Clinical trial results:
A prospective, bicentric, randomised, primarily double blind, placebo-controlled study to evaluate the efficacy of zoledronic acid for the treatment of bone marrow syndrome

Summary

EudraCT number	2010-019415-38
Trial protocol	DE
Global end of trial date	26 August 2015

Results information

Result version number	v1 (current)
This version publication date	22 July 2021
First version publication date	22 July 2021

Trial information

Trial identification

Sponsor protocol code	CZOL446HDE38T

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01348269
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Wuerzburg
Sponsor organisation address	Josef-Schneider-Str. 2, Wuerzburg, Germany, 97080
Public contact	Dr. Lothar Seefried, University Hospital Wuerzburg Clinical Study Unit Department of Orthopaedics Koenig-Ludwig-Haus, 0049 9318033590, l-seefried.klh@uni-wuerzburg.de
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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	03 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2015
Global end of trial reached?	Yes
Global end of trial date	26 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim is to test the reduction of bone marrow edema syndrome after a singular intravenous treatment with Zoledronic Acid within 6 weeks compared to placebo. The volume of the edema is defined as biometric data measured by the use of MRT before and six weeks after treatment. The hypothesis has to be checked whether Zoledronic Acid is efficient in the treatment of painfull bone marrow edema. A statistically significant reduction of the edema in the MRT is considered as evidence for efficacy.

Protection of trial subjects:

Safety monitoring (adverse Events, serious adverse Events, adverse drug reactions) and continous assessment of laboratory values (clinical chemistry, hematology)

Background therapy:

All patients received Vitamin D background therapy.

Evidence for comparator:

Placebo-controlled study. No active comparator was used.

Actual start date of recruitment	01 June 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	42

From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient (FPFV) was enrolled on 13-Jul-2011 and last patient (LPFV) was enrolled on 26-May-2015. All patients were recruited by a single center in Germany.

Pre-assignment

Screening details:

Suitable patients were selected by the investigator. A total of 63 patients were screened. 15 patients were deemed screening failure and eight of these patients were randomized but did not receive intervention.

Pre-assignment period milestones

Number of subjects started	63[1]
Number of subjects completed	48

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 7
Reason: Number of subjects	Screening failure - randomized w/o intervention: 8

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: As not all randomized patients received study medication, more patients were enrolled than specified in worldwide number of enrolled in the trial. Randomized patients not receiving study medication were replaced. In total, 56 patients were enrolled. Of these 56 patients, 48 patients received study medication and were considered for analysis.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Zoledronic acid

Arm description:

Patients in this arm received zoledronic acid

Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

5 mg zoledronic acid (0.05 mg/ml solution; 100 ml)

Arm title	Placebo

Arm description:

Patients in this arm received placebo.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

0.9 % NaCl solution (100 ml)

Number of subjects in period 1	Zoledronic acid	Placebo
Started	34	14
Completed	34	14

Period 2	
Period 2 title	Treatment | Core Study (until week 6)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Zoledronic acid

Arm description:

Patients in this arm received zoledronic acid.

Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

5 mg zoledronic acid (0.05 mg/ml solution; 100 ml)

Arm title	Placebo

Arm description:

Patients in this arm received placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:
0.9 % NaCl solution (100 ml)

Number of subjects in period 2	Zoledronic acid	Placebo
Started	34	14
Completed	34	14

Period 3	
Period 3 title	Follow-up (until week 12)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Zoledronic acid
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion
Dosage and administration details: 5 mg zoledronic acid (0.05 mg/ml solution; 100 ml)	
Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion
Dosage and administration details: 0.9 % NaCl solution (100 ml)	

Number of subjects in period 3	Zoledronic acid	Placebo
Started	34	14
Completed	32	13
Not completed	2	1
Surgical intervention - Not study related	1	-
Subsequent follow-up treatment required	-	1
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Zoledronic acid
Reporting group description:	
Patients in this arm received zoledronic acid	
Reporting group title	Placebo
Reporting group description:	
Patients in this arm received placebo.	

Reporting group values	Zoledronic acid	Placebo	Total
Number of subjects	34	14	48
Age categorical Units: Subjects			
Adults (18-64 years)	29	13	42
From 65-84 years	5	1	6
Age continuous Units: years			
arithmetic mean	50.1	53.6	
standard deviation	± 12.9	± 6.8	-
Gender categorical Units: Subjects			
Female	12	4	16
Male	22	10	32
Severity of disease Units: Subjects			
mild	4	2	6
moderate	22	10	32
severe	8	2	10
Pain (VAS)			
Assessment of pain as measured by a visual analog scale (VAS)			
Units: arbitrary units			
arithmetic mean	36.9	34.1	
standard deviation	± 27.4	± 21.1	-
Qualeffo-41			
Assessment of quality of life by Qualeffo-41 questionnaire - Quality of life questionnaire of the European Foundation for Osteoporosis			
Units: arbitrary units			
arithmetic mean	2.1	2.2	
standard deviation	± 0.5	± 0.6	-
Subjective estimation of medical condition (PDI)			
Subjective estimation of medical condition (Pain Disability Index)			
Units: arbitrary units			
arithmetic mean	20.8	21.3	
standard deviation	± 6.8	± 6.4	-

Subject analysis sets	
Subject analysis set title	Modified ITT | Zoledronic acid
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified ITT for analysis of primary endpoint (omititng outlier value of one patient with in placebo group [>500% increase in edema volumen]).

Subject analysis set title	Modified ITT | Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified ITT for analysis of primary endpoint (omititng outlier value of one patient with in placebo group [>500% increase in edema volumen]).

Reporting group values	Modified ITT | Zoledronic acid	Modified ITT | Placebo	
Number of subjects	34	13	
Age categorical Units: Subjects			
Adults (18-64 years)	29	12	
From 65-84 years	5	1	
Age continuous Units: years arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female Male			
Severity of disease Units: Subjects			
mild moderate severe			
Pain (VAS)			
Assessment of pain as measured by a visual analog scale (VAS)			
Units: arbitrary units arithmetic mean standard deviation	±	±	
Qualeffo-41			
Assessment of quality of life by Qualeffo-41 questionnaire - Quality of life questionnaire of the European Foundation for Osteoporosis			
Units: arbitrary units arithmetic mean standard deviation	±	±	
Subjective estimation of medical condition (PDI)			
Subjective estimation of medical condition (Pain Disability Index)			
Units: arbitrary units arithmetic mean standard deviation	±	±	

End points

End points reporting groups

Reporting group title	Zoledronic acid
Reporting group description: Patients in this arm received zoledronic acid	
Reporting group title	Placebo
Reporting group description: Patients in this arm received placebo.	
Reporting group title	Zoledronic acid
Reporting group description: Patients in this arm received zoledronic acid.	
Reporting group title	Placebo
Reporting group description: Patients in this arm received placebo.	
Reporting group title	Zoledronic acid
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Modified ITT | Zoledronic acid
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified ITT for analysis of primary endpoint (omititng outlier value of one patient with in placebo group [>500% increase in edema volumen]).	
Subject analysis set title	Modified ITT | Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified ITT for analysis of primary endpoint (omititng outlier value of one patient with in placebo group [>500% increase in edema volumen]).	

Primary: Primary endpoint | Bone marrow edeme volume

End point title	Primary endpoint | Bone marrow edeme volume
End point description: The volume of the edema in cm^3 is defined as biometric data measured by the use of MRI before and six weeks after treatment. Edema volume at screening was set to 100% . Edema volume six weeks after study drug administration was provided as percentage reduction compared to the value at screening.	
End point type	Primary
End point timeframe: Bone marrow edema volume six weeks after administration of a single intravenous dose of zoledronic acid (5mg).	

End point values	Zoledronic acid	Placebo	Modified ITT | Zoledronic acid	Modified ITT | Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	34	14	34	13
Units: Percent change in volume				
arithmetic mean (standard deviation)	64.53 (± 41.92)	-14.43 (± 150.46)	64.53 (± 41.92)	23.97 (± 46.52)

Statistical analyses

Statistical analysis title	Primary endpoint | T-test
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.074 [2]
Method	t-test, 2-sided
Variability estimate	Standard deviation

Notes:

[1] - T-test \| Satterthwaite method

[2] - Results biased by outlier value of one patient in placebo group.

Statistical analysis title	Primary endpoint | Change in edema volumen (mITT)
Comparison groups	Modified ITT | Zoledronic acid v Modified ITT | Placebo
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	other[3]
P-value	= 0.006
Method	t-test, 2-sided

Notes:

[3] - T-test (with mITT, omitting outlier value of one patient in placebo group)

Statistical analysis title	Primary endpoint | Mann-Whitney-Test
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	48
Analysis specification	Post-hoc
Analysis type	other[4]
P-value	= 0.007
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - Mann-Whitney-Test

Statistical analysis title	Primary endpoint | Mann-Whitney-Test (mITT)
Comparison groups	Modified ITT | Zoledronic acid v Modified ITT | Placebo
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	other[5]
P-value	= 0.015
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Mann-Whitney-Test

Secondary: Secondary endpoint | Reduction of pain (VAS) - Week 3	
End point title	Secondary endpoint | Reduction of pain (VAS) - Week 3
End point description: Reduction of pain as measured by a visual analog scale (VAS).	
End point type	Secondary
End point timeframe: Assessment at week 3.	

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: arbitrary units				
arithmetic mean (standard deviation)	25.5 (± 22.7)	25.6 (± 24.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint | Reduction of pain (VAS) - Week 6	
End point title	Secondary endpoint | Reduction of pain (VAS) - Week 6
End point description: Reduction of pain as measured by a visual analog scale (VAS).	
End point type	Secondary
End point timeframe: Assessment at week 6.	

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: arbitrary units				
arithmetic mean (standard deviation)	25.0 (± 28.7)	38.5 (± 30.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint | Qualeffo-41 - Week 3	
End point title	Secondary endpoint | Qualeffo-41 - Week 3
End point description: Quality of life as measured by the Qualeffo-41 questionnaire - Quality of life questionnaire of the	

European Foundation for Osteoporosis

End point type	Secondary

End point timeframe:

Assessment at week 3.

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: arbitrary units				
arithmetic mean (standard deviation)	2.1 (± 0.4)	2.1 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint | Qualeffo-41 - Week 6

End point title	Secondary endpoint | Qualeffo-41 - Week 6

End point description:

Quality of life as measured by the Qualeffo-41 questionnaire - Quality of life questionnaire of the European Foundation for Osteoporosis

End point type	Secondary

End point timeframe:

Assessment at week 6.

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: arbitrary units				
arithmetic mean (standard deviation)	2.0 (± 0.5)	2.1 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint | Subjective estimation of medical condition (PDI) - Week 3

End point title	Secondary endpoint | Subjective estimation of medical condition (PDI) - Week 3

End point description:

Subjective estimation of medical condition as assessed by PDI (Pain Disability Index).

End point type	Secondary

End point timeframe:

Assessment at week 3.

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: arbitrary units				
arithmetic mean (standard deviation)	14.8 (± 5.8)	20.5 (± 7.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint | Subjective estimation of medical condition (PDI) - Week 6

End point title	Secondary endpoint | Subjective estimation of medical condition (PDI) - Week 6

End point description:

Subjective estimation of medical condition as assessed by PDI.

End point type	Secondary

End point timeframe:

Assessment at week 6.

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: arbitrary units				
arithmetic mean (standard deviation)	13.1 (± 6.0)	18.8 (± 7.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint | Number of additional medicinal visits - Week 3

End point title	Secondary endpoint | Number of additional medicinal visits - Week 3

End point description:

Number of additional medicinal visits until week 6.

End point type	Secondary

End point timeframe:

Assessment at week 3.

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: Patients with additional visits	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint | Number of additional medicinal visits - Week 6

End point title	Secondary endpoint | Number of additional medicinal visits - Week 6

End point description:

Number of additional medicinal visits until week 6.

End point type	Secondary

End point timeframe:

Assessment at week 6.

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: Patients with additional visits	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint | Number of days of illness - Week 3

End point title	Secondary endpoint | Number of days of illness - Week 3

End point description:

Number of days of illness assessed until week 6.

End point type	Secondary

End point timeframe:

Assessment at week 3.

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: Days				
arithmetic mean (standard deviation)	1.24 (± 5.02)	3.00 (± 7.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint | Number of days of illness - Week 6

End point title	Secondary endpoint | Number of days of illness - Week 6

End point description:

Number of days of illness assessed until week 6.

End point type	Secondary

End point timeframe:

Assessment at week 6.

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: Days				
arithmetic mean (standard deviation)	0.94 (± 4.10)	3.14 (± 4.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint | Number of aseptic bone necrosis and fatigue fractures

End point title	Secondary endpoint | Number of aseptic bone necrosis and fatigue fractures

End point description:

Assessemnt of number of patients with aseptic bone necrosis and/or fatigue fractures.

End point type	Secondary

End point timeframe:

Baseline until end of study (week 12).

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: Number of patients	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint | Changes of parameters concerning osteological values

End point title	Secondary endpoint | Changes of parameters concerning osteological values

End point description:

Assessment of laboratory values related to osteological values (including serum calcium, serum phosphate, serum alkaline phosphatase, gamma-GT, serum creatinine, C-reactive protein, Thyroid stimulating hormone at week 3 and week 6.

End point type	Secondary

End point timeframe:

Week 3 and week 6.

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	14		
Units: Pts with clinical significant values (%)				
number (not applicable)				
Serum Calcium	0	0		
Serum Phosphate	0	0		
Serum Alkaline Phosphatase	0	0		
Gamma-GT	0	0		
Serum Creatinine	0	1		
C-reactive protein	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded from time of enrollment until study completion (end of study).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Zoledronic acid
Reporting group description:	
Patients in this arm received zoledronic acid	
Reporting group title	Placebo
Reporting group description:	
Patients in this arm received placebo.	

Serious adverse events	Zoledronic acid	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 34 (11.76%)	1 / 14 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Post-traumatic neck syndrome			
subjects affected / exposed	1 / 34 (2.94%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			

subjects affected / exposed	1 / 34 (2.94%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 34 (2.94%)	0 / 14 (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: 3 %

Non-serious adverse events	Zoledronic acid	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 34 (100.00%)	11 / 14 (78.57%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 34 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Chills			
subjects affected / exposed	8 / 34 (23.53%)	2 / 14 (14.29%)	
occurrences (all)	8	2	
Fatigue			
subjects affected / exposed	10 / 34 (29.41%)	3 / 14 (21.43%)	
occurrences (all)	11	3	
Influenza like illness			
subjects affected / exposed	3 / 34 (8.82%)	2 / 14 (14.29%)	
occurrences (all)	3	3	
Malaise			
subjects affected / exposed	3 / 34 (8.82%)	0 / 14 (0.00%)	
occurrences (all)	3	0	

Pyrexia			
subjects affected / exposed	7 / 34 (20.59%)	1 / 14 (7.14%)	
occurrences (all)	7	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 34 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	2 / 34 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 34 (38.24%)	5 / 14 (35.71%)	
occurrences (all)	14	6	
Sciatica			
subjects affected / exposed	1 / 34 (2.94%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 34 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Eye disorders			

Blepharospasm			
subjects affected / exposed	2 / 34 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 34 (11.76%)	0 / 14 (0.00%)	
occurrences (all)	4	0	
Dry mouth			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Gastrointestinal disorder			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	2 / 34 (5.88%)	2 / 14 (14.29%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Skin discolouration			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Renal pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	11 / 34 (32.35%)	3 / 14 (21.43%)	
occurrences (all)	11	4	
Arthralgia			
subjects affected / exposed	3 / 34 (8.82%)	2 / 14 (14.29%)	
occurrences (all)	3	2	
Back pain			

subjects affected / exposed	4 / 34 (11.76%)	0 / 14 (0.00%)	
occurrences (all)	4	0	
Bone pain			
subjects affected / exposed	2 / 34 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal discomfort			
subjects affected / exposed	2 / 34 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Myalgia			
subjects affected / exposed	0 / 34 (0.00%)	3 / 14 (21.43%)	
occurrences (all)	0	3	
Osteoarthritis			
subjects affected / exposed	2 / 34 (5.88%)	1 / 14 (7.14%)	
occurrences (all)	2	2	
Rheumatic disorder			
subjects affected / exposed	2 / 34 (5.88%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Spinal pain			
subjects affected / exposed	2 / 34 (5.88%)	3 / 14 (21.43%)	
occurrences (all)	2	3	
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Gastrointestinal infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 34 (2.94%)	3 / 14 (21.43%)	
occurrences (all)	1	3	
Nasopharyngitis			
subjects affected / exposed	4 / 34 (11.76%)	2 / 14 (14.29%)	
occurrences (all)	4	2	
Tonsillitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

Metabolism and nutrition disorders Hyperuricaemia subjects affected / exposed occurrences (all)	 0 / 34 (0.00%) 0	 1 / 14 (7.14%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The originally intended primary analysis did not include outlier analysis. An outlier value in the placebo group (<500% increase in edema size) biased statistical results. Analysis was modified respecting outlier analysis.

Notes: