



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, j.wedzicha@imperial.ac.uk |
| Scientific contact | Jadwiga A 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 | 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:

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:

Population of trial subjects**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:

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 |
| Arm title | 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.

| | |
|------------------|---------|
| Arm title | 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.

| Number of subjects in period 1 | 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 (gestational age < 37 wks) | | | 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) | | | 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: Doxycycline: An oral dose of 100 mg once daily. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo one capsule daily | |

Primary: Rate of Exacerbations

| | |
|--|--------------------------------------|
| End point title | Rate of Exacerbations ^[1] |
| End point description: 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: 12 months | |
| Notes: [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. 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: 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

| | |
|---|-----------------------|
| Statistical analysis title | 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 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 | |
| Bowel blockage 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 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Lung cancer 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 | |
| spontaneous secondary pneumothorax | | | |
| 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 | |
| Elective admission for Endobronchial valve insertion | | | |
| 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, diagnosed with metastatic lung 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 / 1 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatocellular carcinoma diagnosed 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 | |
| Renal and urinary disorders | | | |
| Elective Trans-Urethral Resection of 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 %

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported