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

Andrew I. Ritchie, Simon E. Brill, Ben H. Vlies, Lydia J. Finney, James P. Allinson, Luana Alves-Moreira, Dexter J. Wiseman, Paul P. Walker, Emma Baker, Sarah L Elkin, Patrick Mallia, Martin Law, Gavin C. Donaldson, Peter M. A. Calverley, and Jadwiga A. Wedzicha

ONLINE DATA SUPPLEMENT

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.

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 E1 - Summary of recruited subjects by site to the Targeted Retreatment of Incompletely Recovered COPD Exacerbations with Ciprofloxacin trial.

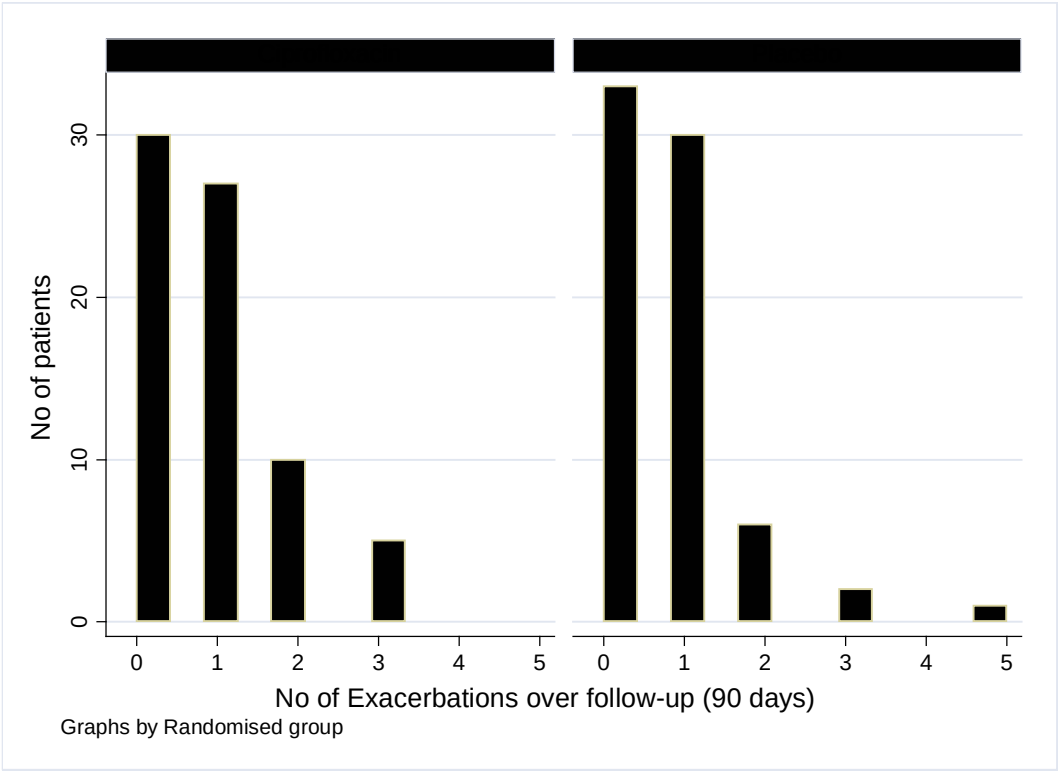

Figure E1 - Distribution of exacerbation frequencies in the two arms of the study. Exacerbations frequency was similar in both treatment arms (p=0.498).

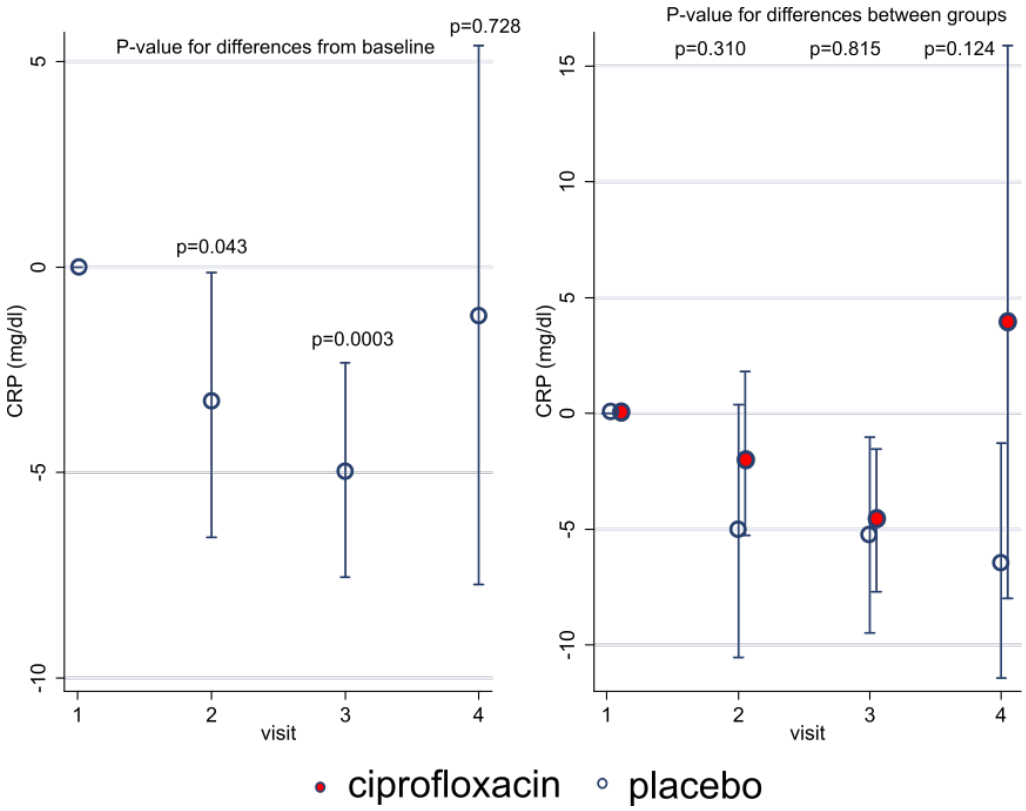

Figure E2 – Effect of the intervention on change in C-reactive protein. A demonstrates the effects on CRP. B examines the effect of the intervention on changes in CRP by treatment group. Day 0 represents the randomization visit.

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

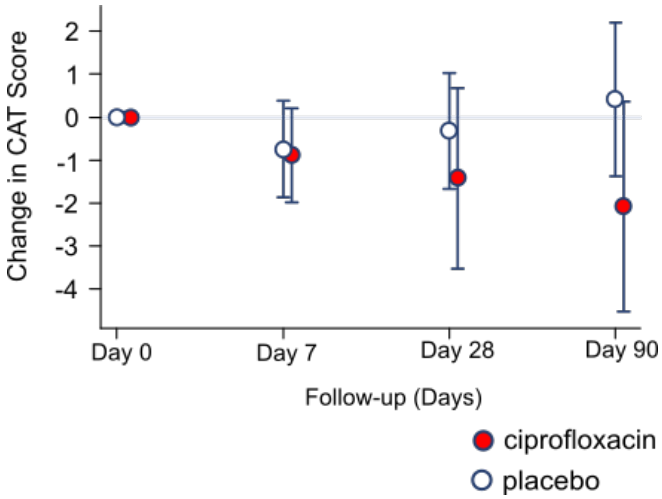

Figure E3 – Effect of the intervention on change in CAT Score by treatment group. Examining the change in CAT score by treatment group when secondary exacerbation data is excluded. Day 0 represents the randomization visit.

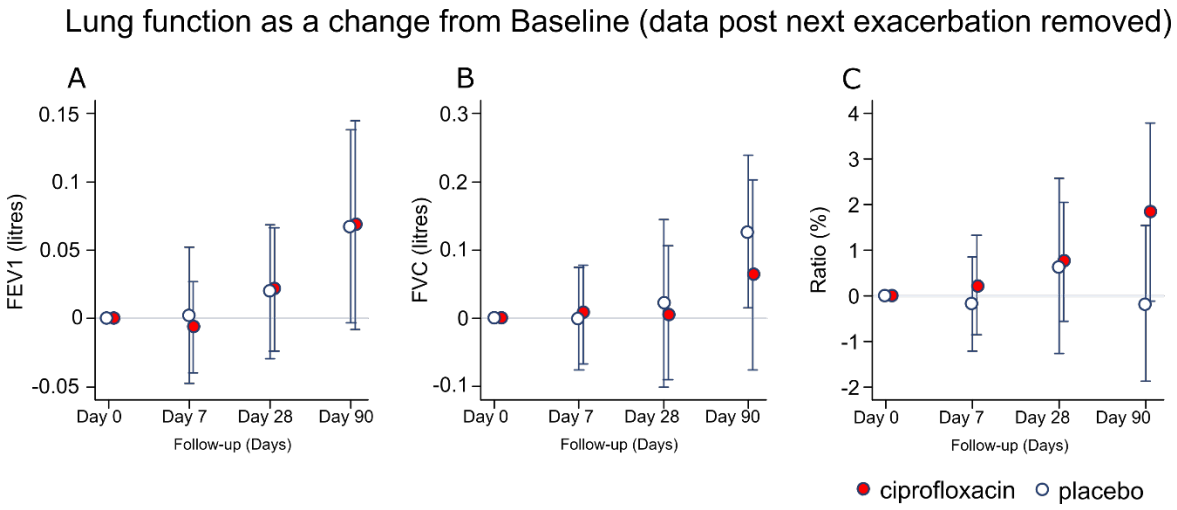

Figure E4 – Effect of the intervention on change in spirometry by treatment group. A-C examines changes in lung function when secondary exacerbation data is excluded.

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.

	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 E2 - 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.