



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
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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
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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
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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			
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			
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
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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Reporting groups

Reporting group title	Levofloxacin
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Reporting group description:

Levofloxacin

Reporting group title	Placebo
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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			

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			

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	

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			

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			

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	

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	

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	

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			

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			

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			

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported