Clinical trial results:
International Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of the Efficacy and Safety of KIACTA™ in Preventing Renal Function Decline in Patients With AA Amyloidosis

Summary

EudraCT number	2010-022313-25
Trial protocol	LT SE GB NL CZ FI DE ES BE PL IT BG PT LV EE
Global end of trial date	04 March 2016

Results information

Result version number	v1 (current)
This version publication date	15 October 2017
First version publication date	15 October 2017

Trial information

Trial identification

Sponsor protocol code	CL-503012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01215747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	A.T. Development Switzerland SARL
Sponsor organisation address	Route de la Corniche 3B, Epalinges, Switzerland,
Public contact	Monika Deme, AD Project Management, PPD , +31 .630037735., Monika.Deme@ppdi.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 March 2016
Global end of trial reached?	Yes
Global end of trial date	04 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this double-blind, randomized, placebo-controlled, Phase 3 study was to assess the efficacy and safety of treatment with Kiacta in adult patients with AA amyloidosis. Efficacy was assessed by the time from Baseline to the primary endpoint. This primary efficacy endpoint was the time from Baseline to the earliest of a persistent decrease in creatinine clearance (CrCl) of 40% or more, a persistent increase in serum creatinine (SCr) of 80% or more, or progression to end-stage renal disease (ESRD). Safety was assessed by the incidence of non-serious adverse events (AEs) and serious AEs (SAEs). Neither progression to ESRD nor a clinically significant change in CrCl or SCr was considered an AE or SAE.

Protection of trial subjects:

The study drug was to be taken a minimum of 1 hour before or 2 hours after morning and evening meals.
Dose regimen of the subjects was adjusted according to CrCl levels (increases or decreases).

Background therapy:

Subjects receiving cytotoxic agents, colchicine, antitumor necrosis factor agents, anti-interleukin-1 or anti-interleukin-6 agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, or a renin inhibitor had to be on stable doses for at least 3 months before the baseline visit. Patients were treated for worsening of hypertension or the underlying inflammatory condition as clinically indicated.

Evidence for comparator:

No patient was maintained under exclusive placebo treatment during the study. The study drug (Kiacta or placebo) was administered in addition to the standard therapy currently available.

Actual start date of recruitment	04 April 2011
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	Mexico: 1
Country: Number of subjects enrolled	Peru: 17
Country: Number of subjects enrolled	Russian Federation: 32
Country: Number of subjects enrolled	Tunisia: 21
Country: Number of subjects enrolled	Turkey: 14
Country: Number of subjects enrolled	Ukraine: 18
Country: Number of subjects enrolled	United States: 10
Country: Number of subjects enrolled	Armenia: 10
Country: Number of subjects enrolled	Egypt: 19
Country: Number of subjects enrolled	Georgia: 5

Country: Number of subjects enrolled	India: 13
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Jordan: 1
Country: Number of subjects enrolled	Lebanon: 3
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Latvia: 3
Country: Number of subjects enrolled	Lithuania: 10
Worldwide total number of subjects	260
EEA total number of subjects	88

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)	225
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was designed to enroll adult patients with AA amyloidosis with persistent proteinuria ≥1 g/day and CrCl ≥25 mL/min/1.73 m2. Randomization was stratified by screening proteinuria (<3 or ≥3 g/day) and screening eGFR as calculated with the modification of diet in renal disease (MDRD) formula (<60 or ≥60 mL/min/1.73 m2).

Pre-assignment

Screening details:

Subjects were assessed at screening and baseline and then every 3 months until a primary endpoint was met or the end of study (EOS) was reached. Those subjects who met inclusion criteria and did not meet exclusion criteria were eligible to participate in the study and were randomized to treatment.

Pre-assignment period milestones

Number of subjects started	462[1]
Number of subjects completed	260

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Screen failure: 201

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 462 patients were screened; 201 patients were screen failures. A total of 261 patients were enrolled to the study, of which 130 patients were randomized to the Kiacta group and 131 patients were randomized to the placebo group.

Period 1

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

Blinding implementation details:

The study was double-blind.
The patients, the investigators, the study site staff, the contract research organization (monitoring, central laboratory, and data management), and the sponsor remained blinded to study drug assignment during the entire study period.
Kiacta and placebo were in the form of capsules, identical in external appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Kiacta

Arm description:

Subjects received 400 mg or 1200 mg (as 1 to 3 capsules of 400 mg) per dose of Kiacta, twice daily

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

Dosage and administration details:

400 mg (1 to 3 capsules) twice daily

Arm title	Placebo
Arm description: 1 to 3 capsules of Placebo, twice daily	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 to 3 capsules of Placebo, twice daily

Number of subjects in period 1	Kiacta	Placebo
Started	129	131
Completed	91	94
Not completed	38	37
Adverse event, serious fatal	15	13
Consent withdrawn by subject	9	12
Physician decision	7	5
Adverse event, non-fatal	4	5
Lost to follow-up	2	2
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Kiacta
Reporting group description:	
Subjects received 400 mg or 1200 mg (as 1 to 3 capsules of 400 mg) per dose of Kiacta, twice daily	
Reporting group title	Placebo
Reporting group description:	
1 to 3 capsules of Placebo, twice daily	

Reporting group values	Kiacta	Placebo	Total
Number of subjects	129	131	260
Age categorical			
Male or nonpregnant, nonlactating females			
Units: Subjects			
Adults (18-64 years)	115	110	225
From 65-84 years	14	21	35
Gender categorical Units: Subjects			
Female	57	63	120
Male	72	68	140

Subject analysis sets	
Subject analysis set title	ITT analysis set - TTE endpoints
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients who were randomized to a treatment group and took at least 1 dose of study drug.	
Subject analysis set title	PP analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients who had 80% to 120% (inclusive) compliance with the study drug (based on percentage of times study drug was taken), had no missing measurements on any relevant analyte (SCr, CrCl, or eGFR data) for 2 or more consecutive visits, had fulfilled all the study inclusion and exclusion criteria, and had no major protocol violations.	
Subject analysis set title	ITT analysis set - non-TTE endpoints
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
For any endpoint, this analysis set included all patients who were randomized to a treatment group, took at least 1 dose of the study drug, and had at least 1 postbaseline assessment.	

Reporting group values	ITT analysis set - TTE endpoints	PP analysis set	ITT analysis set - non-TTE endpoints
Number of subjects	260	216	253
Age categorical			
Male or nonpregnant, nonlactating females			
Units: Subjects			
Adults (18-64 years)	225		
From 65-84 years	35		

Gender categorical Units: Subjects			
Female	120		
Male	140		

End points

End points reporting groups

Reporting group title	Kiacta
Reporting group description:	
Subjects received 400 mg or 1200 mg (as 1 to 3 capsules of 400 mg) per dose of Kiacta, twice daily	
Reporting group title	Placebo
Reporting group description:	
1 to 3 capsules of Placebo, twice daily	
Subject analysis set title	ITT analysis set - TTE endpoints
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients who were randomized to a treatment group and took at least 1 dose of study drug.	
Subject analysis set title	PP analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients who had 80% to 120% (inclusive) compliance with the study drug (based on percentage of times study drug was taken), had no missing measurements on any relevant analyte (SCr, CrCl, or eGFR data) for 2 or more consecutive visits, had fulfilled all the study inclusion and exclusion criteria, and had no major protocol violations.	
Subject analysis set title	ITT analysis set - non-TTE endpoints
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
For any endpoint, this analysis set included all patients who were randomized to a treatment group, took at least 1 dose of the study drug, and had at least 1 postbaseline assessment.	

Primary: Time from baseline to the earliest of a persistent decrease in CrCl of ≥40%, a persistent increase in SCr of ≥80%, or progression to ESRD

End point title	Time from baseline to the earliest of a persistent decrease in CrCl of ≥40%, a persistent increase in SCr of ≥80%, or progression to ESRD
End point description:	
End point type	Primary
End point timeframe:	
The primary efficacy endpoint was to assess the effect of treatment with Kiacta on the time from baseline to the earliest of: a persistent decrease in CrCl ≥40%, a persistent increase in SCr ≥80%, or progression to ESRD.	

End point values	Kiacta	Placebo	ITT analysis set - non-TTE endpoints	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	129	131	253	
Units: months				
median (confidence interval 95%)				
Time to persistent increase in SCr of ≥80%	1.0667 (0.233 to 3.267)	1.0333 (0.2 to 4.333)	1.0333 (0.2 to 4.333)	
Time to persistent decrease in CrCl of ≥40%	76.5 (28.3 to 270)	67 (24.3 to 331)	0.007 (-0.04 to 0.36)	

Time to progression to ESRD	72 (22 to 525)	61 (11 to 468)	3.259 (-18.9 to 3.8)	

Statistical analyses

Statistical analysis title	Statistical analysis plan dated 03 Jun 2016
Comparison groups	Kiacta v Placebo
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.882
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.4
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed from the time the subject signs the informed consent until 30 days after the last dose of the treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Kiacta treatment group
Reporting group description: -	
Reporting group title	Placebo treatment group

Reporting group description: -

Serious adverse events	Kiacta treatment group	Placebo treatment group	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 129 (44.96%)	64 / 131 (48.85%)	
number of deaths (all causes)	15	13	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal cancer			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			

subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 129 (0.78%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior mesenteric artery syndrome			

subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Diarrhoea			
subjects affected / exposed	1 / 129 (0.78%)	6 / 131 (4.58%)	
occurrences causally related to treatment / all	0 / 115	1 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 129 (0.78%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	2 / 129 (1.55%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 2	0 / 1	
Fatigue			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 1	
Generalised oedema			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	

Impaired healing			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ disorder			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 129 (1.55%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal swelling			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testicular mass			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 129 (0.78%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	0 / 129 (0.00%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 129 (0.00%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Femur fracture			
subjects affected / exposed	0 / 129 (0.00%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body in eye			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open fracture			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			

subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Familial mediterranean fever			
subjects affected / exposed	1 / 129 (0.78%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystic fibrosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiac failure			
subjects affected / exposed	2 / 129 (1.55%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac amyloidosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Autonomic neuropathy			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 129 (3.88%)	3 / 131 (2.29%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of chronic disease			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			

subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 129 (0.00%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 129 (0.78%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amaurosis fugax			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angle closure glaucoma			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	0 / 129 (0.00%)	3 / 131 (2.29%)	
occurrences causally related to treatment / all	0 / 115	1 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 129 (1.55%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 129 (0.00%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 129 (0.00%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous stomatitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal stenosis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal failure acute			
subjects affected / exposed	4 / 129 (3.10%)	5 / 131 (3.82%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nephrotic syndrome			
subjects affected / exposed	4 / 129 (3.10%)	4 / 131 (3.05%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 2	0 / 1	
Calculus ureteric			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			

subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	4 / 129 (3.10%)	5 / 131 (3.82%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 129 (0.78%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankylosing spondylitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle atrophy			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			

subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriatic arthropathy			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatic disorder			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 129 (3.10%)	7 / 131 (5.34%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 1	0 / 4	
Gastroenteritis			
subjects affected / exposed	2 / 129 (1.55%)	3 / 131 (2.29%)	
occurrences causally related to treatment / all	1 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			

subjects affected / exposed	3 / 129 (2.33%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 129 (1.55%)	3 / 131 (2.29%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 129 (1.55%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 129 (1.55%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			
subjects affected / exposed	2 / 129 (1.55%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 129 (1.55%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 129 (0.78%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 129 (0.00%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			

subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute tonsillitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alpha haemolytic streptococcal infection			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis viral			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical mycobacterial pneumonia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of male external genital organ			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genitourinary tract infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematoma infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leishmaniasis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			

subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 165	0 / 115	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ophthalmic herpes simplex			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal abscess			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal urinary tract infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 129 (0.78%)	2 / 131 (1.53%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoglycaemia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 115	0 / 165	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Kiacta treatment group	Placebo treatment group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	110 / 129 (85.27%)	114 / 131 (87.02%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	16 / 129 (12.40%)	17 / 131 (12.98%)	
occurrences (all)	33	33	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	13 / 129 (10.08%)	20 / 131 (15.27%)	
occurrences (all)	33	33	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	22 / 129 (17.05%)	17 / 131 (12.98%)	
occurrences (all)	39	39	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	26 / 129 (20.16%)	24 / 131 (18.32%)	
occurrences (all)	50	50	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 129 (11.63%)	23 / 131 (17.56%)	
occurrences (all)	38	38	
Bronchitis			
subjects affected / exposed	16 / 129 (12.40%)	11 / 131 (8.40%)	
occurrences (all)	27	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2013	Protocol CL-503012 Version 5.0 states that details for the analysis of samples taken for assessment of urinary glycosaminoglycans (GAGs), urinary creatinine, and urine proteomics was provided in a separate protocol (Protocol CL-503014). However, Auven Therapeutics (formerly Celtic Therapeutics) subsequently decided not to develop Protocol CL-503014. Samples for urinary GAGs, urinary creatinine, and urine proteomics were collected, stored, and analyzed as planned in Protocol CL-503012 Version 5.0 but the development plan for a diagnostic has not yet been determined. The affected sections of the protocol are as follows: Section 7.5.3.1 Safety Measures – Clinical Laboratory Parameters Section 8.3.1 Safety Evaluations – Clinical Laboratory Parameters

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported