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Verinurad Plus Allopurinol for Heart Failure With Preserved Ejection Fraction
The AMETHYST Randomized Clinical Trial

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IMPORTANCE Elevated serum uric acid (SUA) level may contribute to endothelial dysfunction; therefore, SUA is an attractive target for heart failure with preserved ejection fraction (HFpEF). However, to the authors' knowledge, no prior randomized clinical trials have evaluated SUA lowering in HFpEF.

OBJECTIVE To investigate the efficacy and safety of the novel urate transporter-1 inhibitor, verinurad, in patients with HFpEF and elevated SUA level.

DESIGN, SETTING, AND PARTICIPANTS This was a phase 2, double-blind, randomized clinical trial (32-week duration) conducted from May 2020 to April 2022. The study took place at 59 centers in 12 countries and included patients 40 years and older with HFpEF and SUA level greater than 6 mg/dL. Data were analyzed from August 2022 to May 2024.

INTERVENTIONS Eligible patients were randomized 1:1:1 to once-daily, oral verinurad, 12 mg, plus allopurinol, 300 mg; allopurinol, 300 mg, monotherapy; or placebo for 24 weeks after an 8-week titration period. Allopurinol was combined with verinurad to prevent verinurad-induced urate nephropathy, and the allopurinol monotherapy group was included to account for allopurinol effects in the combination therapy group. All patients received oral colchicine, 0.5 to 0.6 mg, daily for the first 12 weeks after randomization.

MAIN OUTCOMES AND MEASURES Key end points included changes from baseline to week 32 in peak oxygen uptake (VO_2), Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS), and SUA level; and safety/tolerability (including adjudicated cardiovascular events).

RESULTS Among 159 randomized patients (53 per treatment group; median [IQR] age, 71 [40-86] years; 103 male [65%]) with median (IQR) N-terminal pro-brain natriuretic peptide level of 527 (239-1044) pg/mL and SUA level of 7.5 (6.6-8.4) mg/dL, verinurad plus allopurinol (mean change, −59.6%; 95% CI, −64.4% to −54.2%) lowered SUA level to a greater extent than allopurinol (mean change, −37.6%; 95% CI, −45.3% to −28.9%) or placebo (mean change, 0.8%; 95% CI, −11.8% to 15.2%; $P < .001$). Changes in peak VO_2 (verinurad plus allopurinol, 0.27 mL/kg/min; 95% CI, −0.56 to 1.10 mL/kg/min; allopurinol, −0.17 mL/kg/min; 95% CI, −1.03 to 0.69 mL/kg/min; placebo, 0.37 mL/kg/min; 95% CI, −0.45 to 1.19 mL/kg/min) and KCCQ-TSS (verinurad plus allopurinol, 4.3; 95% CI, 0.3-8.3; allopurinol, 4.5; 95% CI, 0.3-8.6; placebo, 1.2; 95% CI, −3.0 to 5.3) were similar across groups. There were no adverse safety signals. Deaths or cardiovascular events occurred in 3 patients (5.7%) in the verinurad plus allopurinol group, 8 patients (15.1%) in the allopurinol monotherapy group, and 6 patients (11.3%) in the placebo group.

CONCLUSIONS AND RELEVANCE Results of this randomized clinical trial show that despite substantial SUA lowering, verinurad plus allopurinol did not result in a significant improvement in peak VO_2 or symptoms compared with allopurinol monotherapy or placebo in HFpEF.

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Visual Abstract

Supplemental content

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Widespread endothelial dysfunction in multiple organs has been hypothesized to underlie the pathogenesis of heart failure with preserved ejection fraction (HFpEF).[1,2] A high prevalence of abnormalities in endothelial or microvascular function is present in overt HFpEF and also in individuals with risk factors for HFpEF and subclinical cardiac abnormalities consistent with HFpEF.[3-9] Increased oxidative stress and impaired mitochondrial function in skeletal muscle also contribute to reduced peak oxygen uptake (VO_2) and exercise intolerance in patients with HFpEF.[10]

Serum uric acid (SUA), both an indicator of and a possible pathogenic factor for endothelial dysfunction, is elevated in up to two-thirds of patients with HFpEF and is associated with a worse prognosis compared with an SUA level in the normal range.[11-14] Elevated SUA level can be a marker of endothelial dysfunction in the kidney where worsening microvascular disease is associated with inability to excrete uric acid in the urine. Hyperuricemia can result from (and can be exacerbated by) loop diuretics, commonly used to counteract volume overload in HFpEF. Hyperuricemia may also cause endothelial and microvascular dysfunction by direct toxicity to endothelial and smooth muscle cells; indeed, uric acid crystals have been identified in coronary vessel walls in some patients with hyperuricemia.[15] Prior trials of xanthine oxidase (XO) inhibitors to lower SUA level in HF have had neutral results, possibly due to insufficient lowering of SUA level and high discontinuation rates due to adverse effects.[16]

Verinurad is a novel urate transporter-1 (URAT1) inhibitor. URAT1 is responsible for reabsorption of UA in the proximal tubule of the kidney.[17,18] Inhibition of URAT1 increases urinary excretion of uric acid, thereby lowering SUA concentration; however, increased tubular urate excretion can result in the formation of obstructive UA crystals, ultimately leading to urate nephropathy.[19,20] Early-phase trials combining verinurad with an XO inhibitor (eg, allopurinol, febuxostat) resulted in approximately 80% SUA lowering in patients with recurrent gout.[21] Verinurad also reduces albuminuria and was therefore tested in patients with chronic kidney disease in the A Study of Verinurad and Allopurinol in Patients with Chronic Kidney Disease and Hyperuricemia (SAPPHIRE) trial.[19]

We hypothesized that the combination of verinurad plus allopurinol could improve microvascular function, reduce oxidative stress, and improve mitochondrial function in HFpEF, thereby improving exercise capacity compared with either allopurinol alone or placebo. We conducted the Study of Verinurad in Heart Failure With Preserved Ejection Fraction (AMETHYST), a multicenter, phase 2, randomized clinical trial in patients with HFpEF and hyperuricemia to evaluate the efficacy and safety of verinurad plus allopurinol compared with allopurinol monotherapy or placebo.

Key Points

Question What are the effects of verinurad, a novel urate transporter-1 inhibitor, on exercise capacity and symptoms in patients with heart failure with preserved ejection fraction (HFpEF) and elevated serum uric acid (SUA) level?

Findings In this randomized clinical trial including 159 patients, the combination of verinurad and allopurinol compared with allopurinol alone or placebo resulted in significantly greater reduction in SUA level after 32 weeks of treatment; however, it did not significantly improve peak oxygen uptake, symptoms, or key echocardiographic parameters in patients with HFpEF and elevated SUA level.

Meaning Combining verinurad with allopurinol to lower SUA level did not improve peak oxygen uptake or symptoms in HFpEF.

Methods

Study Design and Eligibility Criteria

AMETHYST was an international, multicenter, phase 2, double-blind, placebo-controlled, parallel-group, randomized clinical trial to evaluate the efficacy and safety of verinurad plus allopurinol in patients with HF, left ventricular ejection fraction (LVEF) of 45% or greater, and hyperuricemia (SUA >6 mg/dL; to convert to millimoles per liter, multiply by 0.0595). The trial was conducted at 59 sites in 12 countries (Argentina, Australia, Austria, Bulgaria, Canada, Germany, South Korea, Mexico, Poland, Russian Federation, Slovakia, and the US), and the trial protocol was approved by the institutional review board or independent ethics committee at each participating site (trial protocol and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively). All patients provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Patients were included if they had symptomatic HFpEF, including New York Heart Association (NYHA) functional class II or III, symptoms of HF for more than 6 weeks before enrollment, at least intermittent diuretic use, LVEF of 45% or greater, hyperuricemia (sUA >6 mg/dL), ability to exercise to maximal volitional effort (respiratory exchange ratio ≥1.05 during cardiopulmonary exercise training [CPET] at screening), and peak VO_2 of 75% or less of expected using a treadmill or peak VO_2 of 68% or less of expected using a cycle ergometer.[22] Detailed inclusion and exclusion criteria are in the eAppendix in Supplement 3. Patients self-identified with the following races and ethnicities: Asian, Black or African American, Hispanic or Latino, not Hispanic or Latino, White, or other, which included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and other (ie, none previously mentioned). Race and ethnicity information was included in the study because of the potential for race- and ethnicity-based differences in response to treatment in patients with HFpEF.

Eligible patients were randomized by an Interactive Web Response System in a 1:1:1 ratio to receive oral verinurad, 12 mg, plus allopurinol, 300 mg, daily; allopurinol, 300 mg, monotherapy daily; or matched placebo for 24 weeks after an 8-week titration period. Prophylactic colchicine, 0.5 mg (European Union) or 0.6 mg (all other countries), daily was administered orally to all patients during the first 3 months after randomization to prevent systemic inflammation from dissolution of UA crystals for those receiving UA-lowering treatment.

Trial Assessments

eTable 1 in Supplement 3 lists study objectives and end points. The primary efficacy end point was the placebo-adjusted change in peak VO_2 from baseline to week 32, assessed using CPETs conducted at all sites according to a standardized ramp protocol and interpreted by a blinded core laboratory (Massachusetts General Hospital). The same modality of exercise testing (either a treadmill or cycle ergometer) was used at baseline and week 32 for each patient throughout the study. CPETs were performed in a symptom-limited fashion to achieve a requisite respiratory exchange ratio of 1.05 or greater and evidence of impaired peak VO_2 (≤75% predicted for age and sex when using a treadmill or ≤68% predicted when using a cycle ergometer, as based on reference values).[22]

Secondary efficacy end points included the allopurinol monotherapy-adjusted change in peak VO_2 from baseline to week 32 in patients treated with verinurad plus allopurinol, and the effect of verinurad plus allopurinol vs placebo (and vs allopurinol monotherapy) on the change in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) from baseline to week 32.[23,24] Changes in Patient Global Impression of Change and Severity scales were also assessed. Exploratory efficacy end points included incidence of gout flares, cardiovascular death, HF hospitalizations/urgent visits, changes in SUA level, systemic endothelial function, echocardiographic markers, and additional CPET parameters (eg, minute ventilation over carbon dioxide production [V_E/VCO_2], a marker of pulmonary vascular function). Comprehensive echocardiography, including Doppler and tissue Doppler imaging and right ventricular assessment according to societal guidelines,[25,26] was performed locally and interpreted centrally by a blinded echocardiography core laboratory. Peripheral arterial tonometry was conducted to evaluate reactive hyperemia index, a measure of systemic endothelial function, using the EndoPAT device (Itamar Medical Inc). All laboratory tests (including N-terminal pro-brain natriuretic peptide [NT-proBNP]) were conducted centrally. Key safety end points were evaluated from randomization to week 36 (32-week treatment period plus 4 weeks after treatment discontinuation) and included all-cause mortality and adverse events (AEs) leading to premature discontinuation of study treatment. An independent, blinded clinical events adjudication committee reviewed, interpreted, and adjudicated all potential cardiovascular events experienced by patients in the trial and reported by the site investigators. In-person follow-up visits were conducted at weeks 4, 8, 12, 22, and 32 postrandomization and at 4 weeks after the end of treatment.

Statistical Analysis

The sample size calculation for the AMETHYST trial was based on the primary end point (32-week change in peak VO_2). A projected total of 150 patients with HFpEF randomized in a 1:1:1 ratio to verinurad, 12 mg, plus allopurinol, 300 mg; allopurinol, 300 mg, monotherapy; or placebo, would result in 50 patients randomized to the verinurad plus allopurinol group and to the placebo group, respectively. Assuming an SD for the primary end point of 2 mL/kg/min, the width of 95% CIs for estimated differences between treatments was calculated to be approximately 1.57 mL/kg/min. The minimum detectable treatment difference for statistical significance in a 2-group *t* test with a 2-sided significance level of 5% and statistical power of 80%, given the previously mentioned assumptions, was 0.79 mL/kg/min; thus, a total sample size of 150 participants would be adequate to detect a clinically meaningful difference (1.0 mL/kg/min) in peak VO_2 between treatment groups.

Originally, the planned enrollment in the AMETHYST trial was 435 total patients to provide adequate power for the secondary and exploratory end points, with a prespecified interim analysis after 150 patients had been randomized. However, during the conduct of AMETHYST, a similar randomized clinical trial (SAPPHIRE[19]) of verinurad plus allopurinol in patients with chronic kidney disease and hyperuricemia, reported less than expected efficacy of SUA level lowering. Therefore, a decision was made jointly by the sponsor and academic steering committee (blinded to all results, including interim analysis results) to hold recruitment in the AMETHYST trial at the original number of patients targeted for the interim analysis (approximately 150 patients).

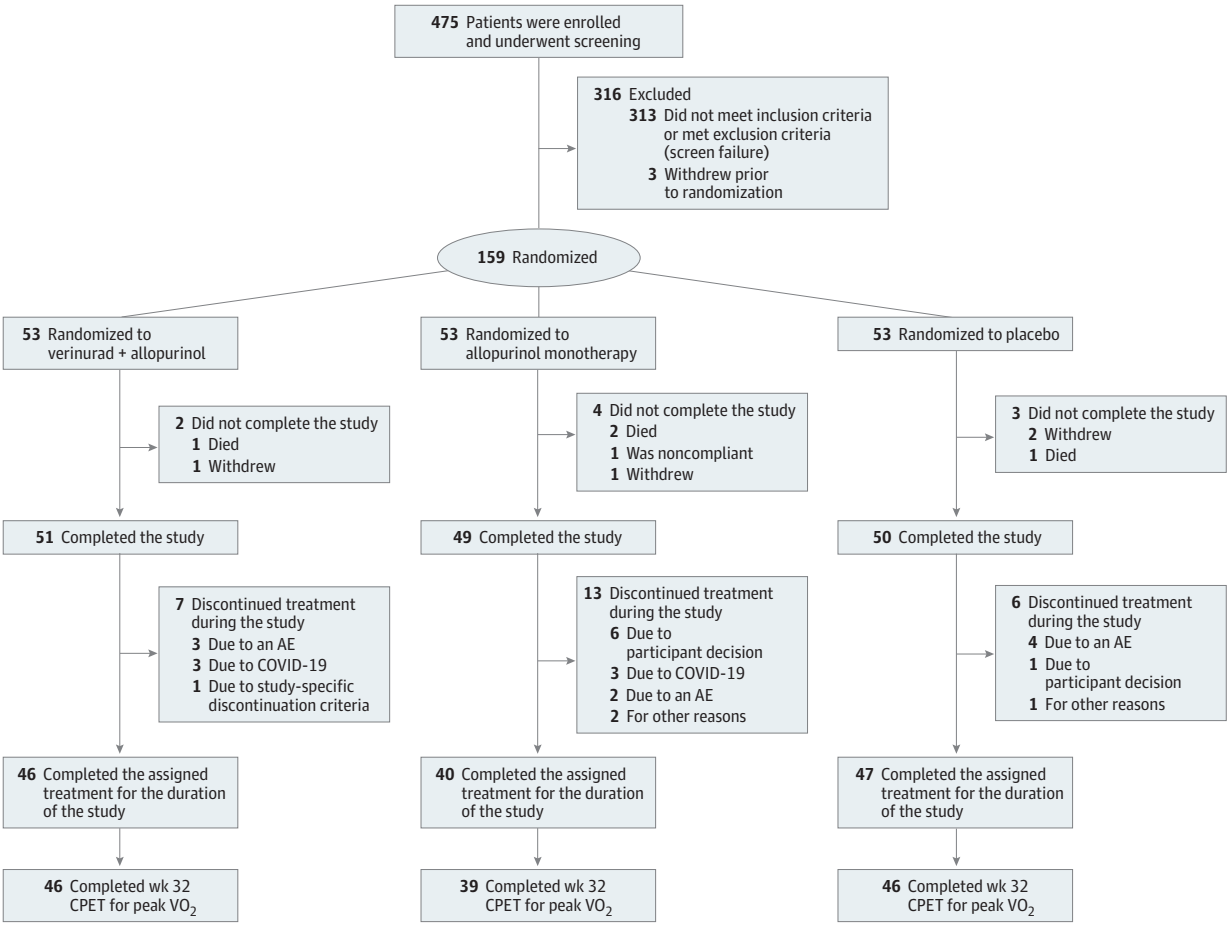
The full analysis set was defined as all patients randomized. The safety analysis set was defined as all patients who received at least 1 dose of study treatment. In both analysis sets, results were analyzed according to the assigned treatment. An intention-to-treat policy based on the full analysis set was applied to the analysis of the primary and secondary end points whereby all data up to week 32 were included regardless of whether a patient remained on study treatment.

An analysis of covariance model was used for comparison of mean change in peak VO_2, with change from baseline as the dependent variable, treatment as the independent variable, and baseline peak VO_2 included as a covariate. Missing values for peak VO_2 at week 32 were imputed using dropout reason-based multiple imputation. A hierarchical test sequence was used for the confirmatory analysis of the primary and secondary end points to control the type I error rate at an overall 2-sided significance level of .05. The testing procedure continued down the hierarchy if the null hypothesis for the preceding end point was rejected at a 2-sided significance level of .05 and stopped if the null hypothesis for the preceding end point was not rejected at a 2-sided significance level of .05. All statistical tests performed after this point were therefore considered exploratory. All statistical analyses were performed from August 2022 to May 2024 using SAS, version 9.4 (SAS Institute Inc).

Results

The first patient was enrolled for screening on May 19, 2020, and the last patient's last visit was April 29, 2022. Of the 475 patients enrolled at 59 study sites across 12 countries, 159 patients were randomized (53 to each treatment group: verinurad plus allopurinol, allopurinol monotherapy, and placebo) (eFigure in Supplement 3). All randomized patients received at least 1 dose of the study drug assigned; therefore, the full analysis set and safety analysis set were identical and included all randomized patients. **Figure 1** displays the patient disposition.

Figure 1. Patient Flowchart



AE indicates adverse event; CPET, cardiopulmonary exercise training; VO_2, peak oxygen uptake.

Baseline Characteristics

Baseline characteristics were generally comparable across all 3 treatment groups (**Table 1**). Median (IQR) age was 71 (40-86) years, 56 female (35%), and 103 male (65%). Patients self-identified with the following races and ethnicities: 14 Asian (8.8%), 4 Black or African American (2.5%), 13 Hispanic or Latino (8.2%), 146 not Hispanic or Latino (91.8%), 140 White (88.1%), and 1 other (1.9%). Comorbidities, including obesity, hypertension, diabetes, atrial fibrillation, and chronic kidney disease, were common; 67 patients (42.1%) had atrial fibrillation. Mean (SD) LVEF was 58% (8%) by investigator report and 62% (11%) by core laboratory analysis. NT-proBNP level was elevated and LV global longitudinal strain was impaired in most patients (**Table 2**). Baseline peak VO_2 was severely reduced (mean [SD] peak VO_2, 14.8 [4.0] mL/kg/min). Randomized patients had a median (IQR) NT-proBNP level of 527 (239-1044) pg/mL (to convert to nanograms per liter, multiply by 1) and SUA level of 7.5 (6.6-8.4) mg/dL.

Protocol and Treatment Compliance

Overall, 150 patients (94.3%) completed the study. The proportion of premature withdrawals was similar across groups, with no premature withdrawal due to the COVID-19 pandemic (Figure 1). Discontinuation due to patient decision was highest in the allopurinol monotherapy group (11.3% [6 patients] vs 0% and 1.9% [1 patient] in the verinurad plus allopurinol and placebo groups, respectively). Overall, 144 patients (90.6%) adhered to study treatment. Adherence was assessed as (total doses administered/total doses expected) × 100. A larger proportion of patients were more than 80% adherent in the verinurad plus allopurinol group vs the allopurinol monotherapy group and placebo group (51 [96.2%] vs 46 [86.8%] and 47 [88.7%], respectively).

Primary and Secondary Efficacy End Points

Changes in peak VO_2 (verinurad plus allopurinol, 0.27 mL/kg/min; 95% CI, −0.56 to 1.10 4 mL/kg/min; allopurinol, −0.17 mL/kg/min; 95% CI, −1.03 to 0.69 mL/kg/min; placebo, 0.37 mL/kg/min; 95% CI, −0.45 to 1.19 mL/kg/min) and KCCQ-TSS (verinurad plus allopurinol, 4.3; 95% CI, 0.3-8.3; allopurinol, 4.5; 95% CI, 0.3-8.6; placebo, 1.2; 95% CI, −3.0 to 5.3) were similar across groups. Between-group differences for the 32-week change from baseline in peak VO_2 were not statistically significant (least squares mean [LSM] difference, 0.44; mL/

Table 1. Baseline Characteristics

Characteristic	Verinurad + allopurinol (n = 53)	Allopurinol monotherapy (n = 53)	Placebo (n = 53)
Age, mean (SD), y	69.6 (9.0)	70.6 (7.0)	67.5 (9.8)
Sex, No. (%)			
Female	21 (39.6)	19 (35.8)	16 (30.2)
Male	32 (60.4)	34 (64.2)	37 (69.8)
Race, No. (%)			
Asian	7 (13.2)	3 (5.7)	4 (7.5)
Black or African American	0 (0)	3 (5.7)	1 (1.9)
White	46 (86.8)	46 (86.8)	48 (90.6)
Other[a]	0 (0)	1 (1.9)	0 (0)
Ethnic group, No. (%)			
Hispanic or Latino	3 (5.7)	6 (11.3)	4 (7.5)
Not Hispanic or Latino	50 (94.3)	47 (88.7)	49 (92.5)
BMI[b]	29.6 (4.8)	30.2 (4.4)	31.6 (5.3)
Obesity (BMI >30), No. (%)	28 (52.8)	30 (56.6)	19 (35.8)
Type 2 diabetes, No. (%)	20 (37.7)	28 (52.8)	18 (34.0)
Atrial fibrillation/flutter, No. (%)	25 (47.2)	20 (37.7)	22 (41.5)
LV ejection fraction (%)	57.7 (7.9)	57.5 (7.8)	59.2 (8.3)
NYHA class, No. (%)			
I	7 (13.2)	1 (1.9)	3 (5.7)
II	37 (69.8)	39 (73.6)	37 (69.8)
III	6 (11.3)	11 (20.8)	12 (22.6)
IV	0 (0)	0 (0)	0 (0)
NT-proBNP, median (IQR), pg/mL	566 (234-1288)	504 (177-931)	575 (367-1044)
eGFR	64.8 (17.4)	58.0 (18.6)	63.0 (18.6)
Peak VO_2, mL/kg/min	14.8 (4.3)	15.0 (3.9)	14.6 (3.8)
Serum uric acid, mg/dL	7.5 (1.3)	7.9 (1.5)	7.6 (1.7)
KCCQ-TSS score	67.2 (15.1)	70.2 (21.0)	66.0 (19.2)
Medication, No. (%)			
Diuretic	47 (88.7)	41 (77.4)	45 (84.9)
β-Blocker	37 (69.8)	38 (71.7)	37 (69.8)
Statin	35 (66.0)	42 (79.2)	34 (64.2)
Antiplatelet agent	24 (45.3)	29 (54.7)	25 (47.2)
ACE inhibitor	19 (35.8)	21 (39.6)	22 (41.5)
Aldosterone antagonist	17 (32.1)	19 (35.8)	21 (39.6)
ARB	17 (32.1)	21 (39.6)	19 (35.8)
ARNI	2 (3.8)	0 (0.0)	2 (3.8)
SGLT2 inhibitor	4 (7.5)	8 (15.1)	2 (3.8)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; eGFR, estimated glomerular filtration rate, KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; LV, left ventricular; NT-proBNP, N-terminal pro–brain natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2; VO_2, oxygen uptake.

SI conversion factor: To convert NT-proBNP to nanograms per liter, multiply by 1; to convert uric acid to millimoles per liter, multiply by 0.0595.

[a] Besides Asian, Black or African American, and White, other options for self-reported race included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and other (ie, none previously mentioned).

[b] Calculated as weight in kilograms divided by height in meters squared.

kg/min; 95% CI, −0.76 to 1.64 mL/kg/min; P = .47 and −0.10 mL/kg/min; 95% CI, −1.28 to 1.08 mL/kg/min; P = .86) in the verinurad plus allopurinol vs allopurinol monotherapy and placebo groups, respectively (**Figure 2**). Between-group differences in the 32-week change from baseline in HF symptom status (assessed using the KCCQ-TSS) also did not meet statistical significance (LSM difference, −0.15; 95% CI, −5.90 to 5.61; P = .96 and 3.15; 95% CI, −2.65 to 8.94; P = .29) in the verinurad plus allopurinol vs allopurinol monotherapy and placebo groups, respectively (Figure 2).

Exploratory End Points

The 32-week reduction from baseline in SUA level was greatest in the verinurad plus allopurinol group. Verinurad plus allopurinol (mean change, −59.6%; 95% CI, −64.4% to −54.2%) lowered SUA level to a greater extent than allopurinol (mean change, −37.6%; 95% CI, −45.3% to −28.9%) or placebo (mean change, 0.8%; 95% CI, −11.8% to 15.2%; both P < .001) (**Figure 3**). The incidence of gout flares was low across all groups.

Analyses of additional prespecified CPET parameters (eTable 2 in Supplement 3) showed no significant between-group differences in VO_2 at anaerobic threshold, VO_2 kinetics during the recovery phase, and exercise duration. There was a smaller increase in V_E/VCO_2 from baseline at week 32 (ie, less worsening) in the verinurad plus allopurinol group vs placebo group (LSM difference −1.98; 95% CI, −3.91 to −0.05). There were no between-group differences for changes in additional KCCQ summary scores and subdomains (eTable 3 in Supplement 3).

Table 2. Change From Baseline to Week 32: Key Echocardiographic End Points, Stratified by Treatment Group

End Point	Group	No.	Time point	Value, mean (SD)	No.	Change from baseline to week 32, mean (SD)
Left ventricular mass index, g/m^2	Verinurad + allopurinol	43	Baseline	92.2 (23.1)	NA	NA
		37	Week 32	90.1 (24.6)	30	-1.0 (12.5)
	Allopurinol monotherapy	40	Baseline	86.6 (19.7)	NA	NA
		36	Week 32	87.2 (22.2)	28	-1.1 (11.1)
	Placebo	42	Baseline	95.6 (32.6)	NA	NA
		35	Week 32	86.4 (22.7)	30	-2.2 (10.5)
Left ventricular global longitudinal strain, %	Verinurad + allopurinol	34	Baseline	-10.8 (6.0)	NA	NA
		45	Week 32	-12.2 (4.5)	29	-1.6 (6.6)
	Allopurinol monotherapy	45	Baseline	-12.0 (6.0)	NA	NA
		44	Week 32	-12.7 (5.8)	37	-0.9 (6.8)
	Placebo	43	Baseline	-11.5 (7.6)	NA	NA
		42	Week 32	-14.1 (4.0)	36	-3.1 (7.8)
Left atrial volume index, mL/m^2	Verinurad + allopurinol	41	Baseline	37.2 (15.9)	NA	NA
		41	Week 32	38.7 (22.7)	34	+0.5 (17.7)
	Allopurinol monotherapy	40	Baseline	29.8 (11.4)	NA	NA
		39	Week 32	32.6 (14.7)	32	-0.6 (8.2)
	Placebo	41	Baseline	32.5 (14.6)	NA	NA
		39	Week 32	29.2 (11.5)	32	-2.7 (7.8)
Early diastolic, e' velocity, cm/s	Verinurad + allopurinol	49	Baseline	81.6 (31.0)	NA	NA
		44	Week 32	80.9 (37.3)	40	-1.6 (19.6)
	Allopurinol monotherapy	46	Baseline	83.6 (32.2)	NA	NA
		43	Week 32	85.8 (33.8)	40	+2.0 (21.9)
	Placebo	49	Baseline	87.1 (34.7)	NA	NA
		46	Week 32	82.5 (31.6)	43	-2.5 (21.3)
E/e' ratio[a]	Verinurad + allopurinol	42	Baseline	10.2 (5.6)	NA	NA
		37	Week 32	12.1 (12.4)	31	+2.5 (8.4)
	Allopurinol monotherapy	42	Baseline	10.7 (5.7)	NA	NA
		34	Week 32	11.3 (6.9)	32	-0.1 (6.6)
	Placebo	37	Baseline	10.4 (3.5)	NA	NA
		35	Week 32	10.3 (3.4)	30	-0.2 (3.4)
Right ventricular systolic pressure, mm Hg	Verinurad + allopurinol	36	Baseline	27.6 (12.7)	NA	NA
		32	Week 32	27.3 (14.0)	27	+0.4 (8.2)
	Allopurinol monotherapy	29	Baseline	28.4 (10.9)	NA	NA
		34	Week 32	28.0 (13.7)	27	-0.3 (6.4)
	Placebo	26	Baseline	26.7 (9.9)	NA	NA
		27	Week 32	27.3 (10.6)	21	+1.4 (8.9)

Abbreviation: NA, not applicable.

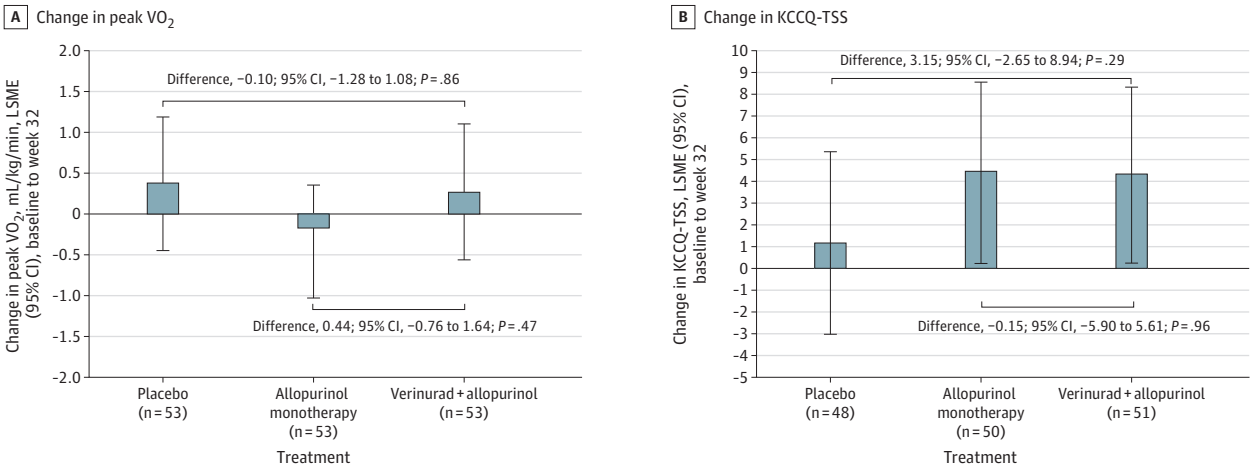
[a] The E/e' ratio, defined as the peak E-wave velocity divided by peak e' velocity, is an estimate of left ventricular end-diastolic pressure.

Changes in systemic endothelial function (measured by reactive hyperemia index) (eTable 4 in Supplement 3) and prespecified echocardiographic end points (LV mass index, left atrial volume index, global longitudinal strain, early diastolic mitral annulus velocity [e'], and transmitral early peak velocity [E/e'] ratio) (Table 2) over 32 weeks were similar across treatment groups, with no statistically significant differences identified. There were no between-group differences in the 32-week changes in assayed biomarkers, including growth NT-proBNP level, differentiation factor 15, interleukin 6, high-sensitivity C-reactive protein, and high-sensitivity troponin (eTable 5 in Supplement 3).

Safety

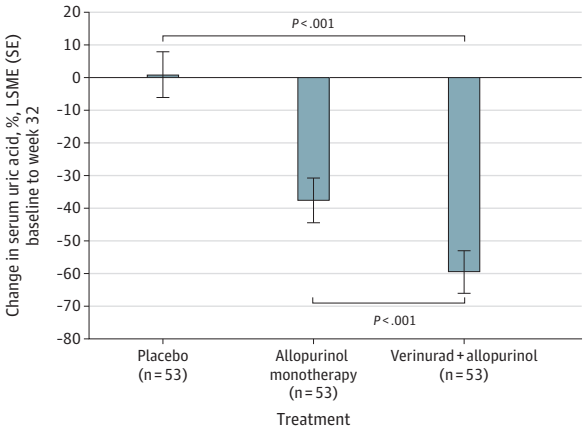
During the 36-week period after randomization (32-week treatment period and 4-week posttreatment observation period), the incidence of AEs was 64.2% (32 of 53 patients), 69.8% (37 of 53 patients), and 75.5% (40 of 53 patients) in the verinurad plus allopurinol, allopurinol monotherapy, and placebo groups, respectively (eTable 6 in Supplement 3). There were no adverse safety signals. Deaths or cardiovascular events occurred in 3 patients (5.7%) in the verinurad plus allopurinol group, 8 patients (15.1%) in the allopurinol monotherapy group, and 6 patients (11.3%) in the placebo group. Diarrhea was the most common AE in the verinurad plus allopurinol group (6

Figure 2. Changes in Peak Oxygen Uptake (VO_2) and Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) From Baseline to Week 32 Among Treatment Groups



A, Peak VO_2. B, KCCQ-TSS. Analyses were performed using an analysis of covariance with change from baseline as the dependent variable (ie, week 32 value − baseline value), with treatment as the independent variable and baseline peak VO_2 included as a covariate. The total number of patients at baseline in each treatment group was 53. Missing values at week 32 were imputed using dropout reason-based multiple imputation. LSME indicates least squares mean estimate.

Figure 3. Percentage Change in Serum Uric Acid Level From Baseline to Week 32 Among Treatment Groups



LSME indicates least squares mean estimate.

patients [11.3%]). Most AEs were mild or moderate in intensity. Serious AEs occurred in 29 patients and included 4 deaths (1 in the verinurad plus allopurinol group due to COVID-19 infection, 2 in the allopurinol monotherapy group due to sudden cardiac death and COVID-19 pneumonia, and 1 in the placebo group due to acute decompensated HF). Fewer patients had adjudicated cardiovascular events or deaths with verinurad plus allopurinol vs allopurinol monotherapy and placebo groups (3 [5.7%] vs 8 [15.1%] and 6 [11.3%], respectively) (eTable 7 in Supplement 3).

Increases (≥1.5 times baseline values) in serum creatinine level were evident in 5 patients (9.4%) in the allopurinol monotherapy group compared with 2 patients (3.8%) in both the verinurad plus allopurinol and placebo groups; no patient had a 2-fold or greater increase in serum creatinine level. Mean 32-week changes in serum creatinine level, cystatin C level, estimated glomerular filtration rate, and urinary albumin-to-creatinine ratio were similar and not statistically significant among the 3 treatment groups (eTable 5 in Supplement 3). Other than SUA concentration, no clinically meaningful trends were observed for clinical laboratory tests, vital signs, or electrocardiographic markers.

Discussion

The AMETHYST trial was the first, to our knowledge, placebo-controlled, randomized clinical trial to evaluate the effects of SUA-lowering therapy in patients with HFpEF. Results show that URAT1 inhibition with verinurad in combination with allopurinol in patients with HFpEF resulted in a substantial reduction in SUA but did not improve exercise capacity (peak VO_2) or symptoms (KCCQ-TSS) compared with either allopurinol monotherapy or placebo. There were no significant between-group differences in other measures of potential benefit, including systemic endothelial function, echocardiographic parameters, or NT-proBNP level. Verinurad plus allopurinol was well tolerated, with a low incidence of gout flares (in the setting of concomitant colchicine exposure for the first 12 weeks), and no evidence of worsening kidney function.

Neutral results in any HFpEF trial could be due to the following: enrollment of patients who did not have HFpEF or had HFpEF that was either insufficiently or too severe, lack of experimental treatment efficacy to achieve the intended mechanism of benefit, poor adherence to study treatment, suboptimal choice of end points, or insufficient statistical power to evaluate the primary end point(s). Patients enrolled in AM-

ETHYST were typical of patients with HFpEF described in epidemiological and observational studies except that they were more likely to be male and had markers suggestive of relatively more advanced HF (eg, severely reduced peak VO_2), which was expected given the study inclusion requirement of an SUA level of greater than 6 mg/dL. However, prior trials of SUA lowering in HF have used higher thresholds of SUA level for trial inclusion, and the low high-sensitivity C-reactive protein levels among the study patients (eTable 5 in Supplement 3) suggest that the patients enrolled in the trial did not have significant systemic inflammation, which could have accounted for the lack of efficacy of verinurad. The trial included end points relevant to both patients with HFpEF and the hypothesized mechanistic target of endothelial dysfunction, and the trial was adequately powered for the primary end point (32-week change in peak VO_2), a well-accepted measure of exercise capacity in HFpEF.

Impaired exercise capacity, high symptom burden, and poor quality of life are key patient-centered outcomes in patients with HFpEF. The peak VO_2 of patients enrolled in the AMETHYST trial was consistent with prior evidence of lower peak VO_2 in patients with HFpEF who have hyperuricemia than in those without hyperuricemia.[14] Despite this inverse association, SUA lowering with verinurad plus allopurinol in the AMETHYST trial did not improve exercise capacity or systemic endothelial function and suggests that SUA level may not be a major contributor to endothelial dysfunction or other mechanisms of exercise intolerance in HFpEF.

The AMETHYST trial joins several prior trials of SUA lowering in HF that have failed to show beneficial effects.[27] Although prior studies of XO inhibitors could have been hindered by inadequate SUA lowering or a high frequency of side effects, verinurad plus allopurinol in the AMETHYST trial significantly lowered SUA level and was well tolerated. The totality of evidence of SUA-lowering therapies in patients with HF, therefore, suggests that UA-induced endothelial and microvascular dysfunction are not major contributors to patient-oriented outcomes in patients with HFpEF or cannot be ameliorated simply by reducing SUA levels. In addition, although recent studies of sodium-glucose cotransporter 2 (SGLT2) inhibition have demonstrated reductions in SUA levels, given the results of the AMETHYST trial and other randomized clinical trials of sUA-lowering therapies in HF, it seems unlikely that the sUA-lowering effect of SGLT inhibitors is a major mechanism of the benefit of these agents in HFpEF.

Strengths and Limitations

The strengths of the AMETHYST trial were inclusion of patients with HFpEF who had evidence of hyperuricemia and severe exercise intolerance, the inclusion of multiple complementary clinically and mechanistically relevant end points, the comparison of verinurad plus allopurinol to not only placebo but also to allopurinol monotherapy (thereby allowing evaluation of the specific effects of verinurad), use of an objective measure of exercise capacity (peak VO_2) as a primary end point, central core laboratories to ensure quality assessments of outcomes, geographically dispersed enrollment sites, and the low treatment discontinuation and high study compliance despite the trial being conducted during the COVID-19 pandemic. Additional strengths included careful study drug titration over the initial 8-week treatment period to reduce risk of allopurinol-related AEs, and concomitant prophylaxis with colchicine during the first 3 months of the trial to reduce inflammation and gout flares due to dissolution of urate microcrystals.[28,29]

Limitations include the lower-than-expected rate of completion of the week 32 CPET (total N = 131, anticipated N = 150), and the higher-than-expected SD of the change from baseline to week 32 peak VO_2 (approximately 3 vs 2 mL/kg/min). Both factors could have led to underpowering to detect between-group differences in peak VO_2. However, the minimal between-group differences in change in peak VO_2 observed make type II error unlikely. Additional limitations include the missingness of some echocardiographic variables, limiting our ability to detect changes in cardiac structure/function and the predominance of White participants; lack of diversity reduces the generalizability of trial results. Finally, patients enrolled in the AMETHYST trial had a relatively advanced form of HFpEF, which may have made them less amenable to therapies such as verinurad that improve endothelial function. Whether verinurad could be effective in patients with less severe HFpEF requires further exploration.

Conclusions

In conclusion, the overall results of the AMETHYST randomized clinical trial suggest that SUA lowering with verinurad does not result in improved peak VO_2 or symptoms in HFpEF.

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