Clinical Study Report Synopsis	
Drug Substance	Verinurad/ RDEA3170
Study Code	D5496C00005
Edition Number	1.0
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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)

Study dates:

First subject enrolled: 19 May 2020

Last subject last visit: 29 Apr 2022

The analyses presented in this report are based on a clinical data lock date of 09 June 2022

Phase of development: Therapeutic exploratory (II)

International Co-ordinating Investigator: Redacted

Sponsor's Responsible Medical Officer: Redacted

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

Patients were enrolled at around 59 sites across 12 countries, including Argentina, Australia, Austria, Bulgaria, Canada, Germany, South Korea, Mexico, Poland, Russian Federation, Slovakia, and the United States of America.

Publications

Kitzman DW, Voors A, Mentz R, Lewis G, Perl S, Myte R, et al. Rationale and design for a phase 2 trial of verinurad plus allopurinol in patients with heart failure with preserved ejection fraction and hyperuricemia. J Am Coll Cardiol 2021; 77 (18_Supplement_1) 597.

Objectives and criteria for evaluation

The objectives and outcome variables for this study are presented in Table S1Table S1Table S1Table S1.

Table S1 Objectives and Endpoints

Objectives	Endpoint/variable
Primary	
• To assess effect of verinurad + allopurinol compared to placebo on exercise capacity	• Change from baseline at Week 32 in peak VO_2
Secondary	
• To assess effect of verinurad + allopurinol compared to allopurinol monotherapy on exercise capacity	• Change from baseline at Week 32 in peak VO_2
• To assess effect of verinurad + allopurinol compared to placebo and compared to allopurinol monotherapy on KCCQ-TSS	• Change from baseline at Week 32 in KCCQ-TSS
Safety	
• To assess the safety and tolerability of verinurad + allopurinol as compared to placebo and to allopurinol in patients with HFpEF.	• Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory and ECG.
CCI [redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

Table S1 Objectives and Endpoints

Objectives	Endpoint/variable
• [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

AE adverse event; CV cardiovascular; ECG Electrocardiography; [redacted] KCCQ Kansas City Cardiomyopathy Questionnaire; [redacted] TSS total symptom score; [redacted] VO_2 volume of oxygen.

Study design

This was a randomised, multicentre, double-blind, parallel arm, active- and placebo-controlled, global Phase II study to assess the efficacy and safety of 12 mg verinurad and 300 mg allopurinol on functional endpoints in patients with hyperuricaemia (serum uric acid [sUA] > 6 mg/dL) and heart failure (HF) preserved ejection fraction (heart failure with preserved left ventricular ejection fraction [(HFpEF]) (left ventricular ejection fraction [LVEF] ≥ 45%). Eligible patients were randomised by Interactive Web Response System in a 1:1:1 ratio to the following three treatment arms: 12 mg verinurad plus 300 mg allopurinol; 300 mg allopurinol; or placebo.

Clinical Study Protocol (CSP) version 4 contained a substantial amendment. The purpose of this amendment was to inform of a decision to hold further study recruitment, remove the interim analysis, and remove a treatment arm (24 mg verinurad in combination with allopurinol) that was previously planned to be included (CSP version 3 [3 February 2021]). This followed amber results from a similar trial of verinurad-allopurinol in patients with chronic kidney disease and hyperuricaemia (SAPPHIRE study), in which lower than expected sUA lowering was observed. Therefore, a decision was taken to hold recruitment at the original number of patients targeted for the interim analysis, ie, reducing the sample size from n=435 to approximately 150 patients. This smaller sample size was considered enough for the evaluation of the primary efficacy objective, and the interim analysis was no longer needed. The reduction of the sample size and the removal of the treatment arm were not based on safety concerns, and the safety profile remained unchanged.

Target subject population and sample size

The target population was patients with hyperuricaemia and HFpEF. Patients should have been treated according to locally recognised guidelines on standard of care treatment for patients with HFpEF. Those treated with a sodium-glucose transport protein 2 inhibitor or sacubitril/valsartan were required to be on a stable dose for ≥ 4 weeks before randomisation. The following criteria was also required:

- Hyperuricaemia defined as sUA level of > 6 mg/dL.
- Documented diagnosis of symptomatic HFpEF according to all of the following criteria:
  - New York Heart Association functional class II-III at enrolment.
  - Medical history of typical symptoms/signs of heart failure (HF) > 6 weeks before enrolment, which was stably treated medically, with at least intermittent need for diuretic treatment.
  - LVEF ≥ 45%.
  - N-terminal pro b-type natriuretic peptide (NT-proBNP) ≥ 125 pg/mL (≥ 14.75 pmol/L) at Visit 1 for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at the time of sample. collection, NT-proBNP must be ≥ 250 pg/mL (≥ 29.51 pmol/L) OR patients must have a history of pulmonary capillary wedge pressure ≥ 15 mmHg during rest or pulmonary capillary wedge pressure ≥ 20 mmHg during exercise.
- Ability to exercise to near exhaustion during a cardiopulmonary exercise test (CPET) as exhibited by respiratory exchange ratio ≥ 1.05 during CPET conducted during screening.
- Peak volume of oxygen (VO_2) ≤ 75% of expected using treadmill, or peak VO_2 ≤ 68% of expected using cycle ergometer, based on normal values.

A total of 150 patients receiving standard of care treatment were planned to be randomized in a 1:1:1 ratio to 12 mg verinurad plus 300 mg allopurinol, 300 mg allopurinol, or placebo. Based on this design with 50 patients randomised to the verinurad + allopurinol group and to the placebo group respectively, and assuming a standard deviation (SD) for the primary endpoint of 2 mL/kg/min, the width of 95% confidence intervals (CIs) for estimated differences between treatments was about 1.57 ml/kg/min. The minimum detectable treatment difference for statistical significance in a two-group t-test with a two-sided significance level of 5% given the assumptions above was 0.794 mL/kg/min. While the number of patients to be randomised was amended from CSP version 3 to version 4, the study was adequately powered.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Verinurad or matching placebo capsules: 3, 7.5, or 12 mg to be taken orally once daily. Manufacturer: AstraZeneca AB.

Batch numbers:

- Verinurad 3 mg: CCI [redacted]
- Verinurad 7.5 mg: CCI [redacted]
- Verinurad 12 mg: CCI [redacted]
- Verinurad placebo: CCI [redacted]

Allopurinol (100 for up-titration, or 300 mg) or matching placebo tablet: once daily.
Manufacturer: CCI [redacted]

Batch numbers:

- Allopurinol 100 mg: CCI [redacted]
- Allopurinol 300 mg: CCI [redacted]
- Allopurinol placebo for 100 mg: CCI [redacted]
- Allopurinol placebo for 300 mg: CCI [redacted]

Duration of treatment

Total study duration was 32 weeks.

Statistical methods

A treatment policy estimand was applied to the analysis of the primary (change from baseline at Week 32 in peak VO_2) and secondary (change from baseline at Week 32 in Kansas City Cardiomyopathy Questionnaire (KCCQ)- total symptom score (TSS) endpoints whereby all data up to Week 32 (Visit 8) are included, regardless of whether or not a patient remained on blinded study treatment.

The main analysis of the primary endpoint, change from baseline in peak VO_2 at Week 32, was a comparison between treatment groups using an analysis of covariance (ANCOVA) model, with change from baseline as the dependent variable, treatment as the independent variable, and baseline peak VO_2 included as a covariate.

The efficacy variable for the analysis of the primary objective to assess the effect of verinurad + allopurinol compared with placebo on exercise capacity was the absolute change from baseline in peak VO_2 at Week 32.

Mean change from baseline at Week 32 in peak VO_2 consumption of verinurad + allopurinol compared with allopurinol monotherapy was analysed using the same ANCOVA model as described above for the main analysis of the primary endpoint.

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

- Comparison between verinurad + allopurinol and placebo in change from baseline in peak VO_2 at Week 32
- Comparison between verinurad + allopurinol and allopurinol monotherapy in change from baseline in peak VO_2 at Week 32
- Comparison between verinurad + allopurinol and placebo in change from baseline in KCCQ-TSS at Week 32
- Comparison between verinurad + allopurinol and allopurinol monotherapy in change from baseline in KCCQ-TSS at Week 32

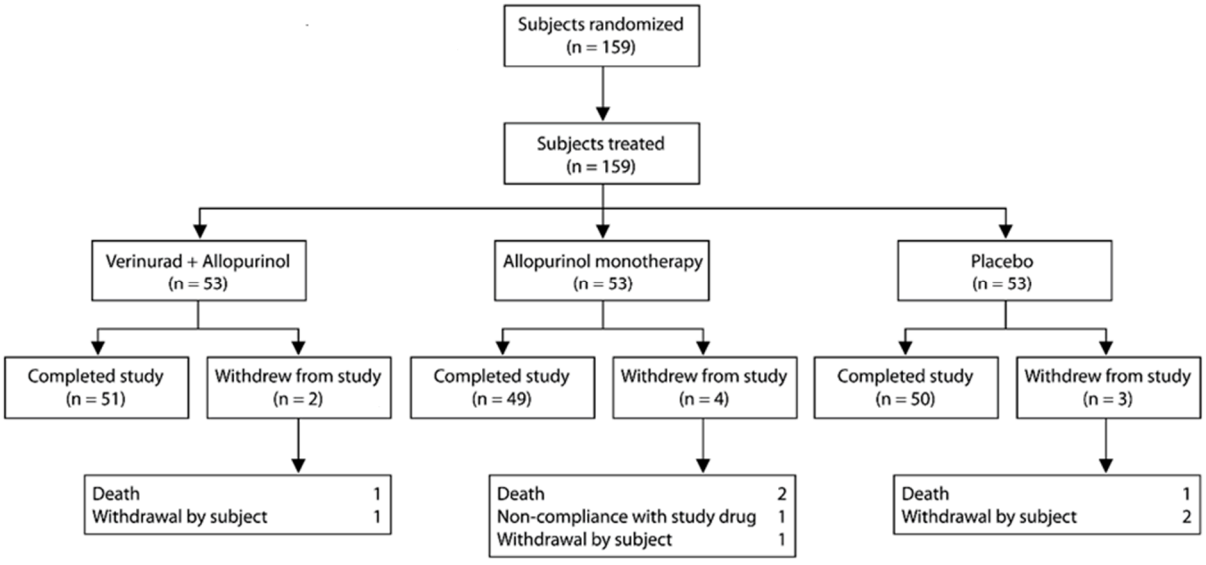
The testing procedure continued down the hierarchy if the preceding endpoint was rejected at a two-sided 0.05 level and stopped if the preceding endpoint was not rejected at a two-sided 0.05 level.

Study population

A total of 475 patients were enrolled in 59 study centres across 12 countries. Of these, 159 patients were randomized equally into 3 treatment groups, verinurad + allopurinol, allopurinol monotherapy, and placebo.

Details of patient disposition are given in Figure S1 and Table S2.

Figure S1 Flow Chart of Patient Disposition



n number of subjects

Table S2 Subject Disposition (Enrolled analysis set)

	Number (%) of subjects			
	12 mg verinurad + 300 mg allopurinol	**Allopurinol monotherapy**	**Placebo**	**Total**
Subjects enroled[a]				475
Subjects randomized	53 (100)	53 (100)	53 (100)	159 (100)
Subjects who were not randomized				316
Screen failure				313
Withdrawal by subject				3
Subjects who received treatment	53 (100)	53 (100)	53 (100)	159 (100)
Subjects who did not receive treatment	0	0	0	0
Subjects who completed treatment	46 (86.8)	40 (75.5)	47 (88.7)	133 (83.6)
Subjects who discontinued treatment	7 (13.2)	13 (24.5)	6 (11.3)	26 (16.4)
Adverse event	3 (5.7)	2 (3.8)	4 (7.5)	9 (5.7)
Development of study specific discontinuation criteria	1 (1.9)	0	0	1 (0.6)
Subject decision	0	6 (11.3)	1 (1.9)	7 (4.4)
Due to COVID-19 pandemic	3 (5.7)	3 (5.7)	0	6 (3.8)
Other	0	2 (3.8)	1 (1.9)	3 (1.9)
Subjects who completed study	51 (96.2)	49 (92.5)	50 (94.3)	150 (94.3)
Subjects withdrawn from study	2 (3.8)	4 (7.5)	3 (5.7)	9 (5.7)
Death	1 (1.9)	2 (3.8)	1 (1.9)	4 (2.5)
Non-compliance with study drug	0	1 (1.9)	0	1 (0.6)
Withdrawal by subject	1 (1.9)	1 (1.9)	2 (3.8)	4 (2.5)
Due to COVID-19 pandemic	0	0	0	0
Subjects in subgroup				
Reactive hyperaemia by EndoPAT	29 (54.7)	29 (54.7)	35 (66.0)	93 (58.5)
CPET	53 (100)	53 (100)	53 (100)	159 (100)
LVEF	53 (100)	53 (100)	53 (100)	159 (100)
History of atrial fibrillation	25 (47.2)	20 (37.7)	22 (41.5)	67 (42.1)
Prophylactic colchicine	47 (88.7)	46 (86.8)	48 (90.6)	141 (88.7)

Source: Table 14.1.1

Informed consent received.

All percentages are based on the number of subjects randomized in each treatment group.

COVID-19 coronavirus disease 2019. CPET cardiopulmonary exercise test. CSP clinical study protocol. LVEF left ventricular ejection fraction.

The demographic characteristics of the patients were generally balanced across the treatment groups. Overall, the population had a median age of 71 years and was predominantly male (64.8%) and White (88.1%).

The disease characteristics were generally balanced across the treatment groups with no clinically meaningful differences between groups in terms of HFpEF and hyperuricaemia.

There was a minor imbalance in estimated glomerular filtration rate (eGFR) as fewer patients with eGFR < 60 ml/min/1.73m^2 were found in the allopurinol monotherapy group (58.04 mL/min/1.73m^2) compared with the verinurad + allopurinol group (64.84 mL/min/1.73m^2) and placebo group (62.99 mL/min/1.73m^2).

Serum uric acid levels were similarly distributed across all groups with a total mean sUA of 7.64 mg/ml.

Investigator reported LVEF was similarly distributed across all groups with a total mean of 58.1%. The mean LVEF by the ECHO lab was 62.0%.

Overall, 42.1% had atrial fibrillation.

Across the entire study population, mean NT-proBNP for those with and without atrial fibrillation was 1172.80 pg/ml and 518.43 pg/ml, respectively (Table 14.1.10).

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Summary of efficacy results

Overall, none of the measured efficacy endpoints changed from baseline to Week 32 for patients in the verinurad and allopurinol group compared with the allopurinol monotherapy group and placebo group.

Primary endpoint

Change in exercise capacity as measured by the absolute change from baseline in peak VO_2 at Week 32, was similar in the verinurad + allopurinol group compared with the placebo group. The difference between groups (least squares means [LS MEANS] difference -0.10 ml/kg/min

[95% CI -1.28, 1.08]) did not meet statistical significance hence, formal statistical testing was stopped.

Secondary endpoints

Change in exercise capacity as measured by the absolute change from baseline in peak VO_2 at Week 32, was similar in the verinurad + allopurinol group compared with the allopurinol monotherapy group; the difference between groups (LS MEANS difference 0.44 ml/kg/min [-0.76, 1.64]) did not meet statistical significance.

Change in HF symptom status, as measured by the change from baseline in the KCCQ-TSS at Week 32, was similar in the verinurad + allopurinol group compared with the allopurinol monotherapy group and placebo group (LS MEANS difference -0.15 [95% CI -5.90, 5.61] and 3.15 [95% CI -2.65, 8.94]), respectively); these differences did not meet statistical significance even on a nominal scale.

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Summary of safety results

The number of subjects with adverse events (AEs) in any category is summarised in Table S3.

Compared with the verinurad + allopurinol group (205.2 days), the mean duration of exposure was less with allopurinol monotherapy and greater with the placebo group (191.2 days versus 217.8 days, respectively). This pattern of duration aligned with the total treatment days in each group (10873 days in the verinurad + allopurinol group versus 10133 days in the allopurinol monotherapy group and 11546 days in the placebo group).

Treatment with verinurad + allopurinol was generally well-tolerated and with no identified safety concerns. The majority of AEs were non-serious and mild or moderate in intensity. A lower proportion of patients in the verinurad + allopurinol group reported AEs compared with the allopurinol monotherapy group and placebo group (64.2% versus 69.8% and 75.5%, respectively).

Table S3 Number of Subjects with Adverse Events in Any Category (Safety analysis set)

	Number (%) of subjects		
AE category	**12 mg verinurad + 300 mg allopurinol (N=53)**	**Allopurinol monotherapy (N=53)**	**Placebo (N=53)**
Any AE	34 (64.2)	37 (69.8)	40 (75.5)
Any AE with outcome = death	1 (1.9)	2 (3.8)	1 (1.9)

Table S3 Number of Subjects with Adverse Events in Any Category (Safety analysis set)

	Number (%) of subjects		
AE category	**12 mg verinurad + 300 mg allopurinol (N=53)**	**Allopurinol monotherapy (N=53)**	**Placebo (N=53)**
Any SAE (including events with outcome = death)	10 (18.9)	10 (18.9)	9 (17.0)
Any AE leading to drug interrupted	5 (9.4)	3 (5.7)	4 (7.5)
Any AE leading to discontinuation of IP	4 (7.5)	3 (5.7)	4 (7.5)
verinurad + allopurinol + placebo	4 (7.5)	3 (5.7)	4 (7.5)
colchicine	3 (5.7)	2 (3.8)	2 (3.8)

Source: Table 14.3.2.2.

Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted only once in each of those categories.

Percentages are based on the total number of subjects in the treatment group (N).

Includes adverse events with an onset date on or after the date of first dose and up to end of study.

MedDRA version 24.1.

AE adverse event; IP investigational product; N number of subjects in treatment group; SAE serious adverse event.

There were 4 deaths reported during the treatment period (1 verinurad + allopurinol group, coronavirus disease-19 (COVID-19); 2 allopurinol monotherapy group, sudden cardiac death, COVID-19 pneumonia; 1 placebo group, cardiac failure acute).

Most AEs were considered to be unrelated to investigational product (IP) by the investigator across all groups and did not lead to discontinuation of IP. The number of patients who discontinued IP due to an AE was similar across treatment groups. The most frequently reported AEs in patients receiving verinurad + allopurinol were diarrhoea (11.3% versus 1.9% and 3.8% in the allopurinol monotherapy group and placebo group, respectively), cardiac failure (7.5% versus 11.3% and 9.4%), and headache (7.5% versus 0% and 0%). Diarrhoea was reported in 6 patients in the verinurad + allopurinol group, 1 patient in the allopurinol monotherapy group, and 2 patients in the placebo group. In the verinurad + allopurinol group, diarrhoea was reported as mild (2 [3.8%]), moderate (3 [5.7%]), and severe (1 [1.9%]). In one patient, severe diarrhoea was a SAE determined by the investigator as not caused by IP. The proportion of patients with any SAE was similar across treatment groups.

Severe AEs were reported in 21 patients with the highest percentage in the allopurinol monotherapy group; 17.0% versus 13.2% and 9.4 % in the verinurad + allopurinol group and placebo group, respectively.

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CCI [redacted]

Few patients had potentially clinically important lab abnormalities during the study. In the allopurinol monotherapy group., there was 1 potential Hy's law event (alanine transaminase] ≥ 3 × ULN or aspartate transaminase] ≥ 3 × ULN and total bilirubin] ≥ 2 × ULN) reported that led to discontinuation of IP. The event was later determined by the investigator to be unrelated to IP. The final primary AE was changed to cholelithiasis and gallstone pancreatitis, a plausible cause of the increased liver enzymes, and therefore it did not fulfil the criteria of a true Hy's law case.

Conclusion(s)

- Despite CCI [redacted] significantly impaired exercise capacity at baseline following treatment with 12 mg verinurad and 300 mg allopurinol, there was no effect on the primary and secondary endpoints in this study.
- CCI [redacted]
- Treatment with 12 mg verinurad and 300 mg allopurinol taken orally in combination once daily was generally well-tolerated and with no new safety concerns in patients with hyperuricaemia and HFpEF.