



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 Kensington 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 (\pm 0.199) | 0.0041 (\pm 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

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