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	67.3	66.4	
standard deviation	± 8.00	± 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 + XOI	Lesinurad + XOI		
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 + XOI	Lesinurad + XOI		
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 + XOI	Lesinurad + XOI		
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)	999999 (± 999999)		
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 + XOI	Lesinurad + XOI		
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 + XOI	Lesinurad + XOI		
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 + XOI	Lesinurad + XOI		
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 (≥1.5 × Baseline) Over the Study Period

End point title	Percentage of Participants With Serum Creatinine (sCr) Elevations (≥1.5 × 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 + XOI	Lesinurad + XOI		
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 + XOI	Lesinurad + XOI		
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 + XOI	Lesinurad + XOI		
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 + XOI	Lesinurad + XOI		
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 + XOI	Lesinurad + XOI		
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 + XOI	Lesinurad + XOI		
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 + XOI	Lesinurad + XOI	
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 XOI and colchicine; recording of overdoses; dispensing of XOI 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