# Clinical trial results:
# Tackling Early Morbidity and Mortality in myeloma: assessing the benefit of antibiotic prophylaxis and its effect on healthcare associated infections

## Summary

| | |
|---|---|
| EudraCT number | 2011-000366-35 |
| Trial protocol | GB |
| Global end of trial date | 06 April 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 06 November 2019 |
| First version publication date | 06 November 2019 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | RG_09-121 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | ISRCTN51731976 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | University of Birmingham |
| Sponsor organisation address | Vincent Drive, Birmingham, United Kingdom, |
| Public contact | Birgit Whitman, University of Birmingham, researchgovernance@contacts.bham.ac.uk |
| Scientific contact | Professor Mark Drayson, University of Birmingham, m.t.drayson@bham.ac.uk |
| Sponsor organisation name | University of Warwick |
| Sponsor organisation address | Gibbet Hill Road, Coventry, United Kingdom, CV4 7AL |
| Public contact | Jane Prewett, University of Warwick, +44 02476575847, sponsorship@warwick.ac.uk |
| Scientific contact | Jane Prewett, University of Warwick, +44 02476575847, sponsorship@warwick.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 | Interim |
| Date of interim/final analysis | 18 August 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 06 June 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 April 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the risks, benefits and cost effectiveness of levofloxacin in newly diagnosed symptomatic myeloma by a prospective, multi-centre, randomised, double-blind, placebo-controlled trial.

Protection of trial subjects:

Confidential reports containing recruitment, protocol compliance, safety data and interim analyses of outcomes were reviewed by the independent data and safety monitoring committee for evidence why the study should be amended or terminated based on recruitment rates, compliance, safety or efficacy.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 August 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 977 |
| Worldwide total number of subjects | 977 |
| EEA total number of subjects | 977 |

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) | 384 |
| From 65 to 84 years | 566 |

| | |
|---|---|
| 85 years and over | 27 |

## Subject disposition

### Recruitment

Recruitment details:

977 patients were recruited between August 15, 2012 and April 29, 2016.

### Pre-assignment

Screening details:

Patients with newly diagnosed myeloma with an intention to treat the patient's myeloma actively.

### Period 1

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

Blinding implementation details:

Levofloxacin and placebo tablets were packaged in coded but otherwise identical blister packs. Neither the patient nor the clinical team responsible for the patients care knew how to break the treatment code. The treatment code could only be broken by the Emergency Scientific and Medical Services (eSMS) team at Guy's and St Thomas' Hospital.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Levofloxacin |

Arm description:

Levofloxacin

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

Dosage and administration details:

When patients are within 14 days either side of starting a programme of anti-myeloma therapy, patients will receive two 250mg Levofloxacin daily for 12 weeks. The start of the anti-myeloma therapy is determined as the start of steroids or chemotherapy, whichever comes first. EGFR was assessed prior to commencement of treatment and reassessed at each scheduled trial visit to identify changes in renal function that would necessitate a change in dose of levofloxacin. eGFR was assessed within 7 -14 days of the patient beginning randomised treatment to determine dosage. People with eGFR>50 ml/min took 2 tablets daily (dose of 500mg), those with eGFR between 20 - 50 ml/min took 1 tablet daily (dose of 250mg), and eGFR <20 ml/min took half a tablet daily (125mg)

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Placebo

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

Dosage and administration details:

Patients will receive two placebo tablets daily for 12 weeks. eGFR was assessed prior to commencement of treatment and reassessed at each scheduled trial visit to identify changes in renal function that would necessitate a change in dose of levofloxacin, these changes were matched for those on placebo. eGFR

was assessed within 7 -14 days of the patient beginning randomised treatment to determine dosage. People with eGFR>50 ml/min took 2 tablets daily, those with eGFR between 20 - 50 ml/min took 1 tablet daily, and eGFR <20 ml/min took half a tablet daily.

| **Number of subjects in period 1** | Levofloxacin | Placebo |
|---|---|---|
| Started | 489 | 488 |
| Completed | 489 | 488 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Levofloxacin |
| Reporting group description: Levofloxacin | |
| Reporting group title | Placebo |
| Reporting group description: Placebo | |

| Reporting group values | Levofloxacin | Placebo | Total |
|---|---|---|---|
| Number of subjects | 489 | 488 | 977 |
| Age categorical<br>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 | | | |
| Age continuous | | | |
| Units: years | | | |
| median | 67 | 67 | |
| inter-quartile range (Q1-Q3) | 59 to 75 | 61 to 75 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 173 | 193 | 366 |
| Male | 316 | 295 | 611 |

## End points

| End points reporting groups | |
|---|---|
| Reporting group title | Levofloxacin |
| Reporting group description: Levofloxacin | |
| Reporting group title | Placebo |
| Reporting group description: Placebo | |

### Primary: Febrile infection or death within 12 weeks

| | |
|---|---|
| End point title | Febrile infection or death within 12 weeks |
| End point description: | |
| End point type | Primary |
| End point timeframe: From start of trial treatment up to 12 weeks | |

| End point values | Levofloxacin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 489 | 488 | | |
| Units: Patients | 95 | 134 | | |

### Statistical analyses

| Statistical analysis title | Time to first febrile episode or death |
|---|---|
| Statistical analysis description: Time to first febrile episode or death within 12 weeks, was carried out using a log-rank comparison, from start of trial medication to the time of an event, or date of censor for those with no events up to 12 weeks. All randomised patients were included in an intention to treat analysis of the primary endpoint which was assessed using Kaplan-Meier curves and the log-rank test. | |
| Comparison groups | Placebo v Levofloxacin |
| Number of subjects included in analysis | 977 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 0.86 |

## Adverse events

| Adverse events information[1] | |
|---|---|
| Timeframe for reporting adverse events: | |
| Adverse events reported between start of trial treatment and 16 weeks | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 4 |

| Reporting groups | |
|---|---|
| Reporting group title | Levofloxacin |
| Reporting group description: | |
| Levofloxacin | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo | |

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Adverse events not collected as part of this study.

| Serious adverse events | Levofloxacin | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 220 / 477 (46.12%) | 203 / 475 (42.74%) | |
| number of deaths (all causes) | 9 | 23 | |
| number of deaths resulting from adverse events | 1 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasms benign, malignant and unspecified other | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vascular disorders | | | |
| Thromboembolic event | | | |
| subjects affected / exposed | 14 / 477 (2.94%) | 18 / 475 (3.79%) | |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 18 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Hypotension | | | |
| subjects affected / exposed | 12 / 477 (2.52%) | 3 / 475 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 13 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Haematoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorder - Other | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Surgical and medical procedures - Other | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 46 / 477 (9.64%) | 48 / 475 (10.11%) | |
| occurrences causally related to treatment / all | 5 / 53 | 5 / 56 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 477 (1.26%) | 6 / 475 (1.26%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 5 / 477 (1.05%) | 4 / 475 (0.84%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 5 / 477 (1.05%) | 4 / 475 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Oedema limbs | | | |
| subjects affected / exposed | 6 / 477 (1.26%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 3 / 477 (0.63%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 3 / 477 (0.63%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flu-like symptoms | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema face | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema trunk | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised oedema | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Immune system disorders | | | |
| Allergic reaction | | | |
| subjects affected / exposed | 5 / 477 (1.05%) | 5 / 475 (1.05%) | |
| occurrences causally related to treatment / all | 1 / 5 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Social circumstances | | | |
| Social circumstances - Other | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Testicular pain | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| 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 | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 21 / 477 (4.40%) | 12 / 475 (2.53%) | |
| occurrences causally related to treatment / all | 0 / 22 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Cough | | | |
| subjects affected / exposed | 11 / 477 (2.31%) | 9 / 475 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 3 / 475 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pleural effusion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 477 (0.63%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 4 / 475 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders - Other | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Aspiration | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal inflammation | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 3 / 477 (0.63%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusion | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 5 / 475 (1.05%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Delirium | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hallucination | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 4 / 477 (0.84%) | 4 / 475 (0.84%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Creatinine increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 477 (1.05%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 477 (0.63%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alkaline phosphatase increased | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations - Other | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac troponin 1 increased | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram QT corrected interval prolonged | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 5 / 475 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 477 (0.63%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vascular access complication | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 11 / 477 (2.31%) | 10 / 475 (2.11%) | |
| occurrences causally related to treatment / all | 2 / 11 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Chest pain - cardiac | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 5 / 475 (1.05%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 3 / 475 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | |
| Cardiac disorder - Other | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 3 / 475 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Heart failure | | | |
| subjects affected / exposed | 4 / 477 (0.84%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 3 / 475 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Acute coronary syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 477 (0.21%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 3 / 477 (0.63%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asystole | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 477 (1.26%) | 4 / 475 (0.84%) | |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Syncope | | | |
| subjects affected / exposed | 5 / 477 (1.05%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorder - Other | | | |
| subjects affected / exposed | 3 / 477 (0.63%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vasovagal reaction | | | |
| subjects affected / exposed | 4 / 477 (0.84%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 3 / 477 (0.63%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lethargy | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 477 (0.42%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stroke | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphasia | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ischaemia cerebrovascular | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tremor | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 12 / 477 (2.52%) | 7 / 475 (1.47%) | |
| occurrences causally related to treatment / all | 4 / 13 | 0 / 8 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 1 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 6 / 475 (1.26%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic disorder - Other | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders - Other | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Eye disorder - Other | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Retinal vascular disorder | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 16 / 477 (3.35%) | 19 / 475 (4.00%) | |
| occurrences causally related to treatment / all | 5 / 17 | 9 / 20 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Vomiting | | | |
| subjects affected / exposed | 10 / 477 (2.10%) | 11 / 475 (2.32%) | |
| occurrences causally related to treatment / all | 4 / 14 | 1 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Constipation | | | |
| subjects affected / exposed | 11 / 477 (2.31%) | 6 / 475 (1.26%) | |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 14 / 477 (2.94%) | 3 / 475 (0.63%) | |
| occurrences causally related to treatment / all | 4 / 14 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 477 (0.63%) | 8 / 475 (1.68%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Colonic perforation | | | |
| subjects affected / exposed | 4 / 477 (0.84%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 477 (0.21%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders - Other | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral pain | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dental caries | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal haemorrhage | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal perforation | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecal incontinence | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucositis oral | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstruction gastric | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatobiliary disorder - Other | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash maculopapular | | | |
| subjects affected / exposed | 13 / 477 (2.73%) | 10 / 475 (2.11%) | |
| occurrences causally related to treatment / all | 6 / 13 | 1 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders - Other | | | |
| subjects affected / exposed | 3 / 477 (0.63%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Erythroderma | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stevens-Johnson syndrome | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin ulceration | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 20 / 477 (4.19%) | 13 / 475 (2.74%) | |
| occurrences causally related to treatment / all | 4 / 20 | 2 / 13 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 4 | |
| Urinary retention | | | |
| subjects affected / exposed | 4 / 477 (0.84%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Cystitis noninfective | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (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 - Other | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Urinary frequency | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract pain | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Endocrine disorders - Other | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 8 / 477 (1.68%) | 8 / 475 (1.68%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

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|---|---|---|---|
| Musculoskeletal and connective tissue disorder - other | | | |
| subjects affected / exposed | 5 / 477 (1.05%) | 3 / 475 (0.63%) | |
| occurrences causally related to treatment / all | 4 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 3 / 477 (0.63%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest wall pain | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised muscle weakness | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle weakness lower limb | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flank pain | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint range of motion decreased cervical spine | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle weakness right-sided | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Infections and infestations** | | | |
| Lung infection | | | |
| subjects affected / exposed | 35 / 477 (7.34%) | 51 / 475 (10.74%) | |
| occurrences causally related to treatment / all | 2 / 36 | 0 / 58 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 8 | |
| Infections and infestations other | | | |
| subjects affected / exposed | 18 / 477 (3.77%) | 24 / 475 (5.05%) | |
| occurrences causally related to treatment / all | 0 / 19 | 0 / 26 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 19 / 477 (3.98%) | 16 / 475 (3.37%) | |
| occurrences causally related to treatment / all | 2 / 19 | 1 / 19 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 6 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 477 (0.84%) | 8 / 475 (1.68%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial infection | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 477 (0.42%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue infection | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 3 / 475 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 2 / 475 (0.42%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phlebitis infective | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder infection | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis infective | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint infection | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney infection | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Papulopustular rash | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural infection | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestine infection | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tooth infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 6 / 475 (1.26%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 477 (0.63%) | 3 / 475 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 3 / 475 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acidosis | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anorexia nervosa | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 477 (0.42%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 477 (0.42%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 1 / 475 (0.21%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 477 (0.21%) | 0 / 475 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Levofloxacin | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 477 (0.00%) | 0 / 475 (0.00%) | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 09 September 2011 | Protocol amendment from v1.0 to v2.0.<br><br>1) Clarification of Inclusion criteria (Section 7.1)<br>2) Removal of mandatory request for skeletal survey as part of myeloma diagnosis (Section 10.1 Local Laboratory Investigations)<br>3) Clarification of the process for retrieving bacterial isolates from local laboratories (10.2.1 Microbiology)<br>4) Adjustment of the study milestones (Section 13.5 Trial Timetable and Milestones) |
| 13 February 2012 | Protocol amendment from v2.0 to v3.0<br><br>1) Change to inclusion criteria<br>2) Change to exclusion criteria<br>3) Change to assessment schedule<br>4) Minor clarifications to make text clearer |
| 11 November 2015 | Protocol amendment from v3.0 to v4.0.<br><br>1) Protocol changed throughout to include new recruitment target of up to 1000 participants<br>2) Protocol changed throughout to include new recruitment timescale. Extension of recruitment up to 30th April 2016<br>3) Minor clarifications to inclusion, exclusion<br>4) Update to the sponsor contact details<br>5) Minor administrative changes |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported