



## Clinical trial results:

### A Phase III double-blind, randomised, placebo controlled trial of long term therapy on Exacerbation Rate in patients with stable COPD using Doxycycline

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-002199-15 |
| Trial protocol           | GB             |
| Global end of trial date | 12 July 2017   |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 18 December 2019 |
| First version publication date | 18 December 2019 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | 12/0036 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02305940 |
| 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 A Wedzicha, Imperial College London,<br>j.wedzicha@imperial.ac.uk |
| Scientific contact           | Jadwiga A Wedzicha, Imperial College London,<br>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:

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**Results analysis stage**

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 02 July 2018 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 12 July 2017 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 12 July 2017 |
| Was the trial ended prematurely?                     | No           |

Notes:

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**General information about the trial**

Main objective of the trial:

The principal research question/objective is to assess whether the use of an antibiotic for 12 months by a group of patients with COPD reduces their rate of COPD exacerbations (periodic flare-ups of COPD symptoms) compared to a control group, taking a placebo.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 01 July 2014 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 222 |
| Worldwide total number of subjects   | 222                 |
| EEA total number of subjects         | 222                 |

Notes:

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**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)                      | 50  |
| From 65 to 84 years                       | 172 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The study was between July 2014 and July 2017.

### Pre-assignment

Screening details:

222 participants were eligible for the study

### 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    |

Blinding implementation details:

The eligible and clinically stable participants randomisation into groups of 1:1 and patients remained blinded to treatment allocation.

### Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | Doxycycline |

Arm description:

Doxycycline: An oral dose of 100 mg once daily.

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

Dosage and administration details:

Oral dose of 100 mg once daily, for a total duration of 52 weeks.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Placebo one capsule daily

|  |          |
|--|----------|
| 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:

Oral dose of one capsule once daily for 52 weeks.

| <b>Number of subjects in period 1</b> | Doxycycline | Placebo |
|---------------------------------------|-------------|---------|
| Started                               | 110         | 112     |
| Completed                             | 89          | 94      |
| Not completed                         | 21          | 18      |
| Consent withdrawn by subject          | 10          | 7       |
| death                                 | 4           | 1       |
| Adverse event, non-fatal              | -           | 3       |
| Lost to follow-up                     | 6           | 5       |
| Protocol deviation                    | 1           | 2       |

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Doxycycline |
|-----------------------|-------------|

Reporting group description:

Doxycycline: An oral dose of 100 mg once daily.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo one capsule daily

| Reporting group values                                | Doxycycline | Placebo | Total |
|---|-------------|---------|-------|
| Number of subjects                                    | 110         | 112     | 222   |
| Age categorical                                       |             |         |       |
| Units: Subjects                                       |             |         |       |
| In utero  |             |         | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) |             |         | 0     |
| Newborns (0-27 days)                                  |             |         | 0     |
| Infants and toddlers (28 days-23<br>months)           |             |         | 0     |
| Children (2-11 years)                                 |             |         | 0     |
| Adolescents (12-17 years)                             |             |         | 0     |
| Adults (18-64 years)                                  |             |         | 0     |
| From 65-84 years                                      |             |         | 0     |
| 85 years and over                                     |             |         | 0     |
| Age continuous  |             |         |       |
| Units: years  |             |         |       |
| geometric mean  | 68.8        | 67      |       |
| standard deviation                                    | ± 8         | ± 8     | -     |
| Gender categorical                                    |             |         |       |
| Units: Subjects                                       |             |         |       |
| Female  | 46          | 50      | 96    |
| Male  | 64          | 62      | 126   |

## End points

### End points reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Doxycycline |
| Reporting group description:<br>Doxycycline: An oral dose of 100 mg once daily. |             |
| Reporting group title   | Placebo     |
| Reporting group description:<br>Placebo one capsule daily                       |             |

### Primary: Rate of Exacerbations

|  |                                      |
|--|--------------------------------------|
| End point title  | Rate of Exacerbations <sup>[1]</sup> |
| End point description:<br>Rate of exacerbations (per person/year) recorded from date of drug issue until date of end of treatment visit.   |                                      |
| End point type   | Primary                              |
| End point timeframe:<br>12 months  |                                      |
| Notes:<br>[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: Rate of exacerbations (per person/year) recorded from date of drug issue until date of end of treatment visit. |                                      |

| End point values                      | Doxycycline     | Placebo         |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 110             | 112             |  |  |
| Units: Exacerbations / year           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 2 (1 to 4)      | 3 (1 to 5)      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Forced Expiratory Volume in 1 Sec (FEV1)

|                                   |  |
|-----------------------------------|--|
| End point title                   | Forced Expiratory Volume in 1 Sec (FEV1) |
| End point description:            |  |
| End point type                    | Secondary                                |
| End point timeframe:<br>12 months |  |

| End point values                          | Doxycycline            | Placebo         |  |  |
|---|------------------------|-----------------|--|--|
| Subject group type                        | Reporting group        | Reporting group |  |  |
| Number of subjects analysed               | 89                     | 94              |  |  |
| Units: litres                             |                        |                 |  |  |
| arithmetic mean (confidence interval 95%) | -0.017 (-0.10 to 0.06) | 0 (0 to 0)      |  |  |

## Statistical analyses

| Statistical analysis title              | Treatments            |
|---|-----------------------|
| Comparison groups                       | Doxycycline v Placebo |
| Number of subjects included in analysis | 183                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | > 0.22                |
| Method                                  | Mixed models analysis |

## Secondary: Total SGRQ score

|   |                  |
|---|------------------|
| End point title   | Total SGRQ score |
| End point description:  |                  |
| The St George's Respiratory Questionnaire (SGRQ) is an instrument for the measuring of Health-Related Quality-of-Life in patients with diseases of airways obstruction. |                  |
| All scales have a score range between 0 and 100 with higher scores indicating a worse quality of life.  |                  |
| End point type  | Secondary        |
| End point timeframe:  |                  |
| 12 months   |                  |

| End point values                         | Doxycycline         | Placebo         |  |  |
|--|---------------------|-----------------|--|--|
| Subject group type                       | Reporting group     | Reporting group |  |  |
| Number of subjects analysed              | 89                  | 94              |  |  |
| Units: score                             |                     |                 |  |  |
| geometric mean (confidence interval 95%) | 5.20 (1.80 to 8.70) | 0 (0 to 0)      |  |  |

## Statistical analyses

| Statistical analysis title | Treatments            |
|----------------------------|-----------------------|
| Comparison groups          | Doxycycline v Placebo |

|   |                                  |
|---|----------------------------------|
| Number of subjects included in analysis | 183                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.0034                         |
| Method                                  | Mixed models analysis            |
| Parameter estimate                      | Median difference (final values) |
| Point estimate                          | 5.2                              |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | 1.8                              |
| upper limit                             | 8.7                              |

## Secondary: Adherence of the Participants

|   |                               |
|---|-------------------------------|
| End point title   | Adherence of the Participants |
| End point description:  |                               |
| Adherence as measured using pill counts, the odds of a patient being adherent (taking their pill) on a given day. |                               |
| End point type  | Secondary                     |
| End point timeframe:  |                               |
| 12 months   |                               |

| End point values                          | Doxycycline         | Placebo         |  |  |
|---|---------------------|-----------------|--|--|
| Subject group type                        | Reporting group     | Reporting group |  |  |
| Number of subjects analysed               | 110                 | 112             |  |  |
| Units: odds of taking pill                |                     |                 |  |  |
| arithmetic mean (confidence interval 95%) | 0.87 (0.43 to 1.80) | 0 (0 to 0)      |  |  |

## Statistical analyses

|   |                       |
|---|-----------------------|
| <b>Statistical analysis title</b>       | Treatments            |
| Comparison groups                       | Doxycycline v Placebo |
| Number of subjects included in analysis | 222                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.71                |
| Method                                  | Regression, Linear    |
| Parameter estimate                      | Log odds ratio        |
| Point estimate                          | 0.87                  |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.43    |
| upper limit         | 1.8     |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

14 weeks

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 10 |
|--------------------|----|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Doxycycline |
|-----------------------|-------------|

Reporting group description:

Doxycycline: An oral dose of 100 mg once daily.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo: Oral dose of one capsule once daily.

| Serious adverse events  | Doxycycline       | Placebo           |  |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed   | 34 / 110 (30.91%) | 23 / 112 (20.54%) |  |
| number of deaths (all causes)                                       | 4                 | 1                 |  |
| number of deaths resulting from adverse events                      | 1                 | 0                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Sarcoma diagnosis   |                   |                   |  |
| subjects affected / exposed   | 1 / 110 (0.91%)   | 0 / 112 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Metastatic prostate cancer  |                   |                   |  |
| subjects affected / exposed   | 1 / 110 (0.91%)   | 0 / 112 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Prostate cancer diagnosis   |                   |                   |  |
| subjects affected / exposed   | 0 / 110 (0.00%)   | 2 / 112 (1.79%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Injury, poisoning and procedural complications                      |                   |                   |  |
| Trauma to left thumb requiring surgical correction                  |                   |                   |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                                 | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Two night hospital stay due to broken arm requiring surgery |                 |                 |  |
| subjects affected / exposed                                 | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Trauma with fracture of 6 ribs pneumothorax                 |                 |                 |  |
| subjects affected / exposed                                 | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Hospital admission, left rib exacerbation COPD              |                 |                 |  |
| subjects affected / exposed                                 | 0 / 110 (0.00%) | 2 / 112 (1.79%) |  |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Hospital admission, right hip                               |                 |                 |  |
| subjects affected / exposed                                 | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Cardiac disorders   |                 |                 |  |
| Acute myocardial infarction                                 |                 |                 |  |
| subjects affected / exposed                                 | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Angina secondary to iron deficiency                         |                 |                 |  |
| subjects affected / exposed                                 | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Death of patient, out of hospital cardiac arrest            |                 |                 |  |
| subjects affected / exposed                                 | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 0 / 1           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Fast AF complicated by pulmonary oedema   |                 |                 |  |
| subjects affected / exposed   | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Acute coronary syndrome   |                 |                 |  |
| subjects affected / exposed   | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Admission for percutaneous coronary intervention and insertion of stent into LAD        |                 |                 |  |
| subjects affected / exposed   | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Dilated cardiomyopathy and mild pulmonary hypertension                                  |                 |                 |  |
| subjects affected / exposed   | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Atypical chest pain with raised troponin  |                 |                 |  |
| subjects affected / exposed   | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Death of patient, myocardial infarction   |                 |                 |  |
| subjects affected / exposed   | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 1           |  |
| Atrial fibrillation with fast ventricular response, leading to left ventricular failure |                 |                 |  |
| subjects affected / exposed   | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all  | 0 / 0           | 0 / 0           |  |
| Left ventricular systolic dysfunction   |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed  | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           |  |
| Angina attack  |                 |                 |  |
| subjects affected / exposed  | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures  |                 |                 |  |
| Elective orthopaedic surgery, correction of longstanding leg deformity     |                 |                 |  |
| subjects affected / exposed  | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           |  |
| Elective left total hip replacement  |                 |                 |  |
| subjects affected / exposed  | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           |  |
| Elective admission for laparotomy for division of adhesions + sigmoidopexy |                 |                 |  |
| subjects affected / exposed  | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           |  |
| Nervous system disorders   |                 |                 |  |
| Admission for craniotomy   |                 |                 |  |
| subjects affected / exposed  | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all                            | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           |  |
| Tonic clonic seizure, alcohol related?                                     |                 |                 |  |
| subjects affected / exposed  | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all                            | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                                 | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions                       |                 |                 |  |
| Unknown  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                                 | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Death of patient  |                 |                 |  |
| subjects affected / exposed                                 | 2 / 110 (1.82%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all             | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 1 / 2           | 0 / 0           |  |
| Consolidation A&E attendance                                |                 |                 |  |
| subjects affected / exposed                                 | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Right arm and right leg weakness, unable to smile + shaking |                 |                 |  |
| subjects affected / exposed                                 | 0 / 110 (0.00%) | 2 / 112 (1.79%) |  |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders                        |                 |                 |  |
| suspected DVT   |                 |                 |  |
| subjects affected / exposed                                 | 0 / 110 (0.00%) | 2 / 112 (1.79%) |  |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                                  |                 |                 |  |
| Small bowel obstruction                                     |                 |                 |  |
| subjects affected / exposed                                 | 2 / 110 (1.82%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| perforated diverticulum                                     |                 |                 |  |
| subjects affected / exposed                                 | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |
| Gallstone cholecystitis diagnosed                           |                 |                 |  |
| subjects affected / exposed                                 | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to treatment / all             | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Incarcerated abdominal wall hernia<br>subjects affected / exposed     | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to<br>treatment / all                    | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                         | 0 / 0           | 0 / 0           |  |
| Bowel blockage<br>subjects affected / exposed                         | 0 / 110 (0.00%) | 1 / 112 (0.89%) |  |
| occurrences causally related to<br>treatment / all                    | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                         | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal<br>disorders                    |                 |                 |  |
| Lung cancer diagnosis<br>subjects affected / exposed                  | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to<br>treatment / all                    | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                         | 0 / 0           | 0 / 0           |  |
| spontaneous secondary<br>pneumothorax                                 |                 |                 |  |
| subjects affected / exposed   | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to<br>treatment / all                    | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                         | 0 / 0           | 0 / 0           |  |
| Elective admission for Endobronchial<br>valve insertion               |                 |                 |  |
| subjects affected / exposed   | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to<br>treatment / all                    | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                         | 0 / 0           | 0 / 0           |  |
| Death of patient, diagnosed with<br>metastatic lung cancer            |                 |                 |  |
| subjects affected / exposed   | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to<br>treatment / all                    | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                         | 0 / 1           | 0 / 0           |  |
| Hepatobiliary disorders   |                 |                 |  |
| Hepatocellular carcinoma diagnosed<br>subjects affected / exposed     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to<br>treatment / all                    | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                         | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders   |                 |                 |  |
| Elective Trans-Urethral Resection of<br>Prostate with 2 day admission |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed  | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0           |  |
| Acute Kidney Injury and Sepsis   |                 |                 |  |
| subjects affected / exposed  | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0           |  |
| Left sided hydronephrosis  |                 |                 |  |
| subjects affected / exposed  | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0           |  |
| Infections and infestations  |                 |                 |  |
| Pneumonia requiring 6 day admission  |                 |                 |  |
| subjects affected / exposed  | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0           |  |
| Pneumonia and Multi-organ failure  |                 |                 |  |
| subjects affected / exposed  | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0           |  |
| Community acquired pneumonia complicated by fast AF, initially treated as COPD exacerbation. |                 |                 |  |
| subjects affected / exposed  | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0           |  |
| Hospital acquired pneumonia  |                 |                 |  |
| subjects affected / exposed  | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0           |  |
| Suspected aspiration treated for chest infection   |                 |                 |  |
| subjects affected / exposed  | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all   | 0 / 0           | 0 / 0           |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Aspirate pneumonia                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 110 (0.91%) | 0 / 112 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Community acquired pneumonia                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 110 (0.00%) | 2 / 112 (1.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                                   | Doxycycline     | Placebo           |  |
|---|-----------------|-------------------|--|
| Total subjects affected by non-serious adverse events               |                 |                   |  |
| subjects affected / exposed   | 9 / 110 (8.18%) | 23 / 112 (20.54%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                   |  |
| Elective prostate biopsy  |                 |                   |  |
| subjects affected / exposed   | 0 / 110 (0.00%) | 1 / 112 (0.89%)   |  |
| occurrences (all)   | 0               | 1                 |  |
| Injury, poisoning and procedural complications                      |                 |                   |  |
| Fall  |                 |                   |  |
| subjects affected / exposed   | 0 / 110 (0.00%) | 1 / 112 (0.89%)   |  |
| occurrences (all)   | 0               | 1                 |  |
| Vascular disorders  |                 |                   |  |
| Peripheral Vascular Disease   |                 |                   |  |
| subjects affected / exposed   | 0 / 110 (0.00%) | 1 / 112 (0.89%)   |  |
| occurrences (all)   | 0               | 1                 |  |
| Surgical and medical procedures                                     |                 |                   |  |
| Elective shoulder replacement                                       |                 |                   |  |
| subjects affected / exposed   | 0 / 110 (0.00%) | 1 / 112 (0.89%)   |  |
| occurrences (all)   | 0               | 1                 |  |
| Cardiac disorders   |                 |                   |  |
| Acute Coronary Syndrome   |                 |                   |  |
| subjects affected / exposed   | 1 / 110 (0.91%) | 0 / 112 (0.00%)   |  |
| occurrences (all)   | 1               | 0                 |  |
| Nervous system disorders  |                 |                   |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Tonic Clonic Seizure<br>subjects affected / exposed<br>occurrences (all)   | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| General disorders and administration<br>site conditions  |                      |                      |  |
| Nausea and skin flushing red<br>subjects affected / exposed<br>occurrences (all)   | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| Accidental unblinding of patient<br>subjects affected / exposed<br>occurrences (all)   | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| A&E attendance, facial swelling<br>following tooth extraction<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| SAE to exclude PE<br>subjects affected / exposed<br>occurrences (all)  | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| Atypical non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| Admission to exclude PE<br>subjects affected / exposed<br>occurrences (all)  | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| Admission with sepsis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| Admission with atypical chest pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| Elective admission for investigations<br>to assess suitability for lung<br>transplantation<br>subjects affected / exposed<br>occurrences (all) | 1 / 110 (0.91%)<br>1 | 0 / 112 (0.00%)<br>0 |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 1 / 110 (0.91%)<br>1 | 0 / 112 (0.00%)<br>0 |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| Right sided uncoordination<br>subjects affected / exposed<br>occurrences (all)  | 1 / 110 (0.91%)<br>1 | 0 / 112 (0.00%)<br>0 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)  | 1 / 110 (0.91%)<br>1 | 0 / 112 (0.00%)<br>0 |  |
| Elective admission for assessment<br>for ongoing non-invasive ventilation<br>subjects affected / exposed<br>occurrences (all) | 1 / 110 (0.91%)<br>1 | 0 / 112 (0.00%)<br>0 |  |
| Gastrointestinal disorders<br>Likely oesophageal spasm<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| Elective cholecystectomy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 110 (0.91%)<br>1 | 0 / 112 (0.00%)<br>0 |  |
| Gastritis/oesophagitis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 110 (0.91%)<br>1 | 0 / 112 (0.00%)<br>0 |  |
| Elective left inguinal hernia repair<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 110 (0.91%)<br>1 | 0 / 112 (0.00%)<br>0 |  |
| Reproductive system and breast<br>disorders<br>Scrotal abscess<br>subjects affected / exposed<br>occurrences (all)            | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| Infected sebaceous cyst on scrotum<br>subjects affected / exposed<br>occurrences (all)  | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |
| Renal and urinary disorders<br>Elective urological operation<br>subjects affected / exposed<br>occurrences (all)              | 0 / 110 (0.00%)<br>0 | 1 / 112 (0.89%)<br>1 |  |

|  |  |  |  |
|--|--|--|--|
| Elective prostate/urethral surgery<br>subjects affected / exposed<br>occurrences (all)   | 0 / 110 (0.00%)<br>0                             | 1 / 112 (0.89%)<br>1                             |  |
| Endocrine disorders<br>Admission with palpitations,<br>hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)   | 0 / 110 (0.00%)<br>0                             | 1 / 112 (0.89%)<br>1                             |  |
| Musculoskeletal and connective tissue disorders<br>Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all)<br><br>New diagnosis polymyalgia<br>rheumatica<br>subjects affected / exposed<br>occurrences (all) | 0 / 110 (0.00%)<br>0<br><br>0 / 110 (0.00%)<br>0 | 2 / 112 (1.79%)<br>2<br><br>1 / 112 (0.89%)<br>1 |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported