Clinical trial results:
Targeted retreatment of incompletely recovered COPD exacerbations with ciprofloxacin: a double-blind, randomised, placebo-controlled, multicentre Phase III trial

Summary

EudraCT number	2012-002198-72
Trial protocol	GB
Global end of trial date	22 January 2019

Results information

Result version number	v1 (current)
This version publication date	29 November 2019
First version publication date	29 November 2019

Trial information

Trial identification

Sponsor protocol code	14IC2031

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02300220
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensingston Campus, London, United Kingdom, SW7 2AZ
Public contact	Jadwiga Wedzicha, Imperial College London, j.wedzicha@imperial.ac.uk
Scientific contact	Jadwiga Wedzicha, Imperial College London, j.wedzicha@imperial.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 January 2019
Global end of trial reached?	Yes
Global end of trial date	22 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research question is whether an extra course of antibiotics, given two weeks after an exacerbation (flare up) of chronic obstructive pulmonary disease, can prevent repeat exacerbations in those patients who have not fully recovered from the first exacerbation.

Protection of trial subjects:

None

Background therapy:

Patients continued on usual therapy as prescribed for the COPD or co-morbidities.

Evidence for comparator:

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 (1, 2, 3,4).
- 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.

1. Rabe K. F., et al. 2007. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am. J. Respir. Crit. Care Med. 176:532–555.
2. Woodhead M., et al. 2005. Guidelines for the management of adult lower respiratory tract infections. Eur. Respir. J. 26:1138–1180.
3. Balter M. S., et al. 2003. Canadian guidelines for the management of acute exacerbations of chronic bronchitis. Can. Respir. J. 10(Suppl.):3B–32B.
4. Kontou P, Chatzika K, Pitsiou G, Stanopoulos I, Argyropoulou-Pataka P, Kioumis I. Pharmacokinetics of ciprofloxacin and its penetration into bronchial secretions of mechanically ventilated patients with chronic obstructive pulmonary disease. Antimicrob Agents Chemother. 2011 Sep;55 (9): 4149-53. Epub 2011 Jun 13.

Actual start date of recruitment	05 May 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	13 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 144

Worldwide total number of subjects	144
EEA total number of subjects	144

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	37
From 65 to 84 years	107
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited between May 2014 to January 2019

Pre-assignment

Screening details:

144 participants were eligible

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ciprofloxacin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ciprofloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

500 mg, twice daily for 1 week

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

twice daily for 1 week

Number of subjects in period 1	Ciprofloxacin	Placebo
Started	72	72
Completed	68	65
Not completed	4	7
Consent withdrawn by subject	-	2
death	1	1
Adverse event, non-fatal	1	1

did not tolerate IDP	-	1
Lost to follow-up	1	2
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ciprofloxacin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Ciprofloxacin	Placebo	Total
Number of subjects	72	72	144
Age categorical Units: Subjects			
Adults (18-64 years)	17	20	37
From 65-84 years	55	52	107
Age continuous Units: years			
geometric mean	69.1	69.1	
standard deviation	± 8.8	± 7.4	-
Gender categorical Units: Subjects			
Female	28	25	53
Male	44	47	91

End points

End points reporting groups	
Reporting group title	Ciprofloxacin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Time to the Next COPD Exacerbation	
End point title	Time to the Next COPD Exacerbation
End point description:	
The primary outcome will be the time to the next COPD exacerbation following targeted retreatment with the IMP or placebo, censored at 90 days.	
End point type	Primary
End point timeframe:	
7 days of treatment	

End point values	Ciprofloxacin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	72		
Units: days				
median (inter-quartile range (Q1-Q3))	72 (29 to 90)	58 (24.5 to 90)		

Statistical analyses

Statistical analysis title	Time to the Next COPD Exacerbation
Comparison groups	Ciprofloxacin v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.764
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.684
upper limit	1.676

Secondary: Duration of the Initial Exacerbation

End point title	Duration of the Initial Exacerbation

End point description:

End point type	Secondary

End point timeframe:

7 days of treatment

End point values	Ciprofloxacin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56[1]	57[2]		
Units: days				
median (inter-quartile range (Q1-Q3))	3 (0 to 8)	4 (0 to 9)		

Notes:

[1] - Missing data from 16 participants

[2] - Missing data from 15 participants

Statistical analyses

Statistical analysis title	Duration of the Initial Exacerbation
Comparison groups	Placebo v Ciprofloxacin
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.703
Method	Wilcoxon (Mann-Whitney)

Secondary: Number of Participants With Serious Non Fatal Adverse Events

End point title	Number of Participants With Serious Non Fatal Adverse Events

End point description:

End point type	Secondary

End point timeframe:

7 days of treatment

End point values	Ciprofloxacin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	72		
Units: number of participants	1	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Lung Function

End point title	Changes in Lung Function

End point description:

End point type	Secondary

End point timeframe:

90 days of treatment

End point values	Ciprofloxacin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: litres				
geometric mean (standard deviation)	0.0229 (± 0.199)	0.0041 (± 0.198)		

Statistical analyses

Statistical analysis title	Changes in Lung Function
Comparison groups	Ciprofloxacin v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.239
Method	t-test, 2-sided

Secondary: Number of Participants Who Have Resistance Bacteria in the Sputum

End point title	Number of Participants Who Have Resistance Bacteria in the Sputum

End point description:

Only participants who had sputum

End point type	Secondary

End point timeframe:

7 days of treatment

End point values	Ciprofloxacin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: number of participants	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
90 days + 1 month	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	Ciproflaxacin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Ciproflaxacin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 72 (1.39%)	9 / 72 (12.50%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oncology			
subjects affected / exposed	1 / 72 (1.39%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiovascular			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal			
subjects affected / exposed	0 / 72 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory			

subjects affected / exposed	0 / 72 (0.00%)	4 / 72 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychological			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Ciproflaxacin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 72 (16.67%)	8 / 72 (11.11%)	
Nervous system disorders			
Dry Mouth			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 72 (1.39%)	1 / 72 (1.39%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	5 / 72 (6.94%)	1 / 72 (1.39%)	
occurrences (all)	5	1	
Dyspepsia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	
occurrences (all)	1	0	
Abdominal Colic/Pain			

subjects affected / exposed	2 / 72 (2.78%)	2 / 72 (2.78%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
Pruritis/Rash			
subjects affected / exposed	0 / 72 (0.00%)	2 / 72 (2.78%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Ankle Pain/Tendonitis			
subjects affected / exposed	2 / 72 (2.78%)	0 / 72 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2015	Addition of St Geroges as site. Minor amendment to PIS/updates to protocol
30 March 2017	Study extension to Dec 2017
30 October 2017	A 6-month no cost extension to this study has been approved by NIHR.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported