



Clinical trial results: Biomarker guided antibiotic treatment in Community-Acquired Pneumoni (BIO-CAP)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-002501-11 |
| Trial protocol | DK |
| Global end of trial date | 30 March 2020 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 15 September 2021 |
| First version publication date | 15 September 2021 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | BIO-CAP_2015 |
|-----------------------|--------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Nordsjællands Hospital |
| Sponsor organisation address | Dyrehavevej 29, Hillerød, Denmark, |
| Public contact | Gertrud Baunbæk-Knudsen, Nordsjællands Hospital, +45 26220865, gertrud.louise.baunbaek-knudsen@regionh.dk |
| Scientific contact | Gertrud Baunbæk-Knudsen, Nordsjællands Hospital, +45 26220865, gertrud.louise.baunbaek-knudsen@regionh.dk |

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 | 30 June 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 March 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of biomarker algorithms to reduce duration of antibiotic exposure in patients hospitalized with CAP compared to standard of care and to evaluate the efficacy of an algorithm based on C-reactive protein compared to an algorithm based on Procalcitonin for this purpose.

Protection of trial subjects:

Participants were treated according to guidelines in regards to choice of antibiotic agent. The intervention determined the length of treatment in the intervention groups, however, we determined a minimum treatment length according to current evidence of 72-hours. Further, the discontinuation of antibiotic treatment according to the biomarker algorithms could be overruled by the treating physician.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 01 March 2017 |
| 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 | Denmark: 300 |
| Worldwide total number of subjects | 300 |
| EEA total number of subjects | 300 |

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) | 99 |
| From 65 to 84 years | 163 |
| 85 years and over | 38 |

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 01-Mar-2017 - 01-Mar-2020.

Pre-assignment

Screening details:

Adult patients (18 years or older) admitted to Nordsjællands Hospital with symptoms compatible with Community Acquired Pneumonia (CAP) were screened for inclusion. The primary causes for no inclusion were no infiltrate on chest x-ray, inability to comprehend study material or unwillingness to participate.

Period 1

| | |
|------------------------------|-------------------------------|
| Period 1 title | Intervention (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | CRP-group |

Arm description:

Antibiotic treatment were given for minimum 72 hours.

After this time point antibiotic treatment were continued/discontinued according to the CRP biomarker algorithm:

CRP < 50 g/dl: discontinue antibiotic treatment

CRP < 75 g/dl and CRP ≥ 50 g/dl and CRP has decreased with at least 20% within the last 24 hours: discontinue antibiotic treatment

CRP ≥ 75 g/dl: continue antibiotic treatment

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

Dosage and administration details:

Dosage and frequency was determined by the treating physician

| | |
|--|--------------------------|
| Investigational medicinal product name | Amoxicillin/clavulansyre |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dosage and frequency was determined by the treating physician

| | |
|--|--|
| Investigational medicinal product name | Ampicillin "PCD |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dosage and frequency was determined by the treating physician

| | |
|--|----------------------------------|
| Investigational medicinal product name | Ampicillin "PCD" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency was determined by the treating physician | |
| Investigational medicinal product name | Benzylpenicillin "Panpharma" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency was determined by the treating physician | |
| Investigational medicinal product name | Cefuroxim "Stragen" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency was determined by the treating physician | |
| Investigational medicinal product name | Ciprofloxacin "Fresenius Kabi" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency was determined by the treating physician | |
| Investigational medicinal product name | Ciprofloxacin "Actavis" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency was determined by the treating physician | |
| Investigational medicinal product name | Clarithromycin "Paranova" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency was determined by the treating physician | |
| Investigational medicinal product name | Clarithromycin "Hexal" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Dicloxacillin "Actavis" |
| Investigational medicinal product code | |
| Other name | |

| | |
|--|---|
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Doxycyclin Europharma |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Meropenem "Fresenius Kabi" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Moxifloxacin "Orion" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Moxifloxacin "Actavis", |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Piperacillin/Tazobactam "Fresenius Kabi", |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Roxithromycin "Orifarm" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Vepicombin Novum |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dosage and frequency were determined by the treating physician

| | |
|------------------|---------------|
| Arm title | Control-group |
|------------------|---------------|

Arm description:

Participant are treated according to current guidelines.

| | |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

No investigational medicinal product assigned in this arm

| | |
|------------------|-----------|
| Arm title | PCT-group |
|------------------|-----------|

Arm description:

Antibiotic treatment were given for minimum 72 hours.

After this time point antibiotic treatment were continues/discontinued according to the PCT (procalcitonin) biomarker algorithm:

PCT < 0,25 µg/l : discontinue antibiotic treatment

CRP ≥ 0,25 µg/l : continue antibiotic treatment

| | |
|--|--------------|
| Arm type | intervention |
| Investigational medicinal product name | Amoxicillin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dosage and frequency was determined by the treating physician

| | |
|--|--------------------------|
| Investigational medicinal product name | Amoxicillin/clavulansyre |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dosage and frequency was determined by the treating physician

| | |
|--|--|
| Investigational medicinal product name | Ampicillin "PCD |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dosage and frequency was determined by the treating physician

| | |
|--|------------------|
| Investigational medicinal product name | Ampicillin "PCD" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dosage and frequency was determined by the treating physician

| | |
|--|----------------------------------|
| Investigational medicinal product name | Benzylpenicillin "Panpharma" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

| | |
|--|----------------------------------|
| Dosage and administration details: | |
| Dosage and frequency was determined by the treating physician | |
| Investigational medicinal product name | Cefuroxim "Stragen" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency was determined by the treating physician | |
| Investigational medicinal product name | Ciprofloxacin "Fresenius Kabi" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency was determined by the treating physician | |
| Investigational medicinal product name | Ciprofloxacin "Actavis" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency was determined by the treating physician | |
| Investigational medicinal product name | Clarithromycin "Paranova" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency was determined by the treating physician | |
| Investigational medicinal product name | Clarithromycin "Hexal" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Dicloxacillin "Actavis" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Doxycyclin Europharma |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |

| | |
|--|---|
| Investigational medicinal product name | Meropenem "Fresenius Kabi" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Moxifloxacin "Orion" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Moxifloxacin "Actavis", |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Piperacillin/Tazobactam "Fresenius Kabi", |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Roxithromycin "Orifarm" |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |
| Investigational medicinal product name | Vepicombin Novum |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Dosage and frequency were determined by the treating physician | |

| Number of subjects in period 1 | CRP-group | Control-group | PCT-group |
|---------------------------------------|-----------|---------------|-----------|
| Started | 100 | 101 | 99 |
| Completed | 100 | 101 | 99 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------------|
| Reporting group title | Intervention (overall period) |
|-----------------------|-------------------------------|

Reporting group description: -

| Reporting group values | Intervention (overall period) | Total | |
|--|-------------------------------|-------|--|
| Number of subjects | 300 | 300 | |
| 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 | | | |
| median | 73 | | |
| full range (min-max) | 23 to 96 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 155 | 155 | |
| Male | 145 | 145 | |

End points

End points reporting groups

| | |
|--|---------------|
| Reporting group title | CRP-group |
| Reporting group description: Antibiotic treatment were given for minimum 72 hours. After this time point antibiotic treatment were continued/discontinued according to the CRP biomarker algorithm: CRP < 50 g/dl: discontinue antibiotic treatment CRP < 75 g/dl and CRP ≥ 50 g/dl and CRP has decreased with at least 20% within the last 24 hours: discontinue antibiotic treatment CRP ≥ 75 g/dl: continue antibiotic treatment | |
| Reporting group title | Control-group |
| Reporting group description: Participant are treated according to current guidelines. | |
| Reporting group title | PCT-group |
| Reporting group description: Antibiotic treatment were given for minimum 72 hours. After this time point antibiotic treatment were continues/discontinued according to the PCT (procalcitonin) biomarker algorithm: PCT < 0,25 µg/l : discontinue antibiotic treatment CRP ≥ 0,25 µg/l : continue antibiotic treatment | |

Primary: Length of antibiotic treatment

| | |
|---|--------------------------------|
| End point title | Length of antibiotic treatment |
| End point description: | |
| End point type | Primary |
| End point timeframe: Within 30 days from inclusion | |

| End point values | CRP-group | Control-group | PCT-group | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 100 | 101 | 99 | |
| Units: Days | 7 | 9 | 7 | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Primary outcome |
| Statistical analysis description: Comparisons of length of antibiotic treatment (days) between the CRP-group and the control group | |
| Comparison groups | CRP-group v Control-group |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 201 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | < 0.001 |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[1] - We used the Wilcoxon Rank sum test as the assumption of a normal distribution was not met.

| | |
|---|-------------------------|
| Statistical analysis title | Primary outcome |
| Comparison groups | PCT-group v CRP-group |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.38 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: treatment failure

| | |
|--|-------------------|
| End point title | treatment failure |
| End point description: treatment failure was defined as readmission or renewed antibiotic treatment due to pneumonia. | |
| End point type | Secondary |
| End point timeframe: within 30 days of inclusion | |

| End point values | CRP-group | Control-group | PCT-group | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 100 | 101 | 99 | |
| Units: yes/no | 19 | 27 | 15 | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Treatment failure |
| Statistical analysis description: Number of patients who experienced treatment failure in the control-group versus the number of patients who experienced treatment failure in the CRP-group | |
| Comparison groups | CRP-group v Control-group |
| Number of subjects included in analysis | 201 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.19 |
| Method | Wilcoxon (Mann-Whitney) |

| | |
|--|-------------------------|
| Statistical analysis title | Treatment failure |
| Statistical analysis description: | |
| Number of patients who experienced treatment failure in the control-group versus number of patients who experienced treatment failure in the PCT-group | |
| Comparison groups | PCT-group v CRP-group |
| Number of subjects included in analysis | 199 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.56 |
| Method | Wilcoxon (Mann-Whitney) |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

May 2016 until 30-March-2021

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 24 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | CRP-group |
|-----------------------|-----------|

Reporting group description: -

| | |
|-----------------------|-----------|
| Reporting group title | PCT-group |
|-----------------------|-----------|

Reporting group description: -

| | |
|-----------------------|---------------|
| Reporting group title | control-group |
|-----------------------|---------------|

Reporting group description: -

| Serious adverse events | CRP-group | PCT-group | control-group |
|---|-------------------|------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 100 (23.00%) | 16 / 99 (16.16%) | 25 / 101 (24.75%) |
| number of deaths (all causes) | 4 | 3 | 5 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung cancer metastatic | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 99 (1.01%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 1 / 99 (1.01%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 99 (1.01%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |

| | | | |
|---|--|----------------|-----------------|
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 99 (1.01%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Social circumstances | | | |
| Death | Additional description: One patient was found death during admission, overdose was suspected, however, no autopsy was performed. Four patients died outside of hospital, all of them where known with severe chronic disorders. | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 2 / 99 (2.02%) | 2 / 101 (1.98%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| Gastrointestinal disorders | | | |
| Ileus | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 99 (1.01%) | 2 / 101 (1.98%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | Additional description: exacerbation | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 3 / 99 (3.03%) | 3 / 101 (2.97%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |

| | | | |
|---|------------------------------------|----------------|-----------------|
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 99 (1.01%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Emphyema | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung abscess | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sputum abnormal | Additional description: Hemoptysis | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | 1 / 99 (1.01%) | 2 / 101 (1.98%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 1 / 99 (1.01%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory acidosis | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Endocrine disorders | | | |
| Hypokalaemia | | | |

| | | | |
|---|---|----------------|-----------------|
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Hip disarticulation | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inflammation | Additional description: Suspected to have venous thrombosis in lower limb, rouled out with ultrasound | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 100 (5.00%) | 3 / 99 (3.03%) | 9 / 101 (8.91%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | 0 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | 1 / 99 (1.01%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | 0 / 99 (0.00%) | 2 / 101 (1.98%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 1 / 99 (1.01%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|-----------------|
| Influenza | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 0.1 %

| Non-serious adverse events | CRP-group | PCT-group | control-group |
|---|-------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 23 / 100 (23.00%) | 29 / 99 (29.29%) | 34 / 101 (33.66%) |
| Vascular disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 99 (1.01%) | 0 / 101 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory acidosis | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all) | 1 | 0 | 1 |
| Bradycardia | | | |

| | | | |
|---|----------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 100 (0.00%) 0 | 0 / 99 (0.00%) 0 | 1 / 101 (0.99%) 1 |
| Fluid overload subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 1 / 99 (1.01%) 1 | 0 / 101 (0.00%) 0 |
| Chest pain subjects affected / exposed occurrences (all) | 0 / 100 (0.00%) 0 | 0 / 99 (0.00%) 0 | 1 / 101 (0.99%) 1 |
| Nervous system disorders Syncope subjects affected / exposed occurrences (all) | 0 / 100 (0.00%) 0 | 0 / 99 (0.00%) 0 | 1 / 101 (0.99%) 1 |
| Headache subjects affected / exposed occurrences (all) | 0 / 100 (0.00%) 0 | 0 / 99 (0.00%) 0 | 1 / 101 (0.99%) 1 |
| Blood and lymphatic system disorders Phlebitis subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 4 / 99 (4.04%) 4 | 0 / 101 (0.00%) 0 |
| Anaemia subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 2 / 99 (2.02%) 2 | 0 / 101 (0.00%) 0 |
| Oedema subjects affected / exposed occurrences (all) | 0 / 100 (0.00%) 0 | 0 / 99 (0.00%) 0 | 1 / 101 (0.99%) 1 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 0 / 99 (0.00%) 0 | 2 / 101 (1.98%) 2 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 6 / 99 (6.06%) 6 | 1 / 101 (0.99%) 1 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 1 / 99 (1.01%) 1 | 1 / 101 (0.99%) 1 |
| Haematochezia | | | |

| | | | |
|--|---|----------------|-----------------|
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all) | 0 | 0 | 1 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 2 / 101 (1.98%) |
| occurrences (all) | 0 | 0 | 2 |
| Constipation | | | |
| subjects affected / exposed | 3 / 100 (3.00%) | 1 / 99 (1.01%) | 4 / 101 (3.96%) |
| occurrences (all) | 3 | 1 | 4 |
| Abscess oral | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 99 (1.01%) | 0 / 101 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hepatobiliary disorders | | | |
| Liver function test | Additional description: elevated liverenzymes | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 2 / 99 (2.02%) | 2 / 101 (1.98%) |
| occurrences (all) | 0 | 2 | 2 |
| Skin irritation | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 1 / 99 (1.01%) | 0 / 101 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 99 (1.01%) | 0 / 101 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endocrine disorders | | | |
| Adrenal mass | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 99 (1.01%) | 0 / 101 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperglycaemia | | | |

| | | | |
|---|---|----------------|-----------------|
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| pain | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 3 / 99 (3.03%) | 1 / 101 (0.99%) |
| occurrences (all) | 1 | 4 | 1 |
| Fracture | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all) | 0 | 0 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all) | 0 | 0 | 1 |
| Vulvovaginal candidiasis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 99 (1.01%) | 0 / 101 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bacterial test positive | Additional description: Colonization with vancomycin-resistant Enterococcus | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 2 / 101 (1.98%) |
| occurrences (all) | 1 | 0 | 2 |
| Lung abscess | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 101 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abscess soft tissue | | | |

| | | | |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 100 (1.00%) 1 | 0 / 99 (0.00%) 0 | 0 / 101 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 10 / 100 (10.00%) | 7 / 99 (7.07%) | 11 / 101 (10.89%) |
| occurrences (all) | 10 | 7 | 11 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 2 / 99 (2.02%) | 1 / 101 (0.99%) |
| occurrences (all) | 0 | 2 | 1 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 2 / 99 (2.02%) | 0 / 101 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all) | 0 | 0 | 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