



Clinical trial results:

A Phase 4, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Lesinurad 200 mg in Combination With a Xanthine Oxidase Inhibitor (XOI), Compared With an XOI Alone, in Subjects With Gout and Estimated Creatinine Clearance 30 to <60 mL/min Who Have Not Achieved Target Serum Uric Acid Levels on an XOI Alone

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2017-001191-30 |
| Trial protocol | CZ HU PL |
| Global end of trial date | 25 February 2019 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 22 October 2021 |
| First version publication date | 22 October 2021 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | RDEA594-401 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03226899 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Ironwood Pharmaceuticals, Inc. |
| Sponsor organisation address | 100 Summer Street Suite 2300 , Boston MA , United States, 02110 |
| Public contact | Ironwood Study Chair, Ironwood Pharmaceuticals, Inc., 001 617-621-7722, Info@ironwoodpharma.com |
| Scientific contact | Ironwood Study Chair, Ironwood Pharmaceuticals, Inc., 001 617-621-7722, Info@ironwoodpharma.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 | 25 February 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 February 2019 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety over 24 months of lesinurad 200 mg once daily (qd) when used in combination with a xanthine oxidase inhibitor (XOI), compared with XOI alone, in subjects with gout and moderate renal impairment (estimated creatinine clearance 30 to <60 mL/min) who have not reached target serum uric acid (sUA) levels on an XOI alone.

Protection of trial subjects:

Prior to participation in any study-specific procedures, each subject must sign and date an EC-approved written ICF in a language the subject can understand. The language in the written information about the study should be as non-technical as practical, and should be understandable to the subject. Before informed consent is obtained, the Investigator should provide the subject ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the subject. The written ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion, with any additional signatures obtained as required by applicable local regulations and EC requirements. Each subject will be informed that participation is voluntary and that he/she can withdraw from the study at any time.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 19 July 2017 |
| 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: 147 |
| Country: Number of subjects enrolled | Poland: 45 |
| Country: Number of subjects enrolled | Czechia: 21 |
| Country: Number of subjects enrolled | Hungary: 29 |
| Worldwide total number of subjects | 242 |
| EEA total number of subjects | 95 |

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) | 83 |
| From 65 to 84 years | 159 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study included an approximate 1-month Screening Period.

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, Carer |

Blinding implementation details:

Treatment group assignments were blinded to minimize bias in study assessments and monitoring.

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo + XOI |

Arm description:

Placebo oral tablet once daily (QD) plus a stable, medically appropriate dose of an xanthine oxidase inhibitor (XOI)

| | |
|--|------------------|
| Arm type | Placebo |
| Investigational medicinal product name | matching placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

All doses of investigational product (IP) were taken daily, in the morning with food and 1 cup (8 oz; 240 mL) of water. Subjects were instructed to drink 2 liters (68 oz) of liquid a day.

| | |
|--|-------------------------|
| Investigational medicinal product name | XOI |
| Investigational medicinal product code | |
| Other name | allopurinol, febuxostat |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

All doses of investigational product (IP) were taken daily, in the morning with food and 1 cup (8 oz; 240 mL) of water. Subjects were instructed to drink 2 liters (68 oz) of liquid a day.

| | |
|--|------------|
| Investigational medicinal product name | colchicine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gout flare prophylaxis: commercially available colchicine was provided through the Month 6 study visit. Actual colchicine dose (0.5 or 0.6 mg qd) and frequency were adjusted based on the local label, subject medical history, and clinical judgement.

| | |
|--|-----------------|
| Investigational medicinal product name | corticosteroids |
| Investigational medicinal product code | |
| Other name | |

| | |
|--------------------------|----------|
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gout flare prophylaxis: Subjects unable to take colchicine are permitted to take a short course of low-dose oral corticosteroids up to the Month 3 study visit

| | |
|------------------|-----------------|
| Arm title | Lesinurad + XOI |
|------------------|-----------------|

Arm description:

Lesinurad 200 mg oral tablet QD plus a stable, medically appropriate dose of an XOI

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lesinurad |
| Investigational medicinal product code | |
| Other name | RDEA594 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

All doses of IP were taken daily, in the morning with food and 1 cup (8 oz; 240 mL) of water. Subjects were instructed to drink 2 liters (68 oz) of liquid a day.

| | |
|--|-------------------------|
| Investigational medicinal product name | XOI |
| Investigational medicinal product code | |
| Other name | allopurinol, febuxostat |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

All doses of investigational product (IP) were taken daily, in the morning with food and 1 cup (8 oz; 240 mL) of water. Subjects were instructed to drink 2 liters (68 oz) of liquid a day.

| | |
|--|------------|
| Investigational medicinal product name | colchicine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gout flare prophylaxis: commercially available colchicine was provided through the Month 6 study visit. Actual colchicine dose (0.5 or 0.6 mg qd) and frequency were adjusted based on the local label, subject medical history, and clinical judgement.

| | |
|--|-----------------|
| Investigational medicinal product name | corticosteroids |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Gout flare prophylaxis: Subjects unable to take colchicine are permitted to take a short course of low-dose oral corticosteroids up to the Month 3 study visit

| Number of subjects in period 1 | Placebo + XOI | Lesinurad + XOI |
|--|---------------|-----------------|
| Started | 118 | 124 |
| Completed | 0 | 0 |
| Not completed | 118 | 124 |
| Did not complete study /24 months of treatment | 118 | 124 |

Baseline characteristics

Reporting groups

| | |
|--|-----------------|
| Reporting group title | Placebo + XOI |
| Reporting group description: Placebo oral tablet once daily (QD) plus a stable, medically appropriate dose of an xanthine oxidase inhibitor (XOI) | |
| Reporting group title | Lesinurad + XOI |
| Reporting group description: Lesinurad 200 mg oral tablet QD plus a stable, medically appropriate dose of an XOI | |

| Reporting group values | Placebo + XOI | Lesinurad + XOI | Total |
|------------------------------------|---------------|-----------------|-------|
| Number of subjects | 118 | 124 | 242 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|----------------|-----------------|-----|
| Age continuous Units: years arithmetic mean standard deviation | 67.3 ± 8.00 | 66.4 ± 10.10 | - |
| Gender categorical Units: Subjects | | | |
| Female | 22 | 28 | 50 |
| Male | 96 | 96 | 192 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 26 | 20 | 46 |
| Not Hispanic or Latino | 92 | 104 | 196 |
| Race Units: Subjects | | | |
| Asian | 1 | 2 | 3 |
| Native Hawaiian or Other Pacific Islander | 2 | 1 | 3 |
| Black or African American | 14 | 24 | 38 |
| White | 99 | 95 | 194 |
| Unknown or Not Reported | 2 | 2 | 4 |

End points

End points reporting groups

| | |
|--|-----------------|
| Reporting group title | Placebo + XOI |
| Reporting group description: Placebo oral tablet once daily (QD) plus a stable, medically appropriate dose of an xanthine oxidase inhibitor (XOI) | |
| Reporting group title | Lesinurad + XOI |
| Reporting group description: Lesinurad 200 mg oral tablet QD plus a stable, medically appropriate dose of an XOI | |

Primary: Percentage of Participants Who Achieve Serum Urate (sUA) < 6.0 mg/dL at Month 6

| | |
|---|--|
| End point title | Percentage of Participants Who Achieve Serum Urate (sUA) < 6.0 mg/dL at Month 6 ^[1] |
| End point description: Modified Intent-to-Treat (mITT) Population: all randomized participants who received at least 1 dose of study drug. N=Participants with a value at Month 6. | |
| End point type | Primary |
| End point timeframe: Month 6 | |

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: Descriptive statistics are presented per protocol. Statistical analyses not performed as the study was prematurely terminated.

| End point values | Placebo + XOI | Lesinurad + XOI | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 80 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 33.8 | 58.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieve sUA < 6.0 mg/dL Over Time

| | |
|---|--|
| End point title | Percentage of Participants Who Achieve sUA < 6.0 mg/dL Over Time |
| End point description: Modified Intent-to-Treat (mITT) Population: all randomized participants who received at least 1 dose of study drug. n=participants with a value at baseline and given time point. | |
| End point type | Secondary |
| End point timeframe: Baseline, Months 1, 3, 6, 9, 12, 15, 18 | |

| End point values | Placebo + XO1 | Lesinurad + XO1 | | |
|-----------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 123 ^[2] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Baseline; n=116, 123 | 10.3 | 10.6 | | |
| Month 1; n=111, 119 | 35.1 | 58.8 | | |
| Month 3; n=99, 101 | 36.4 | 52.5 | | |
| Month 6; n=80, 80 | 33.8 | 58.8 | | |
| Month 9; n=50, 42 | 34.0 | 42.9 | | |
| Month 12; n=28, 23 | 42.9 | 56.5 | | |
| Month 15; n=11, 8 | 45.5 | 62.5 | | |
| Month 18; n=1, 0 | 0.0 | 99999 | | |

