# 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<br>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<br>Units: Years | | | |
| arithmetic mean | 69.6 | 70.6 | 67.5 |
| standard deviation | ± 9.04 | ± 6.98 | ± 9.77 |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 21 | 19 | 16 |
| Male | 32 | 34 | 37 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 46 | 46 | 48 |
| Black or African American | 0 | 3 | 1 |
| Asian | 7 | 3 | 4 |
| Other | 0 | 1 | 0 |
| Ethnicity (NIH/OMB)<br>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<br>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<br>Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 56 | | |
| Male | 103 | | |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 140 | | |
| Black or African American | 4 | | |
| Asian | 14 | | |
| Other | 1 | | |
| Ethnicity (NIH/OMB)<br>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