



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 |
| Scientific contact | Nihar Bhakta, MD, Ardea Biosciences, Inc, +1 858-652-6671, nbhakta@ardeabio.com |

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: - |
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| | |
|-----------------------|--------------------------------|
| 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 approximately 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

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|-----------------|--------|
| 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