Clinical trial results:
A Phase 2, Multicentre, Double-Blind, Placebo and Active Control Efficacy and Safety Study to Evaluate Verinurad combined with Allopurinol in Heart Failure with Preserved Ejection Fraction (AMETHYST)

Summary

EudraCT number	2019-004862-16
Trial protocol	DE BG PL SK AT
Global end of trial date	29 April 2022

Results information

Result version number	v1 (current)
This version publication date	12 May 2023
First version publication date	12 May 2023

Trial information

Trial identification

Sponsor protocol code	D5496C00005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04327024
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Södertälje, Södertälje, Sweden, 151 85
Public contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, +1 (877)240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, +1 (877)240-9479, information.center@astrazeneca.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	09 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 April 2022
Global end of trial reached?	Yes
Global end of trial date	29 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to assess effect of verinurad + allopurinol compared to placebo on exercise capacity by analyzing the change from baseline at week 32 in peak VO2 measurements.

Protection of trial subjects:

Before the start of the clinical study, the clinical study protocol (CSP), Informed consent document (ICDs), and other relevant documents were submitted to the Regulatory Authority for review and approval, in accordance with local regulatory procedures. The study was performed in accordance with ethical principles that had their origin in the Declaration of Helsinki and were consistent with International Council for Harmonization Good Clinical Practice (ICH GCP) and the AstraZeneca policy on Bioethics and Human Biological Samples. The subjects were informed of the nature, significance, implications, and risks of the trial before the study. Informed consent was freely given and evidenced in writing.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 May 2020
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	Russian Federation: 35
Country: Number of subjects enrolled	Slovakia: 23
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Bulgaria: 14
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	United States: 13
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Argentina: 5
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Australia: 6
Worldwide total number of subjects	159
EEA total number of subjects	77

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)	44
From 65 to 84 years	112
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

475 subjects were screened between May 19, 2020, and July 16, 2021, at 59 sites in 12 different countries. Of those screened, 159 were randomized into the study and received treatment, 53 in each arm of the study.

Pre-assignment

Screening details:

Subjects who met all the of inclusion criteria and none of the exclusion criteria were randomized to a study treatment. Study treatment was titrated over 8 weeks. Colchicine prophylaxis was given during the titration period and during the first 4 weeks of treatment at target dose (12 weeks total).

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	Investigator, Subject, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Verinurad + Allopurinol

Arm description:

12 mg verinurad + 300 mg allopurinol

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

Dosage and administration details:

100mg, administered once daily in Weeks 0-3;
200mg, administered once daily in Weeks 4-7;
300mg, administered once daily in Weeks 8-32.

Investigational medicinal product name	Verinurad
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

3mg, administered once daily in Weeks 0-3;
7.5mg, administered once daily in Weeks 4-7;
12mg, administered once daily in Weeks 8-32.

Arm title	Allopurinol

Arm description:

300 mg Allopurinol

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:	
Placebo capsule matching verinurad, administered once daily	
Investigational medicinal product name	Allopurinol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
100mg, administered once daily in Weeks 0-3; 200mg, administered once daily in Weeks 4-7; 300mg, administered once daily in Weeks 8-32.	
Arm title	Placebo
Arm description:	
0 mg placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Placebo tablet matching allopurinol, administered once daily	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Placebo capsule matching verinurad, administered once daily	

Number of subjects in period 1	Verinurad + Allopurinol	Allopurinol	Placebo
Started	53	53	53
Completed	51	49	50
Not completed	2	4	3
Adverse event, serious fatal	1	2	1
Consent withdrawn by subject	1	1	2
Non-compliance with study drug	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Verinurad + Allopurinol
Reporting group description:	
12 mg verinurad + 300 mg allopurinol	
Reporting group title	Allopurinol
Reporting group description:	
300 mg Allopurinol	
Reporting group title	Placebo
Reporting group description:	
0 mg placebo	

Reporting group values	Verinurad + Allopurinol	Allopurinol	Placebo
Number of subjects	53	53	53
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	14	8	22
From 65-84 years	38	43	31
85 years and over	1	2	0
Age Continuous Units: Years			
arithmetic mean	69.6	70.6	67.5
standard deviation	± 9.04	± 6.98	± 9.77
Sex: Female, Male Units: Participants			
Female	21	19	16
Male	32	34	37
Race/Ethnicity, Customized Units: Subjects			
White	46	46	48
Black or African American	0	3	1
Asian	7	3	4
Other	0	1	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	6	4
Not Hispanic or Latino	50	47	49
Unknown or Not Reported	0	0	0

Reporting group values	Total		

Number of subjects	159		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	44		
From 65-84 years	112		
85 years and over	3		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	56		
Male	103		
Race/Ethnicity, Customized Units: Subjects			
White	140		
Black or African American	4		
Asian	14		
Other	1		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	13		
Not Hispanic or Latino	146		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Verinurad + Allopurinol
Reporting group description: 12 mg verinurad + 300 mg allopurinol	
Reporting group title	Allopurinol
Reporting group description: 300 mg Allopurinol	
Reporting group title	Placebo
Reporting group description: 0 mg placebo	

Primary: Change from baseline at Week 32 in peak V02 consumption in verinurad + allopurinol compared to placebo (ANCOVA model)

End point title	Change from baseline at Week 32 in peak V02 consumption in verinurad + allopurinol compared to placebo (ANCOVA model)[1]

End point description:

Mean change from baseline in peak VO2 at Week 32 between the treatment groups was compared using change from baseline (i.e., week 32 value - baseline value) as the dependent variable, treatment as the independent variable and baseline peak VO2 included as covariate.

H0: Difference in mean change from baseline in peak VO2 (verinurad + allopurinol vs placebo) = 0
Ha: Difference in mean change from baseline in peak VO2 (verinurad + allopurinol vs placebo) ≠ 0

A hierarchical test sequence was used for the confirmatory analysis of the primary and secondary objectives in order to address the issue of multiple testing and control the Type I error rate at an overall two-sided 0.05 level.

Resulting p-value was 0.862. Since this was the first test in the hierarchical test sequence and endpoint was not rejected at a two-sided 0.05 level, the testing sequence did not continue.

End point type	Primary
End point timeframe: From baseline to Week 32	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Other arm covered in secondary endpoint

End point values	Verinurad + Allopurinol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: mL/kg/min				
least squares mean (confidence interval 95%)	0.27 (-0.56 to 1.10)	0.37 (-0.45 to 1.19)		

Statistical analyses

Statistical analysis title	ANCOVA analysis
Comparison groups	Placebo v Verinurad + Allopurinol
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.862
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.28
upper limit	1.08

Secondary: Change from baseline at Week 32 in peak V02 consumption in verinurad+ allopurinol compared to allopurinol monotherapy (ANCOVA model)

End point title	Change from baseline at Week 32 in peak V02 consumption in verinurad+ allopurinol compared to allopurinol monotherapy (ANCOVA model)[2]

End point description:

Mean change from baseline in peak VO2 at Week 32 between the treatment groups was compared using change from baseline (i.e., week 32 value - baseline value) as the dependent variable, treatment as the independent variable and baseline peak VO2 included as covariate.

H0: Difference in mean change from baseline in peak VO2 (verinurad + allopurinol vs allopurinol) = 0
Ha: Difference in mean change from baseline in peak VO2 (verinurad + allopurinol vs allopurinol) ≠ 0

A hierarchical test sequence was used for the confirmatory analysis of the primary and secondary objectives in order to address the issue of multiple testing and control the Type I error rate at an overall two-sided 0.05 level.

End point type	Secondary

End point timeframe:

From baseline to Week 32

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Other arm covered in secondary endpoint

End point values	Verinurad + Allopurinol	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	53		
Units: mL/Kg/min				
least squares mean (confidence interval 95%)	0.27 (-0.56 to 1.10)	-0.17 (-1.03 to 0.69)		

Statistical analyses

Statistical analysis title	ANCOVA analysis
Comparison groups	Verinurad + Allopurinol v Allopurinol
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.472
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	1.64

Secondary: Change from baseline at Week 32 in KCCQ-TSS in verinurad+ allopurinol compared to placebo (MMRM)

End point title	Change from baseline at Week 32 in KCCQ-TSS in verinurad+ allopurinol compared to placebo (MMRM)[3]

End point description:

Mean change from baseline in KCCQ-TSS at Week 32 between the treatment groups was compared using MMRM analysis, with change from baseline (i.e., week 32 value - baseline value) as the dependent variable, treatment as the independent variable and visit, visit by treatment, and baseline KCCQ-TSS included as covariates.

H0: Difference in mean change from baseline in KCCQ-TSS (verinurad + allopurinol vs placebo) = 0
Ha: Difference in mean change from baseline in KCCQ-TSS (verinurad + allopurinol vs placebo) ≠ 0

A hierarchical test sequence was used for the confirmatory analysis of the primary and secondary objectives in order to address the issue of multiple testing and control the Type I error rate at an overall two-sided 0.05 level.

End point type	Secondary

End point timeframe:

From baseline to week 32

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Other arm covered in secondary endpoint

End point values	Verinurad + Allopurinol	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	48		
Units: score				
least squares mean (confidence interval 95%)				
Week 22	0.50 (-4.08 to 5.08)	3.55 (-1.29 to 8.39)		
Week 32	4.31 (0.28 to 8.33)	1.16 (-3.02 to 5.34)		

Statistical analyses

Statistical analysis title	Mixed Models with Repeated Measures Analysis
Comparison groups	Verinurad + Allopurinol v Placebo
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.287
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.65
upper limit	8.94

Secondary: Change from baseline at Week 32 in KCCQ-TSS in verinurad+ allopurinol compared to allopurinol monotherapy (MMRM)

End point title	Change from baseline at Week 32 in KCCQ-TSS in verinurad+ allopurinol compared to allopurinol monotherapy (MMRM)[4]

End point description:

Mean change from baseline in KCCQ-TSS at Week 32 between the treatment groups was compared using MMRM analysis, with change from baseline (i.e., week 32 value - baseline value) as the dependent variable, treatment as the independent variable and visit, visit by treatment, and baseline KCCQ-TSS included as covariates.

H0: Difference in mean change from baseline in KCCQ-TSS (verinurad + allopurinol vs allopurinol) = 0
Ha: Difference in mean change from baseline in KCCQ-TSS (verinurad + allopurinol vs allopurinol) ≠ 0

A hierarchical test sequence was used for the confirmatory analysis of the primary and secondary objectives in order to address the issue of multiple testing and control the Type I error rate at an overall two-sided 0.05 level.

End point type	Secondary

End point timeframe:

From baseline to week 32

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Other arm covered in secondary endpoint

End point values	Verinurad + Allopurinol	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	50		
Units: score				
least squares mean (confidence interval 95%)				
Week 22	0.50 (-4.08 to 5.08)	2.85 (-1.91 to 7.62)		
Week 32	4.31 (0.28 to 8.33)	4.45 (0.34 to 8.57)		

Statistical analyses

Statistical analysis title	Mixed Model with Repeated Measures analysis
Comparison groups	Verinurad + Allopurinol v Allopurinol
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.96
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	5.61

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected with onset date on or after first dose and up to the end of the study. Serious adverse events were collected with onset date on or after the signing of the informed consent form and up to the end of the study (week 36).

Adverse event reporting additional description:

All adverse events reported are treatment emergent with onset on or after the first dose and up to the end of the study (week 36).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Allopurinol

Reporting group description:

Description (Arm-group)

Reporting group title	Verinurad 12 mg + Allopurinol

Reporting group description:

Description (Arm-group)

Reporting group title	Placebo

Reporting group description:

0 mg placebo

Serious adverse events	Allopurinol	Verinurad 12 mg + Allopurinol	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 53 (18.87%)	10 / 53 (18.87%)	9 / 53 (16.98%)
number of deaths (all causes)	2	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	5 / 53 (9.43%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 8	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			

subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 53 (0.00%)	2 / 53 (3.77%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Anal fissure haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal hernia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal necrosis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal prolapse			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
COVID-19			

subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Allopurinol	Verinurad 12 mg + Allopurinol	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 53 (49.06%)	24 / 53 (45.28%)	20 / 53 (37.74%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 53 (1.89%)	3 / 53 (5.66%)	0 / 53 (0.00%)
occurrences (all)	1	4	0
Hypertension			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	2 / 53 (3.77%)
occurrences (all)	2	1	2
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	3 / 53 (5.66%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	3	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	2 / 53 (3.77%)
occurrences (all)	1	1	2
Epistaxis			
subjects affected / exposed	2 / 53 (3.77%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Rales			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	2	1	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 53 (0.00%)	3 / 53 (5.66%)	0 / 53 (0.00%)
occurrences (all)	0	3	0
Investigations			

Blood creatinine increased			
subjects affected / exposed	5 / 53 (9.43%)	2 / 53 (3.77%)	2 / 53 (3.77%)
occurrences (all)	5	2	2
Blood pressure increased			
subjects affected / exposed	1 / 53 (1.89%)	3 / 53 (5.66%)	2 / 53 (3.77%)
occurrences (all)	1	3	2
Weight increased			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	0 / 53 (0.00%)
occurrences (all)	2	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 53 (0.00%)	2 / 53 (3.77%)	0 / 53 (0.00%)
occurrences (all)	0	2	0
Ventricular extrasystoles			
subjects affected / exposed	2 / 53 (3.77%)	0 / 53 (0.00%)	0 / 53 (0.00%)
occurrences (all)	2	0	0
Cardiac failure			
subjects affected / exposed	1 / 53 (1.89%)	4 / 53 (7.55%)	4 / 53 (7.55%)
occurrences (all)	1	7	5
Atrial fibrillation			
subjects affected / exposed	2 / 53 (3.77%)	0 / 53 (0.00%)	2 / 53 (3.77%)
occurrences (all)	2	0	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	1 / 53 (1.89%)
occurrences (all)	2	1	1
Headache			
subjects affected / exposed	0 / 53 (0.00%)	4 / 53 (7.55%)	0 / 53 (0.00%)
occurrences (all)	0	4	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 53 (0.00%)	3 / 53 (5.66%)	2 / 53 (3.77%)
occurrences (all)	0	3	2
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	2 / 53 (3.77%)
occurrences (all)	0	1	2

Diarrhoea			
subjects affected / exposed	1 / 53 (1.89%)	5 / 53 (9.43%)	2 / 53 (3.77%)
occurrences (all)	1	7	2
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 53 (1.89%)	2 / 53 (3.77%)	0 / 53 (0.00%)
occurrences (all)	1	2	0
Pruritus			
subjects affected / exposed	1 / 53 (1.89%)	2 / 53 (3.77%)	1 / 53 (1.89%)
occurrences (all)	1	2	1
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	2 / 53 (3.77%)
occurrences (all)	1	1	3
Haematuria			
subjects affected / exposed	2 / 53 (3.77%)	0 / 53 (0.00%)	1 / 53 (1.89%)
occurrences (all)	2	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 53 (1.89%)	2 / 53 (3.77%)	1 / 53 (1.89%)
occurrences (all)	1	2	1
Back pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	2 / 53 (3.77%)
occurrences (all)	0	0	2
Infections and infestations			
COVID-19			
subjects affected / exposed	3 / 53 (5.66%)	1 / 53 (1.89%)	2 / 53 (3.77%)
occurrences (all)	3	1	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 53 (1.89%)	2 / 53 (3.77%)	0 / 53 (0.00%)
occurrences (all)	1	2	0
Gout			
subjects affected / exposed	2 / 53 (3.77%)	2 / 53 (3.77%)	2 / 53 (3.77%)
occurrences (all)	2	2	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2020	• Timelines for study endpoints changed from Week 28 to Week 32. • Extended titration period.
03 February 2021	• Inclusion of additional treatment arm, 24 mg verinurad + allopurinol. • Updated number of patients that will be randomized/enrolled and estimated screen-failure rate.
20 September 2021	• Reduction of sample size from 435 to 150 patients. • Removed interim analysis. • Removed the 24 mg verinurad + allopurinol treatment arm.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported