

## Clinical Trials

# Dual Vasopressin Receptor Antagonism to Improve Congestion in Patients With Acute Heart Failure: Design of the AVANTI Trial

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## ABSTRACT

**Background:** Loop diuretics are the main treatment for patients with acute heart failure, but are associated with neurohormonal stimulation and worsening renal function and do not improve long-term outcomes. Antagonists to arginine vasopressin may provide an alternative strategy to avoid these effects. The AVANTI study will investigate the efficacy and safety of pecavaptan, a novel, balanced dual-acting V1a/V2 vasopressin antagonist, both as adjunctive therapy to loop diuretics after admission for acute heart failure, and later as monotherapy.

**Methods and Results:** AVANTI is a double-blind, randomized phase II study in 571 patients hospitalized with acute heart failure and signs of persistent congestion before discharge. In part A, patients will receive either pecavaptan 30 mg/d or placebo with standard of care for 30 days. In part B, eligible patients will continue treatment or receive pecavaptan or diuretics as monotherapy for another 30 days. The primary end points for part A are changes in body weight and serum creatinine; for part B, changes in body weight and blood urea nitrogen/creatinine ratio.

**Conclusions:** This study will provide the first evidence that a balanced V1a/V2 antagonist may safely enhance decongestion, both as an adjunct to loop diuretics and as an alternative strategy.

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**Key Words:** Congestive heart failure, decongestion, diuretic, vasopressin.

Most hospitalizations for decompensated or acute heart failure (HF) are due to signs and symptoms of congestion and fluid overload.<sup>1</sup> Once patients are hospitalized for HF exacerbation, mortality and readmission rates are very high in the subsequent 60–90 days (up to 15% and 30%, respectively, in recent trials).<sup>2</sup> Despite symptomatic improvement

with standard therapy, many patients still have residual congestion at the time of discharge from the hospital (incomplete decongestion), a condition that has been associated with higher rates of readmission and death.<sup>3</sup>

The mainstay of therapy targeting hypervolemia and congestion is the use of loop diuretics. These agents provide rapid

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See page 8 for disclosure information.

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symptomatic improvement, but clearly outcomes remain poor. The use of loop diuretics has potential limitations that include the activation of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system, electrolyte disturbances (specifically, hypokalemia, hypomagnesemia, and alkalosis), hypertrophy of the distal nephron, and worsening renal function.<sup>4,5</sup> As renal function decreases, it becomes an impediment to the response to diuretics, creating a need for even more diuretics.<sup>6</sup> This can result in cardiorenal syndrome, which in the CARRESS HF trial of ultrafiltration was associated with a very high mortality rate at 60 days.<sup>7</sup> Therefore, adequate management of congestion while offering renal protection remains a relevant target in the treatment of HF.

Several peptide and small molecule antagonists to the receptors for the antidiuretic hormone arginine vasopressin (AVP) have been developed during the last decades. Two of the 3 AVP receptors may particularly contribute to HF pathophysiology: the V1a and V2 receptors.<sup>8</sup> The V1a receptor is found on vascular smooth muscle and myocardial cells, where it mediates vasoconstriction and positive inotropic effects as well as protein synthesis.<sup>8</sup> In the kidney, V1a activation may decrease renal medullary blood flow.<sup>9</sup> The intracellular signaling for these effects is mediated by a G-protein receptor coupled pathway closely related to that of angiotensin II.<sup>8</sup> The V2 receptor is located primarily on renal tubular collecting duct cells and mediates water retention via activation of the aquaporin II protein pathway.<sup>8</sup> Excessive AVP signaling could, therefore, potentially contribute to the pathophysiology of HF in several ways, including by enhancing vasoconstriction and afterload, directly contributing to inappropriate myocardial hypertrophy, adversely affecting renal blood flow, and aggravating fluid retention and hyponatremia.<sup>8,10</sup> Consistent with this hypothesis, 22% of patients hospitalized for worsening chronic HF with signs of fluid overload had AVP levels above the upper limit of normal (8 pg/mL) in 1 study.<sup>11</sup> Elevated AVP levels were associated with increased mortality even after adjustment for baseline factors, comorbidities, and admission medications.

Most clinical experience with AVP antagonism has been with selective V2 antagonists, primarily tolvaptan. Acute administration of this drug to stable patients with HF had a modestly favorable hemodynamic effect on filling pressures, while producing a rapid and significant aquaresis.<sup>12</sup> The results of clinical trials with tolvaptan as adjunctive therapy in patients hospitalized with acute HF resemble those from the largest experience, the EVEREST trial.<sup>13–15</sup> In EVEREST, as adjunctive therapy, tolvaptan compared with placebo produced a significant decongestive effect without worsening renal function while patients were hospitalized.<sup>13</sup> Hyponatremia, when present, was rapidly corrected, and the correction was sustained over time.<sup>13,14</sup> However, there was no benefit of tolvaptan on mortality or morbidity in the long-term phase of the trial.<sup>14</sup>

Less experience is available with V1a and combined V1a/V2 antagonism. Acute V1a antagonism has been shown to decrease systemic resistance in stable patients with elevated AVP levels.<sup>16</sup> Acute combined V1a and V2

antagonism in stable patients (largely with normal AVP levels) has shown a modest effect on the filling pressures, but none on cardiac output or systemic vascular resistance at rest.<sup>17</sup> Only 1 clinical trial with a combined or dual antagonist has been reported in patients with decompensated HF.<sup>18</sup> That trial showed clinical effects similar to those seen in the pure V2 antagonism trials, but because the agent (conivaptan) was available only for intravenous use, the trial duration was very short.

From a theoretical standpoint, it would be desirable to block both V1a and V2 receptors (Fig. 1), but a safe, orally effective agent has been lacking.

Pecavaptan is a new compound that is pharmacologically distinct from the other oral agents in the vaptan family. Pecavaptan is a balanced, dual-acting, AVP receptor antagonist with almost identical affinity for human V1a (Ki: 0.5 nmol/L) and V2 (Ki: 0.6 nmol/L) receptors,<sup>19</sup> whereas conivaptan has a greater affinity for the V1a receptor (Ki: 0.5 nmol/L) than for the V2 receptor (Ki: 3.04 nmol/L).<sup>20</sup> Pre-clinical studies in rats and dogs have shown that pecavaptan decreases systolic blood pressure and increases urine output in AVP-treated animals, with no associated activation of the RAAS system.<sup>19,21</sup> Furthermore, pecavaptan (but not tolvaptan) counteracted the AVP-mediated decrease in cardiac output in anesthetized or conscious dogs.<sup>21</sup> Phase I data for pecavaptan confirmed its aquaretic effect and did not reveal any significant off-target effects.<sup>22</sup>

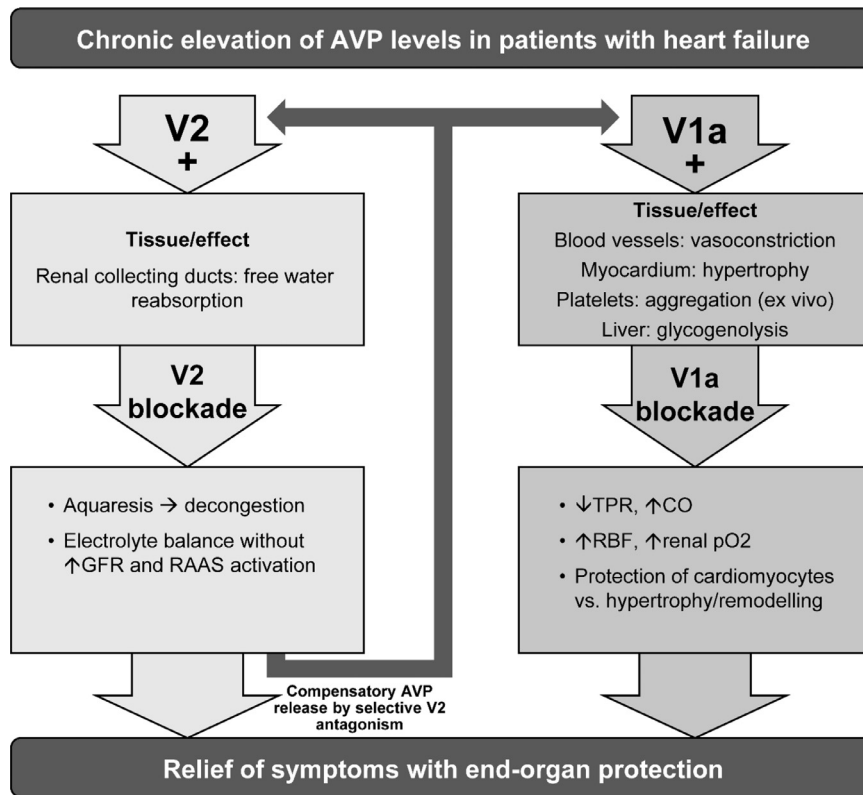
Here, we describe the design of a double-blind, randomized, placebo-controlled phase II trial (AVANTI – Dual Vasopressin Antagonism in Congestive Heart Failure) that will examine the effects of pecavaptan in patients during and after hospitalization for decompensated HF and objective evidence of incomplete decongestion despite standard therapy. The 2-part AVANTI study will comprehensively evaluate the effect of 30 mg pecavaptan compared with placebo on changes in body weight (a marker of congestion) and renal function when administered in addition to standard HF therapies (parts A and B) and as an alternative to loop diuretics (part B), focusing on the most vulnerable phase after an HF index hospitalization. Additional objectives can be found in Table 1.

## Methods

### Trial Design and Study Population

AVANTI will include 571 patients hospitalized with decompensated HF, regardless of ejection fraction, who have signs and symptoms of persistent congestion despite stabilization with intravenous diuretics on day 3–7 of the index hospitalization. Patient participation will be approximately 90 days. Key inclusion and exclusion criteria are detailed in Table 2, with a complete list of eligibility criteria found in Supplementary Table S1.

AVANTI will be carried out in 2 parts (Fig. 2). Part A will investigate whether addition of pecavaptan 30 mg to standard of care (SoC) therapy can decrease markers of congestion and prevent deterioration of renal function



**Fig. 1.** Vasopressin receptor antagonist profile in congestive heart failure. Chronic elevation of AVP levels in patients with heart failure leads to activation of both the V1a and the V2 receptor.<sup>8</sup> Selective blockade of the V2 receptor has been shown to improve decongestion without RAAS activation or worsening renal function,<sup>13</sup> but results in compensatory AVP release leading to V1a receptor activation.<sup>38</sup> It is, therefore, hypothesized that a dual AVP inhibitor could preserve the benefits of V2 receptor antagonism and potentially offer additional benefits mediated through the V1a receptor. AVP, arginine vasopressin; CO, cardiac output; GFR, glomerular filtration rate; pO<sub>2</sub>, partial pressure of oxygen; RAAS, renin–angiotensin–aldosterone system; RBF, renal blood flow; TPR, total peripheral resistance; V1a, vasopressin receptor 1a; V2, vasopressin receptor 2.

[1.5 column width; greyscale in print]

compared with placebo. Patients eligible for inclusion in part A must display at least 1 of the following markers consistent with incomplete decongestion despite the use

**Table 1.** Objectives

Primary objective	To assess the efficacy of pecavaptan 30 mg, with or without furosemide, vs furosemide alone in patients with HF and objective evidence of congestion
Secondary objective	To assess the safety and pharmacodynamics of pecavaptan 30 mg, with or without furosemide, vs furosemide alone in patients with HF and objective evidence of congestion
Exploratory objectives	Further evaluation of efficacy, safety, and patient-reported outcomes with pecavaptan when added to loop diuretics vs loop diuretics alone in the 30- to 60-day period after hospitalization in patients hospitalized with acute HF and objective evidence of congestion To assess the clinical effects of pecavaptan alone vs loop diuretics alone in the 30- to 60-day period after hospitalization Further evaluation of the pharmacodynamics and pharmacokinetics of pecavaptan Further evaluation of the effect of pecavaptan on exploratory biomarkers

HF, heart failure.

of in-hospital intravenous diuretics: sustained elevation of natriuretic peptides (brain natriuretic peptide [BNP]/N-terminal pro-BNP [NT-proBNP]); insufficient loss of body weight with diuretic use at day 4 of index hospitalization (<0.4 kg per 40 mg furosemide); a composite congestion score of 3 or above; hypervolemic hyponatremia; or in-hospital worsening of renal function combined with signs of venous congestion (for more detailed eligibility criteria, see Table 2). In this part of the trial, patients will be randomized to continued SoC therapy + placebo, or to SoC + pecavaptan 30 mg once daily for 30 days, with the day of randomization designated as study day 1.

After completion of part A, eligible patients within each of the 2 cohorts will be rerandomized to pecavaptan only, fixed-dose loop diuretic only (80 mg furosemide), or continuation of part A therapy with SoC + placebo or SoC + pecavaptan. As in part A, the latter 2 arms will allow variable dose loop diuretic as part of SoC therapy. The subsequent 30 days (part B) will investigate whether pecavaptan monotherapy is as effective as furosemide monotherapy in decreasing the symptoms of congestion while maintaining renal function, with an additional

**Table 2.** Key Inclusion and Exclusion Criteria

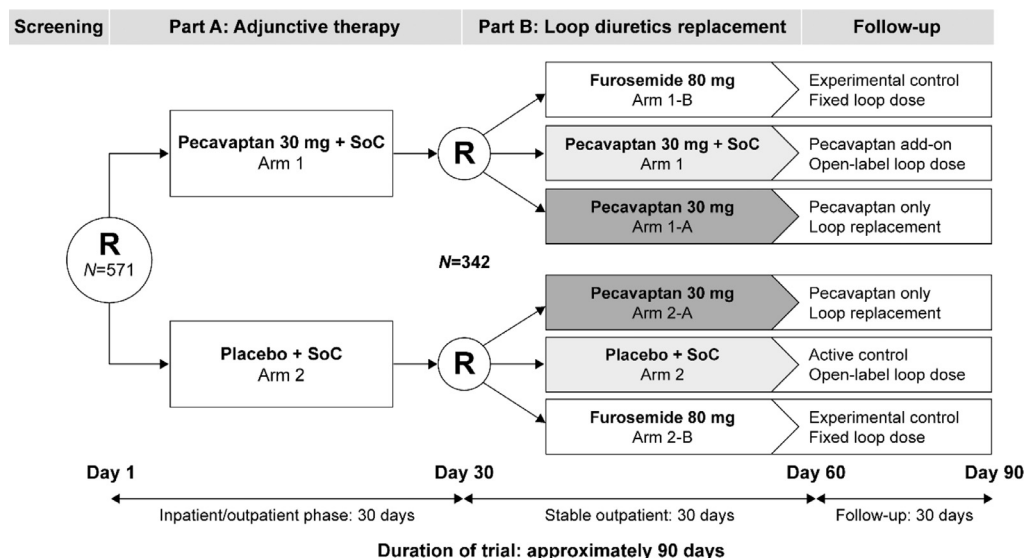
Key Inclusion Criteria	Key Exclusion Criteria
Age $\geq 18$ years and $\leq 85$ years History of chronic HF (HF with reduced, preserved, or mid-range EF) on individually optimized treatment with HF medications unless contraindicated or not tolerated, for $\geq 12$ weeks before the index hospitalization and in accordance with guidelines Patients admitted to the hospital with a primary diagnosis of decompensated HF with signs and symptoms of fluid overload requiring IV diuretic therapy in the ER or any time between day 1 and 3 of index hospitalization Patients on an average/usual daily dose of loop diuretic $\geq 40$ mg of furosemide or equivalent, within 4 weeks before index hospitalization At least one of the following parameters must be present on any day during days 3–7 of the index hospitalization: Natriuretic peptides (BNP/NT-proBNP): Drop in BNP or NT-proBNP of $\leq 30\%$ from admission values (if measured during index hospitalization) or BNP $\geq 500$ pg/mL or NT-proBNP $\geq 1800$ pg/mL at screening (days 3–7 of index hospitalization) Body weight loss $< 0.4$ kg per 40 mg furosemide at day 4 of index hospitalization Composite congestion score $\geq 3$ Hypervolemic hyponatremia defined as serum sodium $< 136$ mmol/L In-hospital worsening renal function defined as increased serum creatinine $\geq 0.3$ mg/dL compared to index hospitalization admission values and at least one of the following: Jugular venous pressure $\geq 10$ cm on physical examination Inferior vena cava diameter $> 21$ mm Inferior vena cava collapse with sniff $< 50\%$ $\geq 2$ peripheral edema or pulmonary edema or pleural effusion on chest radiographs or clinical examination	Acute de novo HF Stroke or carotid angioplasty within 3 months before screening Implantation of a cardiac resynchronization therapy device within 3 months before screening Requirement of mechanical support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation, or any ventricular assist device) or ultrafiltration/hemodialysis Use of IV vasodilators (eg, nitrates) or IV inotropic support within 24 hours before randomization Estimated glomerular filtration rate of $< 30$ mL $\cdot$ min <sup>-1</sup> $\cdot$ 1.73 m <sup>2</sup> determined by the Modification of Diet in Renal Disease equation at screening; reassessments allowed as clinically needed Serum potassium $\geq 5.5$ mmol/L or $\leq 3.3$ mmol/L at screening; reassessments allowed as clinically needed Serum sodium $\geq 146$ mmol/L or $\leq 130$ mmol/L at screening; reassessments allowed as clinically needed Syndrome of inappropriate antidiuretic hormone secretion Diabetes insipidus Exclusion from part B only Subjects with daily doses of furosemide (or the equivalent loop diuretic dose) of $< 40$ mg or $> 200$ mg at the final visit of part A (Visit 6) Subjects who had experienced a rehospitalization for HF after randomization of part A Any other serious medical condition or therapy that would make the subject unsuitable for entering part B at the judgement of the investigator

BNP, brain natriuretic peptide; EF, ejection fraction; ER, emergency room; HF, heart failure; IV, intravenous; NT-proBNP, N-terminal pro-brain natriuretic peptide.

A complete list of eligibility criteria can be found in Supplementary Table S1.

analysis exploring whether loop diuretics in combination with pecavaptan are more effective than loop diuretics only. For safety, patients in part A will not be eligible to participate in part B if they experience rehospitalization for HF after randomization in part A, or if they are

receiving daily doses of furosemide (or an equivalent loop diuretic dose) less than 40 mg or greater than 200 mg (see Table 2 for complete eligibility criteria). Patients who are not eligible for part B may continue part A therapy for 30 days.



**Fig. 2.** Study design. SoC, standard of care.

## End Points

The primary end points for part A are changes in body weight and serum creatinine between day 1 and day 30, whereas the primary end points for part B are changes in body weight and blood urea nitrogen (BUN)/creatinine ratio between day 30 and day 60. For the comparison of pecavaptan monotherapy with furosemide monotherapy in part B, changes in body weight will be assessed for noninferiority, and changes in the BUN/creatinine ratio will be assessed for superiority.

Secondary end points for both part A and part B are safety (assessed by treatment-emergent adverse event reporting), and measures of arterial stiffness including pulse wave velocity using noninvasive methods to assess the potential hemodynamic impact of V1a receptor antagonism expected with pecavaptan.

Additional exploratory end points will include various efficacy and safety end points including, patient-reported outcomes, pharmacokinetics and pharmacodynamics, and neurohormonal biomarkers, including NT-proBNP. At selected sites, lung fluid content will be assessed noninvasively by the remote dielectric sensing (ReDS) device (Sensible Medical, Netanya, Israel). ReDS provides a measurement of lung fluid content within the mid-region of the right lung. The measurement is presented as the percentage of the lung volume composed of fluid, with 20%–35% representing a normal measure of fluid content. A complete list of end points can be found in [Table 3](#).

## Statistical Considerations

The statistical analysis method used to assess the primary end points is an analysis of covariance model wherein the covariates are treatment and baseline end point values. For the first part of the study, multiple imputation methods (regression method under the assumption of a monotone missing pattern) will be used to address the issue of any missing day 30 values. The analyses of the treatment data from part B will use treatment assignment in part A as an additional covariate. A while-on-treatment strategy will be used for the comparison of the monotherapy treatment arms in part B of the study.

All patients assigned to study drug will be analyzed according to their randomized treatment. Several sensitivity analyses will be conducted, including a complete case analysis, a Bayesian analysis, and a bivariate Hotelling's  $T^2$  analysis. Subgroups will be investigated by the presentation of point estimates of the mean change and the corresponding 95% confidence intervals.

AVANTI will be the first study in which patients with congestive HF are treated with pecavaptan; therefore, treatment effect sizes used for sample size calculations are based on minimum effects observed on surrogate parameters in initial studies. Based on an expected dropout rate of approximately 20% during part A, randomization of 492 patients would give part A sufficient power to detect a difference in change between day 1 and day 30 in body weight and serum

**Table 3.** End Points

Primary end points	Part A Changes in body weight and serum creatinine (day 1 vs day 30) Part B Changes in body weight and BUN/creatinine ratio (day 30 vs day 60)
Secondary end points	Treatment-emergent adverse events (including serious adverse events) Pharmacodynamics measured by change in augmentation index
Main exploratory end points	Efficacy end points Composite of CV death, nonfatal myocardial infarction, and nonfatal stroke Changes in the New York Heart Association functional class All-cause mortality Decrease of loop diuretic use by $\geq 50\%$ Change in loop diuretic dose (number and percentage of patients with reduced, increased, or equal dose of loop diuretics) Changes in the composite congestion score <sup>27</sup> Safety end points Number of subjects with worsening renal function, hypo- or hyperkalemia, or hyper- or hyponatremia Urinary sodium/potassium ratio and urinary sodium concentration Patient-reported outcomes Symptom frequency as measured by the Kansas City Cardiomyopathy Questionnaire Pharmacokinetics and pharmacodynamics Trough and peak concentrations of pecavaptan Changes in thoracic fluid content (measured by ReDS device) Changes in body weight Pulse wave analysis Biomarkers (eg, NT-proBNP, aldosterone, renin, copeptin, KIM-1)

BUN, blood urea nitrogen; CV, cardiovascular; KIM-1, kidney injury molecule 1; NT-proBNP, N-terminal pro-brain natriuretic peptide; ReDS, remote dielectric sensing.

creatinine of 1.5 kg and 0.3 mg/dL, respectively, at a 1-sided significance level of 5%. This sample size was increased to 571 to account for an unexpectedly high number of premature discontinuations owing to the novel coronavirus disease-2019 (COVID-19) pandemic. For this part of the study to be successful, both primary end points must be significantly different in patients receiving SoC + pecavaptan compared with those receiving SoC + placebo.

Assuming that a further 20% of patients will complete part A but will not be eligible for continuation to part B, it is expected that the inclusion of 492 patients in part A would lead to randomization of 295 patients for part B of the study. However, with the additional patients enrolled to compensate for the COVID-19 pandemic, we expect to randomize a further 47 patients in part B, to give a total of 342 patients. This would give the study power to assess noninferiority of pecavaptan monotherapy compared with loop diuretic only with regard to change in body weight between day 30 and day 60, and superiority of pecavaptan monotherapy compared with loop diuretic with regard to change in BUN/creatinine ratio between day 30 and day 60. For the difference in body weight, a noninferiority margin of 1 kg is assumed based on



available literature<sup>23,24</sup>; for the difference in BUN/creatinine ratio, a difference of  $-0.114$  has been reported.<sup>13</sup> Because AVANTI is a proof-of-concept study, a generous 1-sided significance level of 20% will be used for these assessments. The sample size is calculated to reach a sufficient overall power for the primary analyses of part A and part B of at least 80% and about 90% for part A only.

The primary end points for parts A and B will be analyzed further according to the following prespecified subgroups: ejection fraction (preserved vs reduced); reduction in BNP or NT-proBNP levels between index hospitalization and screening for part A ( $\leq 30\%$  vs  $>30\%$ ); NT-proBNP concentration at randomization for part A ( $<1800$  pg/mL vs  $\geq 1800$  pg/mL); copeptin concentration at randomization for part A ( $<10$  pmol/L vs  $\geq 10$  pmol/L); and serum sodium concentration at randomization for part A ( $<136$  mmol/L vs  $\geq 136$  mmol/L).

## Discussion

The AVANTI trial will provide proof-of-concept data as to whether pecavaptan is an effective and safe adjunctive agent to loop diuretics during and for up to 2 months after an admission for acute HF. It will also provide, for the first time, data regarding the safety and efficacy of the use of any AVP antagonist as an alternative decongestive approach in the second month after admission for acute HF. Standard measures of weight loss and changes in renal function will be the core metrics, along with a host of markers to assess alterations in such potentially important pathophysiologic factors as neurohormonal activity and arterial stiffness, reflecting V1a activity. Measures of clinical well-being and safety will also be fully captured.

Prior experience with AVP antagonism in acute HF was briefly discussed in the introduction. Most of this experience has been with selective V2 antagonism which, as shown in the largest trial, EVEREST, reliably increases urine output and relieves dyspnea without worsening renal function compared to SoC with loop diuretics.<sup>13</sup> Smaller trials with different primary end points reported similar findings.<sup>15</sup>

Despite favorable short-term effects in the long-term follow-up of the EVEREST trial, there was no favorable effect on morbidity or mortality after discharge for an acute HF hospitalization.<sup>14</sup> This finding aligns with the results of METEOR, another trial that showed no detectable effect, neither adverse nor beneficial, of 1 year of tolvaptan therapy on left ventricular remodelling.<sup>25</sup> It has been hypothesized that, because the predominant effect of tolvaptan is to block the V2 receptor, the increase in plasma AVP levels owing to the small increase in serum osmolality that this causes may have resulted in enhanced agonism at the V1a receptor, with potentially adverse myocardial effects. In addition, preclinical data have shown that AVP decreases renal medullary blood flow via activation of the V1a receptor.<sup>9</sup> These unfavorable effects mediated by the V1a receptor may have offset any favorable effects of aquaresis and reduced filling

pressures afforded by a V2 receptor antagonist, resulting in neutral clinical outcomes.

As noted elsewhere in this article, the only current dual AVP antagonist that has been studied in HF is conivaptan. When given to patients with severe but stable HF, no changes in systemic vascular resistance or cardiac output were seen at rest, despite a dose-dependent increase in urine output indicative of V2 receptor blockade.<sup>17</sup> Plasma AVP levels in those patients were normal; however, and V1a effects may be dose dependent, based on earlier work.<sup>16</sup> The 1 clinical trial with a dual antagonist in acute HF used conivaptan and was necessarily of short duration.<sup>18</sup> The results were similar to those with tolvaptan. Importantly for pecavaptan, no hypotension was seen in that study, suggesting either the absence of a V1a effect or compensatory improvement in cardiac output in response to decreased systemic vascular resistance.<sup>18</sup> No hemodynamic data were collected in that study, nor were plasma AVP levels.

Preclinical studies of pecavaptan suggest more balanced effects of this agent on the V1a and V2 receptors than conivaptan.<sup>19</sup> This novel property will be more thoroughly tested in the AVANTI trial than in the clinical trial with conivaptan, in which only blood pressure measurements were available. In AVANTI, the V1a receptor antagonist effect will be assessed by changes in the augmentation index derived from arterial wave reflection, as measured by validated noninvasive methods.<sup>26</sup> Hemodynamic improvement without hypotension would be an important finding and certainly relevant to any future longer term trials.

The target population for this trial is patients with persistent congestion despite 2–6 days of in-hospital treatment for HF. This group includes many with the worst prognosis,<sup>24</sup> although, as noted, the prognosis is poor for all patients with acute HF. In AVANTI, we will in a novel manner incorporate multiple previously published parameters reflecting incomplete decongestion to more broadly capture such patients than has been done in prior studies. We have identified five domains reflecting incomplete decongestion to use as potential inclusion criteria (Table 2), all of which have been shown in recent studies to be associated with an increased risk of rehospitalization and mortality.<sup>3,24,27,28</sup> This trial is the first to incorporate these multiple markers of incomplete decongestion as entry criteria, with the goal of enriching the study sample population with patients potentially able to benefit from the mechanism of this intervention. For part A of this trial, we hypothesize that patients with these markers of incomplete decongestion despite loop diuretic treatment may benefit from the aquaretic effects of V2 antagonism, and this should be captured by the end point of weight loss. Moreover, based on numerous prior trials of V2 antagonism, it is also hypothesized that weight loss will be accompanied by stability of renal function.<sup>13,15</sup>

The results of part A of this study will probably resemble the first few weeks of the EVEREST<sup>13</sup> trial with pure V2 antagonism, because the major early effects of this agent are likely to be those connected with fluid balance. If these

results can be replicated without any important safety concerns owing to the V1a-blocking feature of the drug, then the results would provide support for a phase III study along the lines of EVEREST, given the comprehensive blockade provided by pecavaptan. The rationale here would be that longer periods of time would be required to demonstrate a benefit of V1a antagonism, by analogy with other agents such as angiotensin receptor blocker, which rely on blocking similar intracellular pathways.

An additional novel aspect of the trial design is the roll-over of patients from part A to part B, which includes a randomization arm including pecavaptan monotherapy without concomitant loop diuretic treatment. Support for this is both theoretical and based on the results of 2 prior trials of tolvaptan monotherapy versus diuretics. In one, tolvaptan was compared with a loop diuretic over 7 days of therapy in stable outpatients with HF. Signs of congestion, urine output and weight loss were similar (or greater) with tolvaptan.<sup>29</sup> In the second study, in patients with acutely decompensated HF, 5 days of monotherapy with tolvaptan was associated with similar decongestion and better preservation of renal function compared with diuretics.<sup>30</sup> In both studies there was less activation of the RAAS system with tolvaptan than with loop diuretics. Increased RAAS activity causes reabsorption of urea in the proximal tubules, which is greatly increased in the presence of AVP via upregulation of urea transporters. For this reason, BUN/creatinine ratio was selected as one of the primary end points for part B of this study. A third study recently compared tolvaptan monotherapy with continuous infusion of furosemide in patients hospitalized with acute HF with hyponatremia.<sup>31</sup> As in the previous studies, tolvaptan monotherapy was associated with similar diuresis compared with furosemide. Unlike the study by Jujo et al,<sup>30</sup> no significant between-group differences were observed for markers of renal preservation or RAAS activation; however, this result may reflect the smaller study population and shorter duration of this study compared with the earlier study.<sup>31</sup>

The main potential limitation to a benefit from pecavaptan in part B relates to the relative effects of pecavaptan and loop diuretics on sodium excretion. V2 antagonists do not directly affect sodium excretion,<sup>8</sup> yet the results of the prior comparative therapy studies suggest that the effects on sodium excretion and renal function via less activation of the renin–angiotensin system must also be considered if furosemide is the comparator. However, because this is a longer study, low-salt diets will be encouraged and, unless contraindicated, the use of aldosterone antagonists will be required. There is also the potential of blocking the V1a effect in the renal medulla to improve renal blood flow and oxygenation.<sup>9,32</sup>

The main reason to further investigate the hypothesis that a dual V1a/V2 antagonist might replace or at least substantially diminish the use of loop diuretics is that loop diuretics have potentially undesirable effects in HF.<sup>5</sup> These effects are not shared by a V2 antagonist.<sup>7</sup> AVANTI will greatly enhance our knowledge of the potential value of this

approach. If part B results are promising, a 3-arm phase III trial in which pecavaptan is studied in greater numbers of patients both as adjunctive and alternative therapy would be worth considering. The potentially salutary effects of chronic V1a antagonism from pecavaptan could be demonstrable in future studies focusing on either the adjunctive or alternative therapy options. As an alternative therapy, additional benefits arising from antagonism of either or both receptors could be expected owing to withdrawal of potential adverse effects of loop diuretics.

This study will include patients with both normal and reduced ejection fraction. The justification for pursuing long-term efficacy of a dual antagonist is more robust in patients with reduced ejection fraction, given the importance of neurohormonal imbalance in disease progression. Less is known about neurohormonal imbalance in HF with preserved ejection fraction. However, congestion is a central feature of both syndromes,<sup>33</sup> and worsening renal function during decongestion therapy has been suggested to have a particularly unfavorable impact in those with a normal ejection fraction. Furthermore, 2 clinical trials and a recent postmarketing surveillance study with the V2 receptor antagonist tolvaptan did not show any significant difference in treatment effect between patients with reduced and preserved ejection fraction.<sup>34–36</sup> This is a rapidly changing field and so it seems reasonable to obtain experience with this novel agent in both syndromes, at least in phase II.

This study is being performed during the global COVID-19 pandemic, which has resulted in a number of unplanned study discontinuations because patients are unable or unwilling to attend onsite visits. To account for this, the study design was amended to increase the number of patients screened and randomized, ensuring that the study would still be powered despite a higher discontinuation rate than originally anticipated.

## Conclusions

The fundamental justification for this study is the continuing poor outcomes in patients with acute HF.<sup>1,7</sup> As either adjunctive or substitutive therapy, pecavaptan offers the promise of reduced reliance on loop diuretics, potentially mitigating the drawbacks of these drugs. Furthermore, by causing water excretion, aquaretic agents such as pecavaptan lower the osmolarity of the circulating blood, potentially improving translocation of fluid from the tissues to the circulation and thus relieving tissue congestion, which is typically resistant to loop diuretics.<sup>37</sup> The use of a dual antagonist may, therefore, offer benefits even in combination with the use of loop diuretics. Positive results in this phase II trial with this new agent if later confirmed in a larger trial could be the first step in a paradigm shift in the treatment of decompensated HF, and potentially as well to further studies in more stable patients.

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### Supplementary materials

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