115) forthe antibiotic-only treated exacerbations (Mann-Whitney; p=0.35). CRP was not recorded for 3 exacerbations.

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Index exacerbation characteristics CAT, CRP and bacterial culture.

At randomisation 46/144 subjects (31.9%) provided sputum for bacterial culture, which yielded a positive result in 45.7%. Ciprofloxacin resistant organisms were not present in sputum cultures subsequently collected from any participants receiving ciprofloxacin (table 4 and 5).

Adverse events

Two patients, one from each treatment arm, died within the 90-day follow-up window, one from an AECOPD and one from bowel ischaemia and multi organ failure; these deaths were not considered to be related to the trial interventions (Table 7). During the 90 days of follow-up, 5 of 72 patients (6.9%) with available data in the ciprofloxacin group and 6 of 72 (8.3%) patients with available data in the placebo group were hospitalised.

There were no clinically important between-group differences in adverse events (Table 6 and 7).

Discussion

This is the first study to examine retreatment with antibiotics of incompletely recovered AECOPD. We observed no effect of retreatment with ciprofloxacin compared to placebo on the primary outcome of time to the next exacerbation. There were also no effects on lung function, quality of life, CRP, or the duration of symptoms following the index exacerbation. The intervention was well tolerated, with no significant differences in the frequency of adverse events.

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Although most COPD exacerbations last for approximately 10 days, some may last longer and at 5 weeks, 25% may not have fully recovered (10). Another feature of COPD exacerbations is the increased risk of developing another exacerbation within an eight week period (9, 14), and we have previously reported that a raised serum C-Reactive Protein (CRP) concentration measured 14 days after a first exacerbation is predictive of a second, suggesting that failure to normalise the inflammatory response may predispose to another (recurrent) exacerbation (14). Exacerbations are associated with heterogeneous inflammatory processes, mainly neutrophilic, and usually triggered by respiratory viral infections followed by secondary bacterial infection (18) (19). or primary bacterial infection. For these reasons we aimed in this study to test an innovative approach to the use of antibiotics in preventing recurrent COPD exacerbations: the targeted re-treatment of patients following a first exacerbation who have incomplete symptom or inflammatory recovery.

The lack of an effect of ciprofloxacin in this trial would suggest that by day 14, these persistent symptoms and elevated CRP are driven predominantly by residual airway inflammatory load without a significant bacterial infective component, and this is reinforced by the low rates of bacterial sputum culture positivity in these patients. Further studies are required to study mechanisms of exacerbation recovery so that potential anti-inflammatory therapies can be targeted. A recent study reported the use of oral macrolides at hospitalization and continuing for 3 months after discharge (20, 21). Despite the trial under-recruiting, a trend favoured the azithromycin intervention over placebo in preventing subsequent AECOPD (treatment failure 49% versus 60% p=0.0526). Taking our observations into account, this finding could be the result of anti-inflammatory immunomodulatory effects of macrolides rather than antimicrobial action (22).

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Time to next exacerbation is a commonly used outcome measure in clinical trials (23). All exacerbations were moderate to severe with many treated or hospitalized by independent physicians. The CAT scores and CRP concentrations of patients when they initially presented with exacerbation were similar to those reported at exacerbation presentation in other studies.(20, 24, 25). The retreatment antibiotic, ciprofloxacin, was selected as a reasonable second line antibiotic choice based on global guidelines for bacterial respiratory infection (16, 26, 27). It is important to acknowledge that the dose selected was not optimized to cover for active pseudomonas infection (usually 750mg/12 h for 14 days). However, we observed that only 3.5% (5 participants) yielded a positive bacterial culture for Pseudomonas, suggesting this was not a major contributor to re-exacerbation. It is also possible that the immunomodulatory effects of macrolides would have had more effect. The recruitment target was met but even if the sample size had been larger it is unlikely that a beneficial effect would have been detected. Importantly the observed rate of a subsequent exacerbation was lower than anticipated by the power calculation. Our study anticipated a large effect size (HR 0.46) which we felt would be meaningful to patients but created the possibility of type II error, or failure to detect a smaller beneficial effect of retreatment, when a beneficial effect exists. However, the study recruited to target and the absence of any trend favouring treatment makes this less likely. It is possible that a divergence in outcome between the ciprofloxacin and placebo group might have developed had the participants been followed for 12 months rather than the 90 days we specified. However, previous work from our group suggested that a further exacerbation occurred in 36% of cases by 50 days(14). Furthermore, patients were recruited from emergency and outpatient clinic departments rather than an established longitudinal cohort and so commitment to a

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12-month follow up period could have increased the difficulty of recruitment. Thus 90 days was considered a reasonable length of time to expect individuals to participate and mitigate the loss to follow up.

We chose CRP as a familiar clinical parameter that can be measured with a relatively inexpensive point-of-care device. The utility of point-of-care testing in the context of AECOPD is also emerging. Butler and colleagues show that at AECOPD onset a rapid detection of CRP can successfully rationalise antibiotic use (15). Instead we have used point-of-care CRP testing at day 14 to assess non-recovery. However, CRP cannot distinguish between a bacterial and viral triggered exacerbation. Around half of all AECOPD are triggered by respiratory viruses (22-64%) particularly human rhinovirus (28). Empirical antibiotics do still offer a benefit (7), as recent work suggests that rhinovirus directly influences the lung's innate immunity to impair bacterial phagocytosis allowing bacterial outgrowth (28, 29).

Spirometry data collected at the V2-V4 time-points may have been influenced by secondary exacerbations. However, once lung function collected after a second exacerbation within the 90 day study period were excluded, significant improvements were seen in FEV_1 and FVC, but not FEV_1/FVC ratio, in both treatment groups following the index exacerbation. This is in line with exacerbation recovery but there were no significant differences between treatment groups.

Another approach to improving the targeted retreatment would be to obtain bacterial sputum culture, though as observed in our study, and by others with a similar cohort demographic (20), many patients do not spontaneously expectorate 14 days after an index exacerbation. In our study only 44 individuals (31.9%) were able to provide

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sputum, and a bacterial positive yield was obtained in 18.7% (20.8% active, 16.6% placebo).

During recruitment for this study, 38/80 (48%) patients were excluded at the screening visit because they had recovered. This fits with our understanding of the normal time-course of AECOPD (10). However, a notable finding was that 29% of individuals identified as suitable for the study were excluded because they had already commenced antibiotic retreatment prior to screening at day 14. This suggests that a sizable subpopulation of AECOPD experience treatment failure or require treatment intensification, a step-up in hospital care or readmission early. The results of this study would suggest that there is scope to reduce unnecessary antibuiotic retreatment.

The strengths of this study were that it was multi-centre and met the pre-specified recruitment target. We also found that the duration of symptoms post-randomisation as one of our secondary outcomes could not be determined easily because patients poorly recorded symptoms on the diary cards. Of the 144 participants, 43 did not record any increase in symptoms on day 1 and day 2 post-randomisation, 6 patients continuously recorded symptoms during the whole follow-up period, and 25 participants never recorded any symptoms. This was surprisingly poor compliance compared to our experience with the London COPD cohort and could be explained by inexperience with the daily diary cards, as well as being a post-exacerbation rather than stable cohort.

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Conclusion

This randomized, placebo control trial found no benefit of treatment with ciprofloxacin of exacerbations with persistent respiratory symptoms or a raised CRP (>=8 mg/dl) at 14 days post exacerbation onset. This suggests that non-recovered exacerbations which may lead to hospital readmission potentially need to be targeted with anti-inflammatory therapies and further research is now warranted to investigate exacerbation recovery.

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Tables/Figures

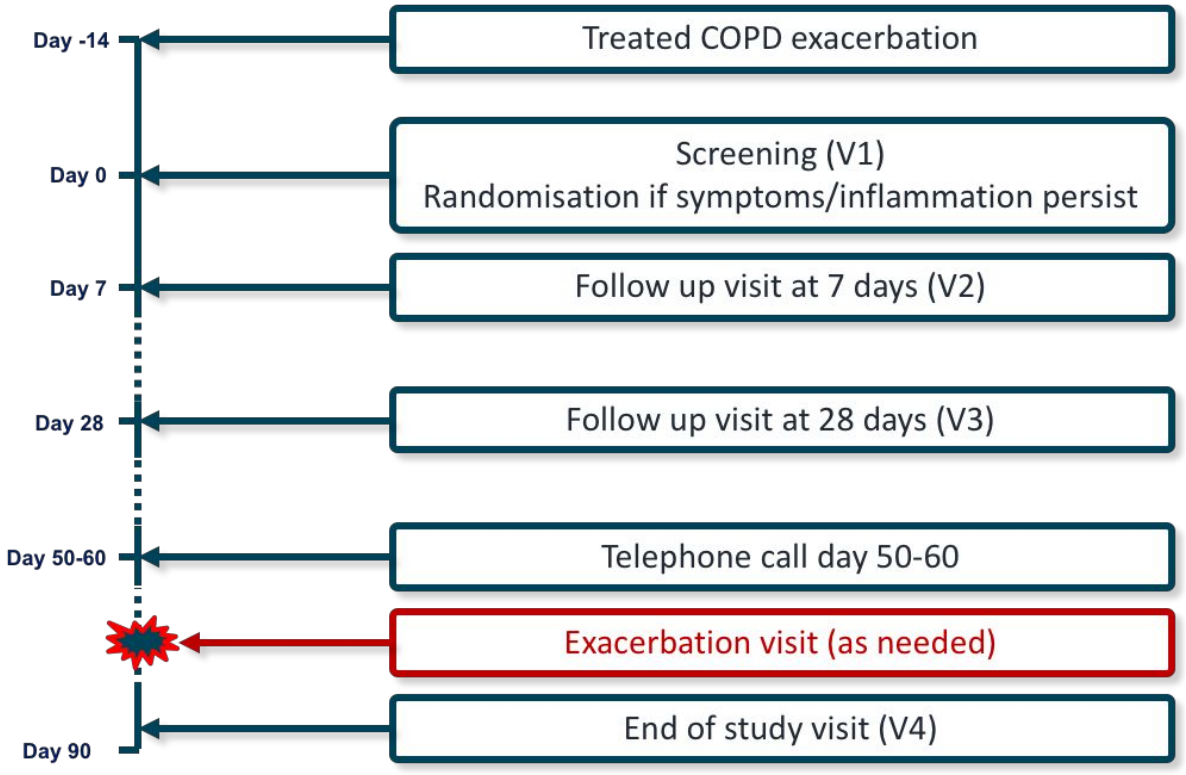

Figure 1 – The trial study design.

Abbreviations: COPD,chronic obstructive pulmonary disease; V1, visit 1; V2, visit 2; V3, visit 3; V4, visit 4.

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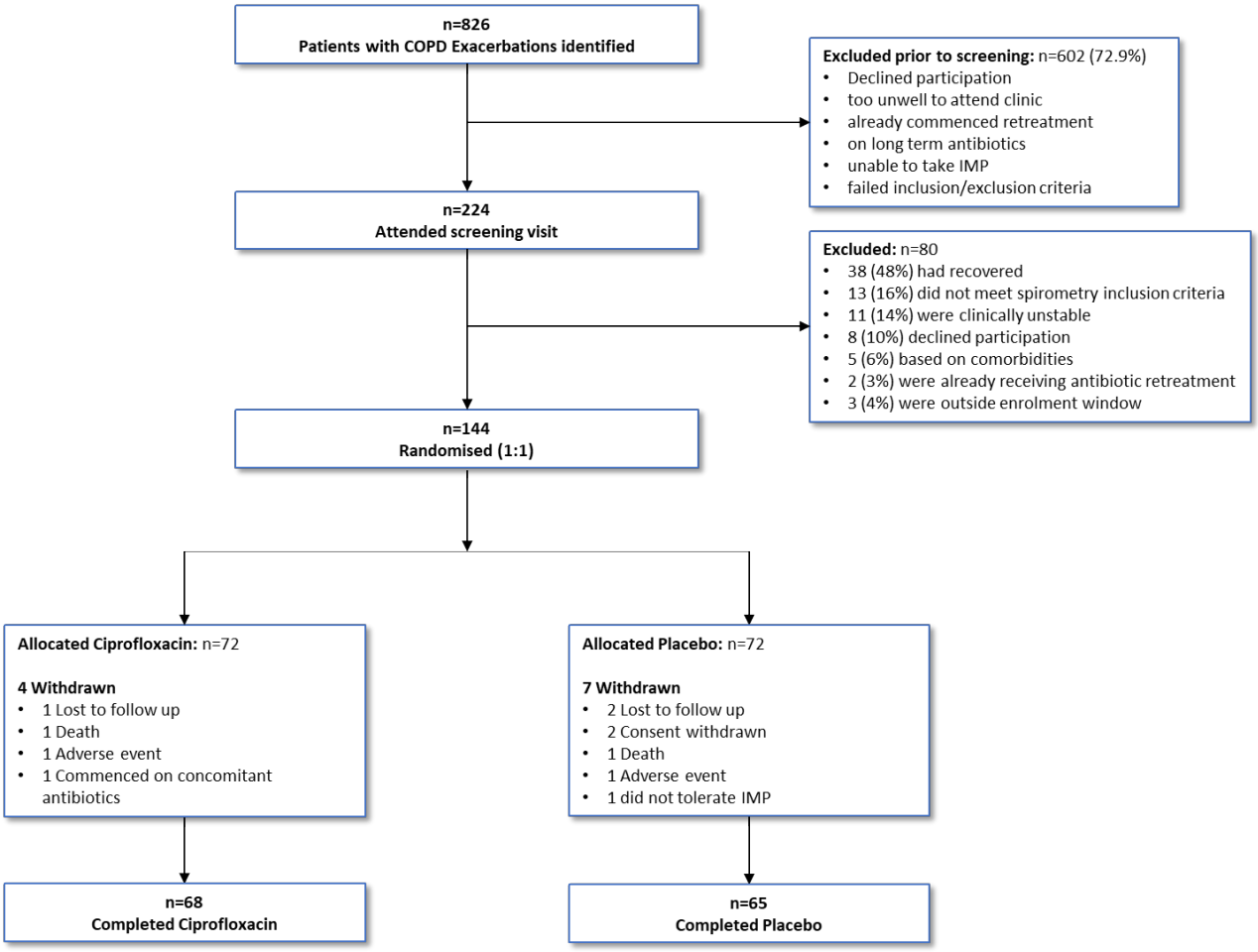

Figure 2 - Consolidated Standards of Reporting Trials Diagram of the Targeted Retreatment of Exacerbations in COPD: A Double blind, Randomised, Placebo-controlled, Multicentre Phase III Trial.

Abbreviations: IMP, Investigational medicinal product.

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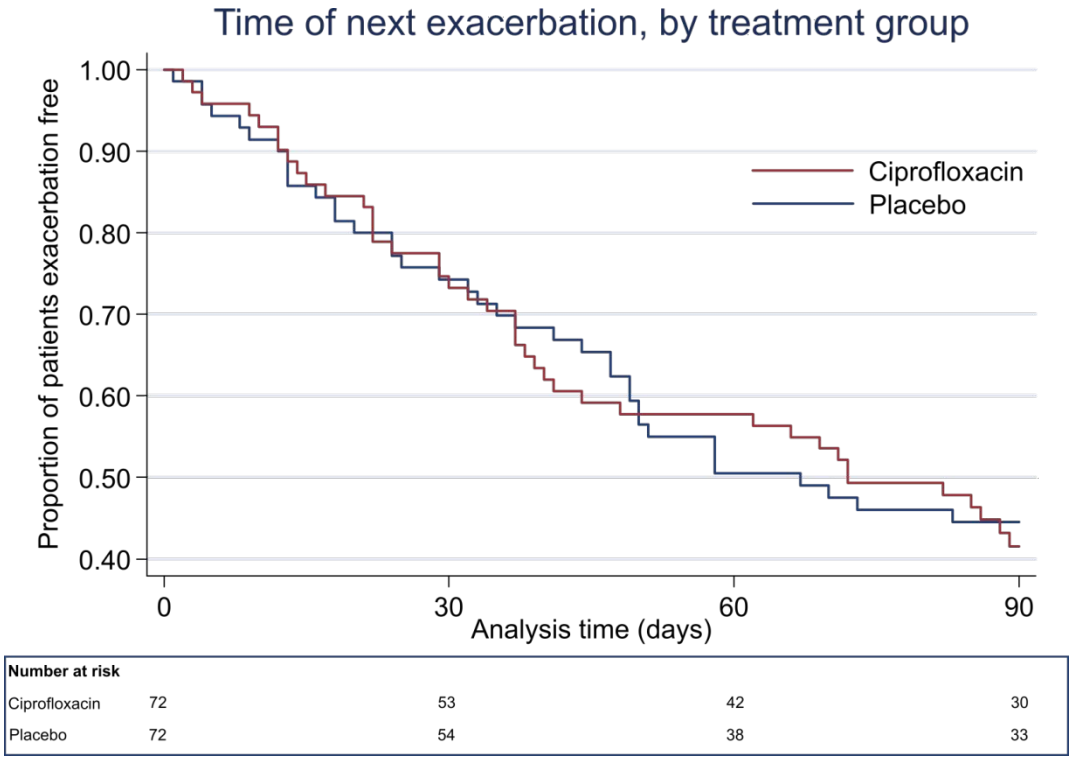

Figure 3 - Kaplan-Meier survival estimate demonstrating the primary endpoint - proportion of patients free from exacerbation.

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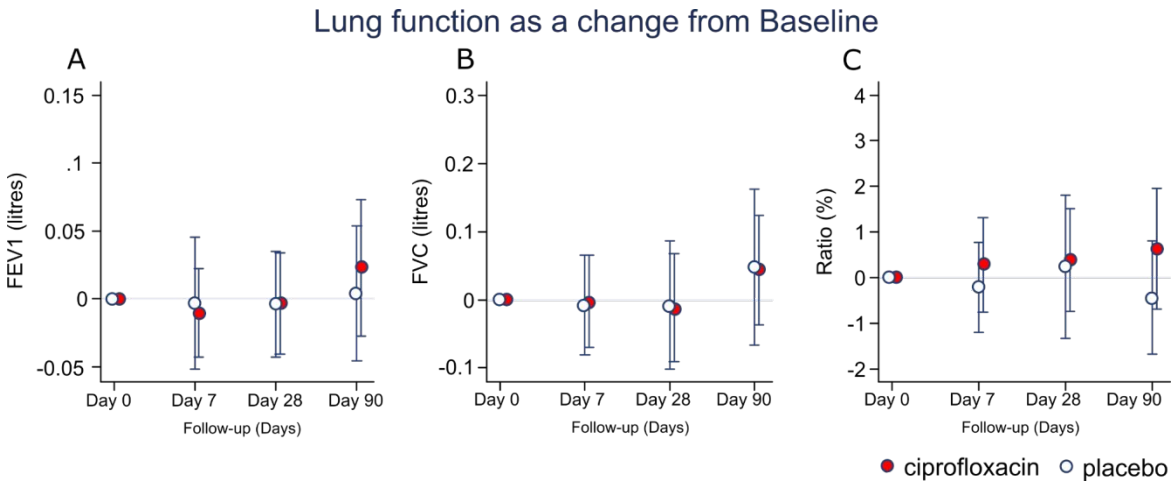

Figure 4 – Effect of the intervention on change in spirometry by treatment group. A-C demonstrates the change in FEV1, FVC and FEV1/FVC ratio respectively.

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

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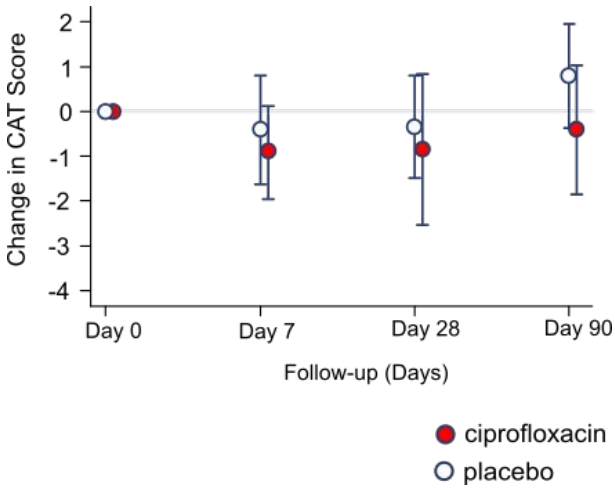

Figure 5 – Effect of the intervention on change in CAT Score by treatment group. Demonstrating the effect of the intervention on change in CAT score by treatment group.

Abbreviations: CAT, COPD assessment test.

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	Ciprofloxacin N=72	Placebo N=72	p-value
Demographics			
Age - years	69.1 (8.8)	69.1 (7.4)	1.000
Weight – kg	77.4 (16.5)	77.1 (21.0)	0.909
Height - m	1.68 (0.11)	1.70 (0.09)	0.295
BMI	27.5 (5.8)	26.5 (6.0)	0.312
Males – n (%)	44 (61.1)	47 (65.2)	0.604
Current Smoker - n	24	26	0.726
Pack Years	48.7 (3.5)	43.3 (23.9)	0.231
Annual Exacerbation rate* (IQR)	3 (1-4)	2 (1-4)	0.879
Anthonisen Criteria			
Type I	11	11	0.763
Type II	15	19	0.467
Type III	31	32	0.859
Examination findings			
FEV1 - litres	1.29 (0.52)	1.38 (0.51)	0.269
FEV1 - % predicted	48.7 (16.5)	50.0 (14.9)	0.608
FVC - litres	2.79 (0.89)	2.91 (0.76)	0.380
FEV1/FVC	0.47 (0.14)	0.48 (0.13)	0.734
Oxygen Sats - %	94.8 (2.24)	95.0 (1.97)	0.555
Resp. Rate	17.4 (2.7)	17.8 (2.8)	0.322
Point of Care Sampling			
CRP	15.2 (12.2)	19.9 (16.3)	0.158
Disease Burden Questionnaires			
SGRQ Total	53.4 (18.1)	52.4 (17.2)	0.732
CAT	21.1 (8.3)	19.8 (7.7)	0.324

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Table 1 – Characteristics of patients at randomisation, by treatment group

Abbreviations: kg, kilograms; BMI, body mass index; IQR, interquartile range; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; CRP, C-reactive protein; SGRQ, St Georges Respiratory Questionnaire; CAT, COPD assessment test.

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Reason for inclusion	Haz. Ratio	Lower CI	Upper CI	p-value
Persistent symptoms (n=128) $	1.167	0.734	1.856	0.513
CRP >=8 mg/dl (n=64)	0.968	0.480	1.952	0.928
No persistent symptoms but only CRP >=8 mg/dl (n=16)	0.667	0.073	6.06	0.719

Table 2 – Characteristics of patients at randomisation, by treatment group

Abbreviations: CRP, C-reactive protein.

$ Those with persistent symptoms included 48 participants whose CRP exceeded or was equal to 8 mg/dl

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	Visit 1 71 Placebo /69 Cipro	**Visit 4** 64 Placebo /63 Cipro	**Visit 4 – Visit 1** 63 Placebo /61 Cipro	p-value (V4-V1, by treatment)
SGRQ Total - Placebo	52.4 (17.2)	47.8 (16.0)	-3.37 (11.5)	
SGRQ Total - Cipro	53.4 (18.1)	50.5 (17.8)	-1.93 (9.1)	0.440
SGRQ Impact - Placebo	40.8 (20.0)	38.5 (18.4)	-1.97 (12.8)	
SGRQ Impact - Cipro	39.0 (20.0)	35.8 (17.8)	-0.74 (10.8)	0.560
SGRQ Activity - Placebo	68.2 (21.8)	65.1 (20.2)	-1.74 (17.1)	
SGRQ Activity - Cipro	67.3 (21.7)	67.8 (22.5)	1.17 (12.8)	0.283
SGRQ Symptoms - Placebo	66.4 (15.3)	54.3 (19.3)	-11.3 (20.1)	
SGRQ Symptoms - Cipro	68.9 (16.6)	55.7 (22.0)	-11.5 (21.5)	0.949

Table 3 - Demonstrates the changes in total as well as the impact, activity and symptom subsections of the SGRQ score between visit 1 and 4.

Abbreviations: Cipro, ciprofloxacin; SGRQ, St Georges Respiratory Questionnaire.

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	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**
	72 placebo/71 Ciprofloxacin	65 placebo/66 Ciprofloxacin	64 placebo/63 Ciprofloxacin	63 placebo/63 Ciprofloxacin
CRP Placebo	**15.1 (17.2)**	**11.0 (17.2)**	**9.8 (17.7)**	**9.0 (15.2)**
CRP Ciprofloxacin	10.9 (12.3)	9.8 (13.1)	7.0 (17.7)	15.2 (46.9)
As change from baseline		63 placebo/66 Ciprofloxacin	62 placebo/62 Ciprofloxacin	61 placebo/62 Ciprofloxacin
CRP Placebo		**-5.1 (22.1)**	**-5.3 (17.0)**	**-6.4 (20.1)**
CRP Ciprofloxacin		-1.7 (14.7)	-4.6 (12.4)	3.9 (48.0)
p-value (t-test)		**0.310**	**0.815**	**0.124**
Median (IQR)				
CRP Placebo		-2 (-13 to 0)	-1.75 (-9 to 0.1)	-2 (-11.5 to 1)
CRP Ciprofloxacin		**0 (-5 to 2)**	**-1 (-5 to 1)**	**-1 (-4 to 0)**
Mann-Whitney		0.030	0.741	0.195

Table 4 - compares the changes in CRP seen in the ciprofloxacin and placebo groups at study visits.

Abbreviations: CRP, C-reactive protein; IQR, interquartile range.

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	Ciprofloxacin		Placebo	
Baseline	N=	%	N=	%
Number of patients with a sputum sample	25	(34.7)	22	(30.5)
Number bacterial cultures positive for a pathogen	15	(20.8)	12	(16.6)
Haemophilus influenzae	6	(8.3)	4	(5.5)
Streptococcus pneumoniae	1	(1.4)	2	(2.8)
Pseudomonas aeruginosa	2	(2.8)	3	(4.2)
Morexella catarrhalis	3	(4.2)	1	(1.4)
Staphylococcus aureus	0		1	(1.4)
Other gram-negative bacteria	3	(4.2)	1	(1.4)
Cultures with ciprofloxacin resistant bacteria	1	(1.4)	0	
Day 90				
Number of patients with a sputum sample	16	(22.2)	17	(23.6)
Number bacterial cultures positive for a pathogen	7	(9.7)	7	(9.7)
Number with newly acquired ciprofloxacin resistance	0		1	(1.4)

Table 5 - Summary of spontaneous sputum samples bacterial cultures

Brackets indicate % unless otherwise specified.

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Adverse events	Ciprofloxacin	Placebo
Gastrointestinal		
Nausea	1	1
Vomiting	0	1
Diarrhoea	5	1
Dyspepsia	1	0
Abdominal colic/Pain	2	2
Miscellaneous		
Pruritis/Rash	0	2
Dry mouth	1	0
Ankle pain/tendinitis	2	0
Tremor	0	1

Table 6 - Summary of study adverse events

Brackets indicate % unless otherwise specified.

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Serious Adverse events	Ciprofloxacin	Placebo
FATAL		
Gastrointestinal	0	1
Respiratory	1	0
NON-FATAL		
Cardiovascular	0	1
Gastrointestinal	0	2
Psychological	0	1
Oncology	1	1
Respiratory	0	4

Table 7 - Summary of study adverse events

Brackets indicate % unless otherwise specified.

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Supplementary material

Author Contributions

SEB, LA-M, JPA, BHV, PPW, PMAC, GCD and JAW contributed to the study design, protocol and study materials. AIR, SEB, BHV, LJF, JPA, LA-M, EB, SLE, PPW and PM contributed to patient recruitment and collection of study data at participating centres. ML designed the statistical plan and performed pre-study power calculations. GCD performed the statistical analysis. AIR and SEB wrote the first draft of the manuscript. All authors contributed to interpretation of the data and revision of the manuscript.

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List of study sites

Recruitment site	Participants (n=144)
Royal Brompton and Harefield NHS Trust	106
Aintree University Hospital NHS Foundation Trust	25
St Mary's Hospital, Imperial College Healthcare NHS Trust	8
St George's University Hospitals NHS Trust	5

Table 1 - Summary of recruited subjects by site to the Targeted Retreatment of Incompletely Recovered COPD Exacerbations with Ciprofloxacin trial.

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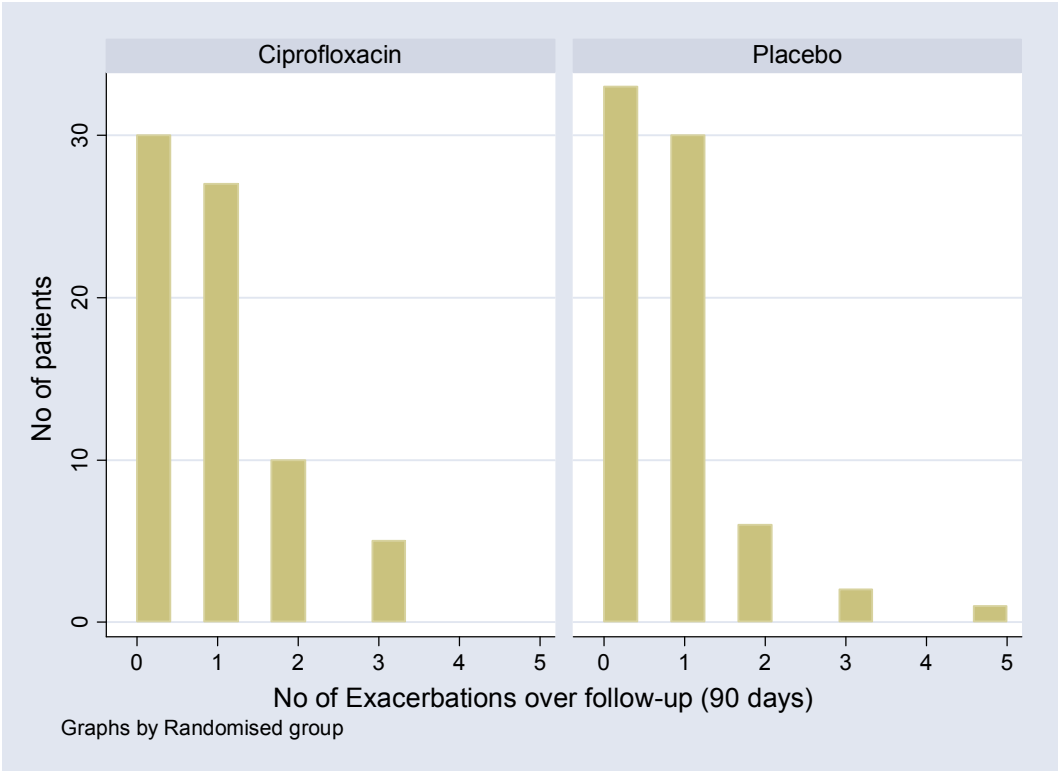

Figure 1 - Distribution of exacerbation frequencies in the two arms of the study. Exacerbations frequency was similar in both treatment arms (p=0.498).

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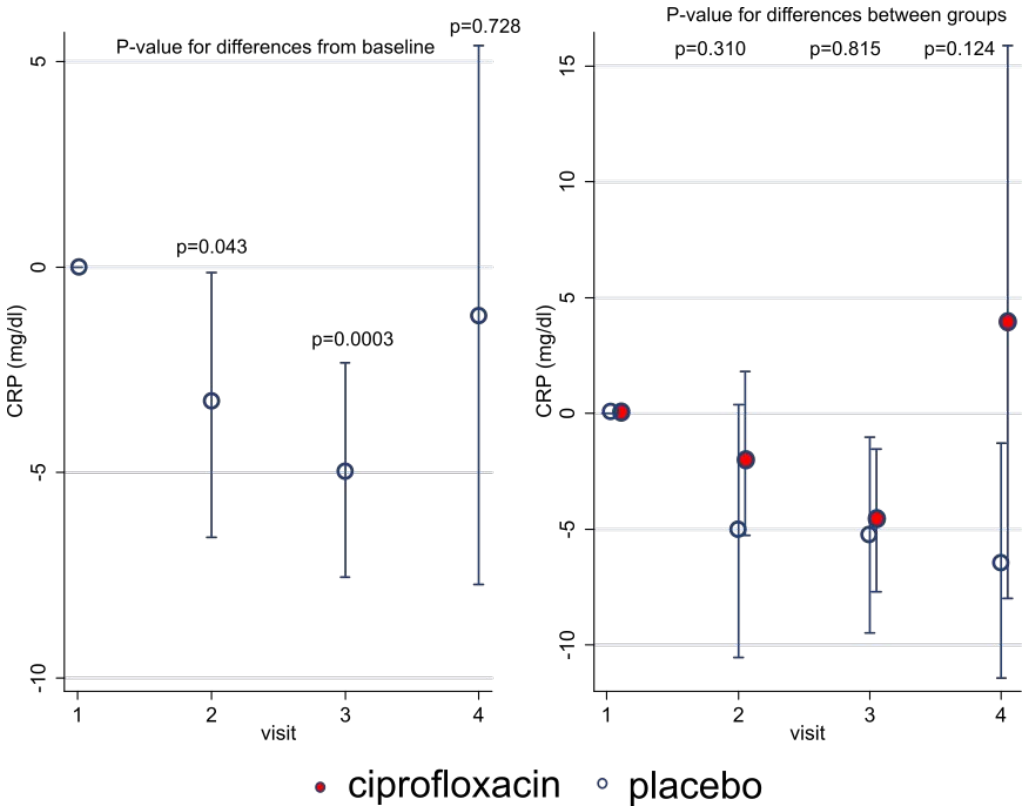

Figure 2 – Effect of the intervention on change in C-reactive protein. A demonstrates the effects on CRP. B examines the effect of the intervention on changes in CRP by treatment group. Day 0 represents the randomization visit.

Abbreviations: CRP, C-reactive protein; mg, milligrams; dL, decilitres.

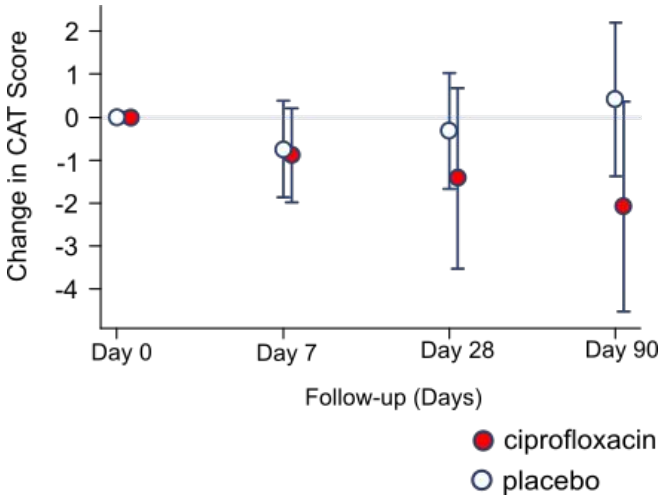

Figure 3 – Effect of the intervention on change in CAT Score by treatment group. Examining the change in CAT score by treatment group when secondary exacerbation data is excluded. Day 0 represents the randomization visit.

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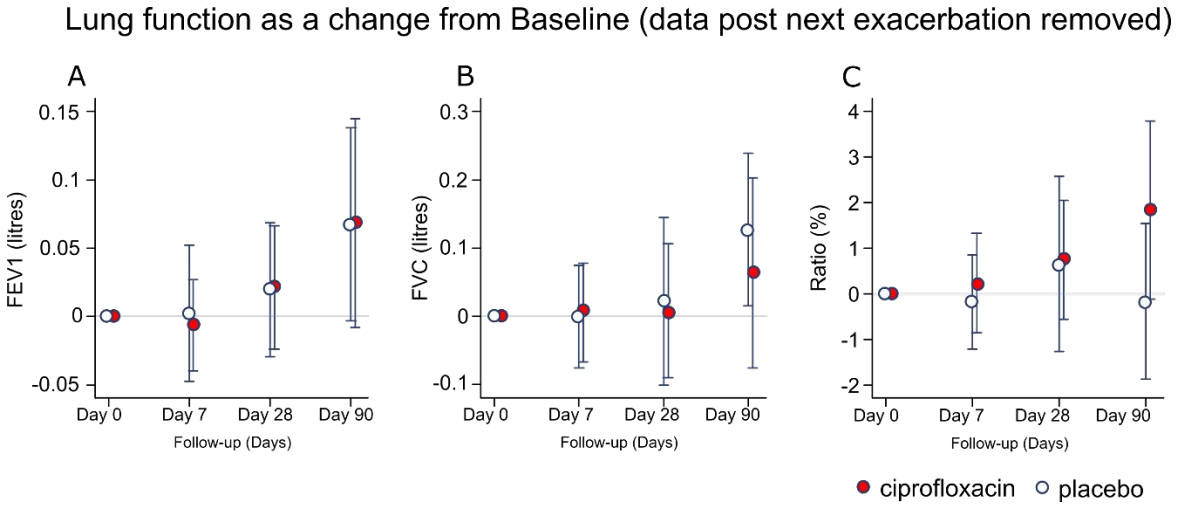

Figure 4 – Effect of the intervention on change in spirometry by treatment group. A-C examines changes in lung function when secondary exacerbation data is excluded.

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Inclusion and Exclusion criteria

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 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

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 tendinopathy 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.

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	Ciprofloxacin	Placebo
Baseline		
N=72 Ciprofloxacin; 72 Placebo		
FEV1	1.29 (0.52)	1.38 (0.51)
FVC	2.79 (0.89)	2.91 (0.76)
FEV1/FVC ratio	47.2 (13.8)	47.9 (13.2)
Day 7		
N=68 Ciprofloxacin; 67 Placebo		
FEV1	1.31 (0.49)	1.37 (0.53)
FVC	2.87 (0.90)	2.87 (0.79)
FEV1/FVC ratio	47.4 (14.1)	48.0 (13.8)
Day 28		
N=64 Ciprofloxacin; 62 Placebo		
FEV1	1.31 (0.49)	1.37 (0.52)
FVC	2.85 (0.82)	2.90 (0.91)
FEV1/FVC ratio	47.0 (14.4)	47.9 (13.2)
Day 90		
N=63 Ciprofloxacin; 63 Placebo		
FEV1	1.36 (0.51)	1.37 (0.55)
FVC	2.95 (0.86)	2.96 (0.93)
FEV1/FVC ratio	47.4 (14.8)	46.9 (13.6)

Table 2 - shows means (SD), and number of patients measured. The number of measurement decreased in both the placebo and ciprofloxacin groups as participant withdrew from the study.

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