Notes:

[2] - 99999=not applicable; no participants in this arm at this time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in sUA Over Time, Including the Last Value On and Off Treatment

| | |
|--|--|
| End point title | Change From Baseline in sUA Over Time, Including the Last Value On and Off Treatment |
| End point description: | |
| Safety Population: all randomized participants who received at least 1 dose of lesinurad or placebo. n=participants with a value at baseline and given time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Months 1, 3, 6, 9, 12, 15, 18 | |

| End point values | Placebo + XO1 | Lesinurad + XO1 | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 ^[3] | 123 ^[4] | | |
| Units: µmol/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Month 1; n=111, 119 | -57.0 (± 96.2) | -120.3 (± 105.3) | | |
| Change at Month 3; n=99, 101 | -59.8 (± 98.6) | -106.8 (± 116.2) | | |
| Change at Month 6; n=80, 80 | -54.6 (± 103.1) | -125.8 (± 140.0) | | |
| Change at Month 9; n=50, 42 | -70.6 (± 128.4) | -95.9 (± 106.5) | | |
| Change at Month 12; n=28, 23 | -78.7 (± 122.4) | -69.6 (± 110.4) | | |

| | | | | |
|-------------------------------|-----------------|------------------|--|--|
| Change at Month 15; n=11, 8 | -92.6 (± 91.4) | -116.6 (± 76.3) | | |
| Change at Month 18; n=1, 0 | 0.00 (± 999999) | 99999 (± 99999) | | |
| Last On-Treatment; n=111, 119 | -57.0 (± 104.7) | -125.5 (± 121.4) | | |
| Last Off-Treatment; n=6, 11 | -70.7 (± 105.4) | -156.6 (± 149.2) | | |

Notes:

[3] - 99999=not applicable; 1 participant in this arm at this time point.

[4] - 999999=not applicable; 0 participants in this arm at this time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in sUA Over Time, Including the Last Value On and Off Treatment

| | |
|---|--|
| End point title | Percent Change From Baseline in sUA Over Time, Including the Last Value On and Off Treatment |
| End point description: | |
| Safety Population: all randomized participants who received at least 1 dose of lesinurad or placebo. n=participants with a value at baseline and given time point. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Months 1, 3, 6, 9, 12, 15, 18 | |

| End point values | Placebo + XO1 | Lesinurad + XO1 | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 ^[5] | 123 ^[6] | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Month 1; n=111, 119 | -11.3 (± 18.8) | -24.0 (± 19.3) | | |
| Change at Month 3; n=99, 101 | -11.1 (± 18.8) | -21.2 (± 21.7) | | |
| Change at Month 6; n=80, 80 | -10.0 (± 21.7) | -23.9 (± 24.4) | | |
| Change at Month 9; n=50, 42 | -12.6 (± 27.3) | -18.6 (± 20.2) | | |
| Change at Month 12; n=28, 23 | -15.2 (± 22.8) | -14.7 (± 26.7) | | |
| Change at Month 15; n=11, 8 | -18.9 (± 17.5) | -26.1 (± 16.3) | | |
| Change at Month 18; n=1, 0 | 0.00 (± 99999) | 99999 (± 99999) | | |
| Last On-Treatment; n=111, 119 | -10.6 (± 22.1) | -24.8 (± 22.8) | | |
| Last Off-Treatment; n=6, 11 | -16.1 (± 25.8) | -27.3 (± 22.6) | | |

Notes:

[5] - 99999=not applicable; 1 participant in this arm at this time point.

[6] - 999999=not applicable; 0 participants in this arm at this time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Estimated Creatinine Clearance (eCrCl) at

Month 24

| | |
|--|--|
| End point title | Change From Baseline in Estimated Creatinine Clearance (eCrCl) at Month 24 |
| End point description: The eCrCl was calculated by the Cockcroft-Gault formula using ideal body weight. | |
| End point type | Secondary |
| End point timeframe: Baseline, 24 months | |

| End point values | Placebo + XO1 | Lesinurad + XO1 | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[7] | 0 ^[8] | | |
| Units: mL/min | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[7] - Due to early study termination, no participant reached Month 24; these data are not available.

[8] - Due to early study termination, no participant reached Month 24; these data are not available.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in eCrCl at Month 24

| | |
|--|---|
| End point title | Percent Change From Baseline in eCrCl at Month 24 |
| End point description: The eCrCl was calculated by the Cockcroft-Gault formula using ideal body weight. | |
| End point type | Secondary |
| End point timeframe: Baseline, 24 months | |

| End point values | Placebo + XO1 | Lesinurad + XO1 | | |
|--------------------------------------|------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[9] | 0 ^[10] | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[9] - Due to early study termination, no participant reached Month 24; these data are not available.

[10] - Due to early study termination, no participant reached Month 24; these data are not available.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in eCrCl Over the Study Period, Including the Last Value On and Off Treatment

| | |
|---|--|
| End point title | Change From Baseline in eCrCl Over the Study Period, Including the Last Value On and Off Treatment |
| End point description: The eCrCl was calculated by the Cockcroft-Gault formula using ideal body weight. | |
| Safety Population: all randomized participants who received at least 1 dose of lesinurad or placebo. n=Participants with a value at baseline and given time point. | |
| End point type | Secondary |
| End point timeframe: Baseline, Months 1, 3, 6, 9, 12, 15, 18 | |

| End point values | Placebo + XOI | Lesinurad + XOI | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 ^[11] | 123 ^[12] | | |
| Units: mL/min | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Month 1; n=111, 119 | 0.13 (± 9.67) | -1.29 (± 6.45) | | |
| Change at Month 3; n=99, 101 | -0.69 (± 7.41) | -1.53 (± 8.65) | | |
| Change at Month 6; n=80, 80 | -1.84 (± 7.58) | -1.80 (± 7.02) | | |
| Change at Month 9; n=50, 42 | -0.78 (± 6.85) | -2.10 (± 7.97) | | |
| Change at Month 12; n=28, 23 | -2.14 (± 7.03) | -4.30 (± 6.34) | | |
| Change at Month 15; n=11, 8 | 0.36 (± 6.07) | -6.00 (± 8.49) | | |
| Change at Month 18; n=1, 0 | -19.0 (± 99999) | 999999 (± 999999) | | |
| Last On-Treatment; n=111, 119 | -1.03 (± 6.97) | -1.91 (± 8.19) | | |
| Last Off-Treatment; n=6, 11 | 2.33 (± 5.61) | -2.45 (± 5.41) | | |

Notes:

[11] - 99999=not applicable; 1 participant in the arm at this time point.

[12] - 999999=not applicable; 0 participants in the arm at this time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in eCrCl Over the Study Period, Including the Last Value On and Off Treatment

| | |
|---|--|
| End point title | Percent Change From Baseline in eCrCl Over the Study Period, Including the Last Value On and Off Treatment |
| End point description: The eCrCl was calculated by the Cockcroft-Gault formula using ideal body weight. | |
| Safety Population: all randomized participants who received at least 1 dose of lesinurad or placebo. n=Participants with a value at baseline and given time point. | |
| End point type | Secondary |
| End point timeframe: Baseline, Months 1, 3, 6, 9, 12, 15, 18 | |

| End point values | Placebo + XO1 | Lesinurad + XO1 | | |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 ^[13] | 123 ^[14] | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Month 1; n=111, 119 | 1.16 (± 19.90) | -2.07 (± 15.30) | | |
| Change at Month 3; n=99, 101 | -0.18 (± 17.70) | -2.14 (± 20.12) | | |
| Change at Month 6; n=80, 80 | -2.49 (± 17.96) | -3.01 (± 15.32) | | |
| Change at Month 9; n=50, 42 | -0.26 (± 18.67) | -3.42 (± 17.05) | | |
| Change at Month 12; n=28, 23 | -3.38 (± 15.71) | -8.1 (± 12.9) | | |
| Change at Month 15; n=11, 8 | 3.67 (± 18.6) | -11.0 (± 16.5) | | |
| Change at Month 18; n=1, 0 | -31.7 (± 99999) | 999999 (± 999999) | | |
| Last On-Treatment; n=111, 119 | -1.13 (± 16.86) | -3.04 (± 18.21) | | |
| Last Off-Treatment; n=6, 11 | 4.14 (± 13.67) | -5.35 (± 13.52) | | |

Notes:

[13] - 99999=not applicable; 1 participant in the arm at this time point.

[14] - 999999=not applicable; 0 participants in the arm at this time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Serum Creatinine (sCr) Elevations ($\geq 1.5 \times$ Baseline) Over the Study Period

| | |
|-----------------|---|
| End point title | Percentage of Participants With Serum Creatinine (sCr) Elevations ($\geq 1.5 \times$ Baseline) Over the Study Period |
|-----------------|---|

End point description:

Safety Population: all randomized participants who received at least 1 dose of lesinurad or placebo.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

up to 18 months

| End point values | Placebo + XO1 | Lesinurad + XO1 | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 123 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 5.2 | 7.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Meeting Criteria (eg, Based on sCr or eCrCl Criteria) for Treatment Discontinuations Over the Study Period

| | |
|-----------------|---|
| End point title | Percentage of Participants Meeting Criteria (eg, Based on sCr or eCrCl Criteria) for Treatment Discontinuations Over the Study Period |
|-----------------|---|

End point description:

Kidney function was monitored throughout the study by measuring sCr and calculating eCrCl by Cockcroft-Gault formula using ideal body weight. Treatment discontinuations were required if a participant experienced an absolute sCr ≥ 4.0 mg/dL or an eCrCl < 20 mL/min (based on central laboratory results).

Safety Population: all randomized participants who received at least 1 dose of lesinurad or placebo.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

up to 18 months

| End point values | Placebo + XO1 | Lesinurad + XO1 | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 123 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 0.0 | 0.0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Renal-Related and Kidney Stone Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Percentage of Participants Renal-Related and Kidney Stone Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) |
|-----------------|---|

End point description:

Renal-related and kidney stone events were based on Medical Dictionary for Regulatory Activities (MedDRA) "Renal and Urinary Disorders" system organ classification. AEs that started on or after the first dose of study drug in this study, or those AEs with onset prior to the first dose of study drug but worsened after the first dose of study drug, were considered treatment emergent.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first dose of study drug through each participant's study duration, up to approximately 18 months.

| End point values | Placebo + XO1 | Lesinurad + XO1 | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 118 | 124 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Treatment-Emergent SAEs | 0.0 | 0.8 | | |
| Treatment-Emergent AEs | 4.2 | 5.6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Contributing Factors to Renal SAEs as Adjudicated by the Renal Event Adjudication Committee (REAC)

| | |
|-----------------|--|
| End point title | Percentage of Participants With Contributing Factors to Renal SAEs as Adjudicated by the Renal Event Adjudication Committee (REAC) |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first dose of study drug through each participant's study duration, up to approximately 18 months.

| End point values | Placebo + XO1 | Lesinurad + XO1 | | |
|-----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[15] | 0 ^[16] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[15] - This was not analyzed; no events were adjudicated since the study was terminated early.

[16] - This was not analyzed; no events were adjudicated since the study was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Cardiac Event Adjudication Committee (CEAC)-Adjudicated Major Adverse Cardiovascular Events (MACEs)

| | |
|-----------------|---|
| End point title | Percentage of Participants With Cardiac Event Adjudication Committee (CEAC)-Adjudicated Major Adverse Cardiovascular Events (MACEs) |
|-----------------|---|

End point description:

MACEs are defined as Cardiovascular Death, Nonfatal Myocardial Infarction, and Nonfatal Stroke.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first dose of study drug through each participant's study duration, up to approximately 18 months.

| End point values | Placebo + XO1 | Lesinurad + XO1 | | |
|-----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[17] | 0 ^[18] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[17] - This was not analyzed; no events were adjudicated since the study was terminated early.

[18] - This was not analyzed; no events were adjudicated since the study was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of CEAC-Adjudicated MACEs or Hospitalization for Unstable Angina (MACE+)

| | |
|-----------------|--|
| End point title | Incidence of CEAC-Adjudicated MACEs or Hospitalization for Unstable Angina (MACE+) |
|-----------------|--|

End point description:

MACEs are defined as Cardiovascular Death, Nonfatal Myocardial Infarction, and Nonfatal Stroke.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first dose of study drug through each participant's study duration, up to approximately 18 months.

| End point values | Placebo + XO1 | Lesinurad + XO1 | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[19] | 0 ^[20] | | |
| Units: events/year | | | | |
| number (not applicable) | | | | |

Notes:

[19] - This was not analyzed; no events were adjudicated since the study was terminated early.

[20] - This was not analyzed; no events were adjudicated since the study was terminated early.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through each participant's study duration, up to approximately 18 months.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Placebo + XOI |
|-----------------------|---------------|

Reporting group description:

Placebo oral tablet once daily (QD) plus a stable, medically appropriate dose of an xanthine oxidase inhibitor (XOI)

| | |
|-----------------------|-----------------|
| Reporting group title | Lesinurad + XOI |
|-----------------------|-----------------|

Reporting group description:

Lesinurad 200 mg oral tablet QD plus a stable, medically appropriate dose of an XOI

| Serious adverse events | Placebo + XOI | Lesinurad + XOI | |
|---|-----------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 7 / 118 (5.93%) | 13 / 124 (10.48%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer recurrent | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |

| | | | |
|--|-----------------|-----------------|--|
| Arteriosclerosis coronary artery subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation subjects affected / exposed | 1 / 118 (0.85%) | 0 / 124 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery occlusion subjects affected / exposed | 1 / 118 (0.85%) | 0 / 124 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocarditis subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tricuspid valve incompetence subjects affected / exposed | 1 / 118 (0.85%) | 0 / 124 (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 Syncope subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|-----------------|-----------------|--|
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| 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 / 118 (0.00%) | 2 / 124 (1.61%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular stent occlusion | | | |
| subjects affected / exposed | 1 / 118 (0.85%) | 0 / 124 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diverticulum | | | |
| subjects affected / exposed | 1 / 118 (0.85%) | 0 / 124 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 118 (0.85%) | 0 / 124 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 118 (0.85%) | 0 / 124 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 118 (0.85%) | 0 / 124 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Emphysema | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| 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 | 1 / 118 (0.85%) | 0 / 124 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 1 / 124 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Placebo + XO1 | Lesinurad + XO1 | |
|---|-----------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 118 (7.63%) | 18 / 124 (14.52%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 4 / 118 (3.39%) | 3 / 124 (2.42%) | |
| occurrences (all) | 4 | 3 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 118 (0.85%) | 3 / 124 (2.42%) | |
| occurrences (all) | 1 | 3 | |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 4 / 124 (3.23%) | |
| occurrences (all) | 0 | 5 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 118 (3.39%) | 5 / 124 (4.03%) | |
| occurrences (all) | 5 | 5 | |
| Metabolism and nutrition disorders | | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 118 (0.00%) | 3 / 124 (2.42%) | |
| occurrences (all) | 0 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 16 March 2017 | The primary purpose of this amendment was to address regulatory feedback and to add a Month 1 study visit. Per the original protocol, the first on-treatment visit was scheduled for Month 3. In addition, minor revisions to improve clarity or provide additional detail were made to language describing study entry criteria; pregnancy and fertility testing; sourcing, dispensing, and dosing of study medications; premature discontinuation from the study; analysis populations; definition of adverse events (AEs); AEs of special interest; gout flare assessments; and current cumulative lesinurad exposure data. |
| 21 June 2017 | The primary purpose of this amendment was to address a request from the United States Food and Drug Administration (FDA) to omit "Investigator decision" and "Sponsor's decision" from the list of possible reasons for early discontinuation from the study. The FDA also requested revisions to the charter of the Renal Events Adjudication Committee (REAC); protocol language related to the responsibilities of the REAC was amended to reflect those revisions. In addition, minor changes were made to improve clarity and consistency with respect to the following: treatment "discontinuation" and study "withdrawal"; subjects who prematurely discontinue investigational product (IP); referencing study visits to the Baseline Visit rather than to Day 1; destruction of unused XO1 and colchicine; recording of overdoses; dispensing of XO1 at the Month 24 Visit; vital status assessment at the End of Study Visit. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported