Clinical trial results:
A Long-Term Extension Study of Lesinurad in Combination with Allopurinol for Subjects Completing an Efficacy and Safety Study of Lesinurad and Allopurinol.

Summary

EudraCT number	2012-004389-16
Trial protocol	DE ES BE
Global end of trial date	17 November 2016

Results information

Result version number	v1 (current)
This version publication date	29 December 2017
First version publication date	29 December 2017

Trial information

Trial identification

Sponsor protocol code	RDEA594-306

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ardea Biosciences, Inc
Sponsor organisation address	9390 Towne Centre Dr., San Diego, United States,
Public contact	Nihar Bhakta, MD, Ardea Biosciences, Inc., +1 858-652-6671, nbhakta@ardeabio.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	17 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 August 2016
Global end of trial reached?	Yes
Global end of trial date	17 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the long-term efficacy and safety of lesinurad in combination with allopurinol.

Protection of trial subjects:

This study was conducted in accordance with the protocol, International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP), the Declaration of Helsinki (2008), and all other applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2013
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 States: 512
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Ukraine: 58
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	South Africa: 66
Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	New Zealand: 16
Worldwide total number of subjects	716
EEA total number of subjects	39

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	640
From 65 to 84 years	76
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who had been randomized to lesinurad 200 mg or 400 mg plus allopurinol in Study RDEA594-301 or Study RDEA594-302 continued to receive the same dose of lesinurad plus allopurinol in this extension study (LESU 200 mg CONT + ALLO group or LESU 400 mg CONT + ALLO group).

Pre-assignment

Screening details:

718 subjects (59.2%) enrolled in this optional extension Study RDEA594-306. Although 717 subjects were randomized to a lesinurad dose group or were to continue on their same dose of lesinurad, only 716 subjects received at least 1 dose of lesinurad in the extension study.

Period 1

Period 1 title	Overall Study (overall period)
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	lesinurad 200 mg + allopurinol

Arm description: -

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

Dosage and administration details:

200 mg

Arm title	lesinurad 400 mg + allopurinol

Arm description: -

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

Dosage and administration details:

400 mg

Number of subjects in period 1	lesinurad 200 mg + allopurinol	lesinurad 400 mg + allopurinol
Started	362	354
Completed	216	216
Not completed	146	138
Adverse event, serious fatal	7	5
Consent withdrawn by subject	46	52
Prohibited or contraindicated medication	5	2
Adverse event, non-fatal	34	41
Gout flare	-	2
Lost to follow-up	26	18
Sponsor terminated study	6	5
Protocol deviation	22	13

Baseline characteristics

Reporting groups	
Reporting group title	lesinurad 200 mg + allopurinol
Reporting group description: -	
Reporting group title	lesinurad 400 mg + allopurinol
Reporting group description: -	

Reporting group values	lesinurad 200 mg + allopurinol	lesinurad 400 mg + allopurinol	Total
Number of subjects	362	354	716
Age Categorical Units: Subjects			
< 65 years	325	315	640
>=65 years	37	39	76
Age Continuous Units: Years			
arithmetic mean	51.0	51.7	
standard deviation	± 11.04	± 10.55	-
Gender, Male/Female Units: Subjects			
Female	13	12	25
Male	349	342	691
Region of Enrollment			
Includes subjects who were randomized and received at least one dose of study medication in the extension study.			
Units: Subjects			
United States	252	260	512
Canada	9	3	12
Ukraine	33	25	58
Poland	6	13	19
Germany	7	5	12
Spain	2	2	4
Belgium	3	1	4
Switzerland	1	0	1
South Africa	33	33	66
Australia	6	6	12
New Zealand	10	6	16

End points

End points reporting groups

Reporting group title	lesinurad 200 mg + allopurinol
Reporting group description: -	
Reporting group title	lesinurad 400 mg + allopurinol
Reporting group description: -	

Primary: Proportion of subjects with an sUA level that is < 6.0 mg/dL

End point title	Proportion of subjects with an sUA level that is < 6.0 mg/dL[1]
End point description:	
Proportion of Subjects in Study 306 With sUA < 6.0 mg/dL from the Core Studies 301 and 302 and Extension Study 306, assessed after each subject had completed 12 months in the extension study - Observed Cases	
End point type	Primary
End point timeframe:	
Up to approximately 2.5 years (at Extension Month 12)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis available as EndPoint groups are a total of Placebo + Allopurinol and Lesinurad + Allopurinol.

End point values	lesinurad 200 mg + allopurinol	lesinurad 400 mg + allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276	213		
Units: Proportion of Subjects				
number (not applicable)	63.8	75.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of at least 1 target tophus

End point title	Resolution of at least 1 target tophus
End point description:	
The proportion of subjects with ≥ 1 target tophus at Baseline in Study RDEA594-301 or RDEA594-302 who experience complete resolution of at least 1 target tophus at any time up to Month 12 of the extension - Observed Cases	
End point type	Secondary
End point timeframe:	
Up to approximatley 2.5 years (at Extension Month 12)	

End point values	lesinurad 200 mg + allopurinol	lesinurad 400 mg + allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	37		
Units: Proportion of Subjects				
number (not applicable)	45.0	48.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The maximum time on lesinurad plus allopurinol was 1198 days in this extension study. The median and range of duration of exposure to lesinurad in this extension study, including dosing interruptions, was comparable across the groups.

Adverse event reporting additional description:

Safety is assessed on the population of randomized subjects who received at least 1 dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	lesinurad 400 mg + allopurinol

Reporting group description:

Subjects who had been randomized to lesinurad 200 mg or 400 mg plus allopurinol in Study RDEA594-301 or Study RDEA594-302 continued to receive the same dose of lesinurad plus allopurinol in this extension study.

Reporting group title	lesinurad 200 mg + allopurinol

Reporting group description:

Subjects who had been randomized to lesinurad 200 mg or 400 mg plus allopurinol in Study RDEA594-301 or Study RDEA594-302 continued to receive the same dose of lesinurad plus allopurinol in this extension study.

Serious adverse events	lesinurad 400 mg + allopurinol	lesinurad 200 mg + allopurinol	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 354 (12.71%)	48 / 362 (13.26%)	
number of deaths (all causes)	5	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 354 (0.28%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	2 / 354 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 354 (0.56%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 354 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral arterial stenosis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery stenosis			

subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardiac ablation			
subjects affected / exposed	1 / 354 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device battery replacement			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (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			
Chest pain			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sudden death			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
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			
Prostatitis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 354 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 354 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Delusional disorder, unspecified type			

subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			

subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
XIIth nerve injury			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 354 (0.56%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 354 (0.56%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	3 / 354 (0.85%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	1 / 354 (0.28%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 354 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hemiparesis			

subjects affected / exposed	0 / 354 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 354 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery occlusion			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Complicated migraine			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegic migraine			

subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Migraine			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (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			
Coagulopathy			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	2 / 354 (0.56%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia, obstructive			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 354 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	3 / 354 (0.85%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 354 (0.28%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (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			
Renal failure acute			
subjects affected / exposed	8 / 354 (2.26%)	3 / 362 (0.83%)	
occurrences causally related to treatment / all	5 / 8	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nephrolithiasis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (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	2 / 354 (0.56%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee deformity			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 354 (0.00%)	5 / 362 (1.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 354 (0.56%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 354 (0.00%)	2 / 362 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Labyrinthitis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis chronic			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian infection			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			

subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 354 (0.00%)	1 / 362 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 354 (0.28%)	0 / 362 (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: 5 %

Non-serious adverse events	lesinurad 400 mg + allopurinol	lesinurad 200 mg + allopurinol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	184 / 354 (51.98%)	185 / 362 (51.10%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	56 / 354 (15.82%)	44 / 362 (12.15%)	
occurrences (all)	77	57	
Vascular disorders			
Hypertension			
subjects affected / exposed	36 / 354 (10.17%)	27 / 362 (7.46%)	
occurrences (all)	49	29	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 354 (3.11%)	21 / 362 (5.80%)	
occurrences (all)	12	21	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	33 / 354 (9.32%)	31 / 362 (8.56%)	
occurrences (all)	40	36	
Back pain			
subjects affected / exposed	25 / 354 (7.06%)	30 / 362 (8.29%)	
occurrences (all)	29	40	
Pain in extremity			
subjects affected / exposed	20 / 354 (5.65%)	19 / 362 (5.25%)	
occurrences (all)	25	23	
Musculoskeletal pain			
subjects affected / exposed	16 / 354 (4.52%)	9 / 362 (2.49%)	
occurrences (all)	18	12	
Osteoarthritis			
subjects affected / exposed	11 / 354 (3.11%)	13 / 362 (3.59%)	
occurrences (all)	13	16	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	45 / 354 (12.71%)	44 / 362 (12.15%)	
occurrences (all)	65	58	
Nasopharyngitis			

subjects affected / exposed	33 / 354 (9.32%)	38 / 362 (10.50%)	
occurrences (all)	46	50	
Bronchitis			
subjects affected / exposed	23 / 354 (6.50%)	16 / 362 (4.42%)	
occurrences (all)	24	18	
Sinusitis			
subjects affected / exposed	16 / 354 (4.52%)	23 / 362 (6.35%)	
occurrences (all)	23	30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2013	The primary purpose of this amendment was to expand guidance on subject hydration and to expand the management algorithm if a subject experiences an elevated serum creatinine or kidney stone.
02 January 2014	The primary purpose of this amendment was to modify the combination therapy extension study, RDEA594-306, in all countries where the study is ongoing to ensure patient safety. The changes were intended to better reflect the association of acute renal failure with lesinurad, especially in the monotherapy setting, and to emphasize the requirement for subjects to concomitantly take lesinurad with a xanthine oxidase inhibitor (allopurinol).
07 October 2015	The primary purpose of this amendment was to require all active subjects who are receiving lesinurad 400 mg in combination with allopurinol to have the dose of lesinurad decreased to 200 mg. Lesinurad 200 mg in combination with an XO inhibitor continues to have a favorable benefit-risk profile.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported