

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

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Running head: Rationale and Design of the AVANTI Study

Trial registration: [clinicaltrials.gov NCT03901729](https://clinicaltrials.gov/ct2/show/study/NCT03901729)

Word count: 3867

No. of tables: 3 + 1 supplementary table

No. of figures: 2

No. of references: 38

Abbreviations:

AVP, arginine vasopressin; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; RAAS, renin-angiotensin-aldosterone system; SoC, standard of care.

Abstract

Background: Loop diuretics are the main treatment for patients with acute heart failure (HF) 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 following admission for acute HF, and later as monotherapy.

Methods: AVANTI is a double-blind, randomized phase II study in 571 patients hospitalized with acute HF and signs of persistent congestion prior to discharge. In Part A, patients will receive either pecavaptan 30 mg daily 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 endpoints 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.

Trial registration number: NCT03901729

Abstract word count: 199 of 200

Key words: congestive heart failure; decongestion; diuretic; vasopressin

Introduction

Most hospitalizations for decompensated or acute heart failure (HF) are due to signs and symptoms of congestion and fluid overload.¹ Once patients are hospitalized for HF exacerbation, mortality and re-admission rates are very high in the subsequent 60–90 days (up to 15% and 30%, respectively, in recent trials).² 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 re-admission and death.³

The mainstay of therapy targeting hypervolemia and congestion is the use of loop diuretics. These agents provide rapid 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.^{4,5} As renal function declines, it becomes an impediment to the response to diuretics, creating a need for even more diuretics.⁶ 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.⁷ 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 three AVP receptors may particularly contribute to HF pathophysiology: the V1a and V2 receptors.⁸ 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.⁸ In the kidney, V1a activation may reduce renal medullary blood flow.⁹ The intracellular signaling for these effects is mediated by a G-protein receptor-coupled pathway closely related to that of angiotensin II.⁸ The V2 receptor is located primarily on renal tubular

collecting duct cells and mediates water retention via activation of the aquaporin II protein pathway.⁸ Excessive AVP signaling could, therefore, potentially contribute to the pathophysiology of HF in several ways, including by enhancing vasoconstriction/afterload, directly contributing to inappropriate myocardial hypertrophy, adversely affecting renal blood flow, and aggravating fluid retention and hyponatremia.^{8,10} 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 one study.¹¹ 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 HF patients had a modestly favorable hemodynamic effect on filling pressures, while producing a rapid and significant aquaresis.¹² 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.¹³⁻¹⁵ In EVEREST, as adjunctive therapy, tolvaptan compared with placebo produced a significant decongestive effect without worsening renal function while patients were hospitalized.¹³ Hyponatremia, when present, was rapidly corrected, and the correction was sustained over time.^{13,14} However, there was no benefit of tolvaptan on mortality or morbidity in the long-term phase of the trial.¹⁴

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.¹⁶ 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.¹⁷ Only one clinical trial with a combined or dual antagonist has been reported in patients with decompensated HF.¹⁸ 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 (IV) use, the trial duration was very short.

From a theoretical standpoint, it would be desirable to block both V1a and V2 receptors (**Figure 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 nM) and V2 (Ki: 0.6 nM) receptors,¹⁹ whereas conivaptan has a greater affinity for the V1a receptor (Ki: 0.5 nM) than for the V2 receptor (Ki: 3.04 nM).²⁰ Preclinical studies in rats and dogs have shown that pecavaptan reduces systolic blood pressure and increases urine output in AVP-treated animals, with no associated activation of the RAAS system.^{19,21} Furthermore, pecavaptan (but not tolvaptan) counteracted the AVP-mediated decrease in cardiac output in anesthetized or conscious dogs.²¹ Phase I data for pecavaptan confirmed its aquaretic effect and did not reveal any significant off-target effects.²²

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 two-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 (EF), who have signs and symptoms of persistent congestion despite

stabilization with IV 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 two parts (**Figure 2**). Part A will investigate whether addition of pecavaptan 30 mg to standard of care (SoC) therapy can reduce markers of congestion and prevent deterioration of renal function compared with placebo. Patients eligible for inclusion in Part A must display at least one of the following markers consistent with incomplete decongestion despite the use of in-hospital IV diuretics: sustained elevation of natriuretic peptides (brain natriuretic peptide [BNP]/N-terminal pro-brain natriuretic peptide [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 two cohorts will be re-randomized 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 two 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 reducing the symptoms of congestion while maintaining renal function, with an additional 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.

Endpoints

The primary endpoints for Part A will be changes in body weight and serum creatinine between Day 1 and Day 30, whereas the primary endpoints for Part B will be 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 non-inferiority, and changes in BUN/creatinine ratio will be assessed for superiority.

Secondary endpoints for both Part A and Part B will be safety (assessed by treatment-emergent adverse event reporting), and measures of arterial stiffness including pulse wave velocity using non-invasive methods to assess the potential hemodynamic impact of V1a receptor antagonism expected with pecavaptan.

Additional exploratory endpoints will include various efficacy and safety endpoints including, patient-reported outcomes, pharmacokinetics and pharmacodynamics, and neurohormonal biomarkers including NT-proBNP. At selected sites, lung fluid content will be assessed non-invasively 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 endpoints can be found in **Table 3**.

Statistical Considerations

The statistical analysis method used to assess the primary endpoints is an analysis of covariance model wherein the covariates are treatment and baseline endpoint 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 creatinine of 1.5 kg and 0.3 mg/dL, respectively, at a one-sided significance level of 5%. This sample size was increased to 571 in order to account for an unexpectedly high number of premature discontinuations due to the COVID-19 pandemic. For this part of the study to be successful, both primary endpoints 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 non-inferiority 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 non-inferiority margin of 1 kg is assumed based on available literature,^{23,24} for the difference in BUN/creatinine ratio, a difference of -0.114 has been reported.¹³ Because AVANTI is a proof-of concept-study, a generous one-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 endpoints 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. ≥ 1800 pg/mL); copeptin concentration at randomization for Part A (<10 pmol/L vs. ≥ 10 pmol/L); and serum sodium concentration at randomization for Part A (<136 mmol/L vs. ≥ 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 following 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 standard of care with loop diuretics.¹³ Smaller trials with different primary endpoints reported similar findings.¹⁵

Despite favorable short-term effects in the long-term follow-up of the EVEREST trial, there was no favorable effect on morbidity or mortality following discharge for an acute HF hospitalization.¹⁴ This 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.²⁵ It has been hypothesized that because the predominant effect of tolvaptan is to block the V2 receptor, the increase in plasma AVP levels due 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 reduces renal medullary blood flow via activation of the V1a receptor.⁹ 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 in the introduction, 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.¹⁷ Plasma AVP levels in those patients were normal; however, and V1a effects may be dose-dependent based on earlier work.¹⁶ The one clinical trial with a dual antagonist in acute HF used conivaptan and was necessarily of short duration.¹⁸ The results were similar to those with tolvaptan. Importantly for pecavaptan, no hypotension was seen in that study, suggesting either absence of V1a effect or compensatory improvement in cardiac output in response to decreased systemic vascular resistance.¹⁸ 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.¹⁹ 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 non-invasive methods.²⁶ 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,²⁴ though, as noted, prognosis is poor for all acute HF patients. 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 (see **Table 2**), all of which have been shown in recent studies to be associated with an increased risk of re-hospitalization and mortality.^{3,24,27,28} 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 endpoint 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.^{13,15}

The results of Part A of this study will probably resemble the first few weeks of the EVEREST¹³ 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 due 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 rollover 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 two prior trials of tolvaptan monotherapy vs. 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.²⁹ 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.³⁰ 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 endpoints 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.³¹ As in the previous studies, tolvaptan monotherapy was associated with similar diuresis compared with furosemide. Unlike the study by Jujo et al.,³⁰ no significant between-group differences were observed for markers of renal preservation or RAAS activation; however, this may reflect the smaller study population and shorter duration of this study compared with the earlier study.³¹

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,⁸ 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.^{9,32}

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.⁵ These effects are not shared by a V2 antagonist.⁷ AVANTI will greatly enhance our knowledge of the potential value of this approach. If Part B results are promising, a three-arm phase III trial in which pecavaptan is studied in larger 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 due 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,³³ and worsening renal function during decongestion therapy has been suggested to have a particularly unfavorable impact in those with normal EF. Furthermore, two clinical trials and a recent post-marketing 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.³⁴⁻³⁶ 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. In order 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.

Conclusion

The fundamental justification for this study is the continuing poor outcomes in patients with acute HF.^{1,7} 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.³⁷ 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.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Table S1. Full inclusion and exclusion criteria.

Acknowledgments

The authors would like to acknowledge Victoria Warwick from Chameleon Communications International, who provided editorial assistance with the preparation of the manuscript, with funding from Bayer AG. We would like to thank the Study Manager Saila Jahangir for her important contribution to set up and initiate this trial. We also would like to thank Ivonne Jarick and Svenja Burger for statistical support.

Funding

This work was supported by funding from Bayer AG.

Conflicts of interest

S.R.G. has received personal fees from Bayer AG for his role in the AVANTI steering committee and honoraria for speaking from Otsuka Pharmaceuticals. D.B. has received

personal fees from Bayer AG. F.G. has received personal fees from Bayer AG, Boehringer Ingelheim, AstraZeneca, Novartis, Pfizer, Orion Pharma, and Abbott and has received grants from Pfizer and Orion Pharma. A.V. received personal fees from Bayer AG for his role in the AVANTI steering committee, personal fees from Amgen, Cytokinetics, Boehringer Ingelheim, Roche, Novartis, AstraZeneca, Bayer AG, Myokardia, and Merck, and grants from Roche. F.Z. reports personal fees from Bayer AG for his role in the AVANTI steering committee, personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, Boehringer Ingelheim, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, and Merck, and is the founder of Cardiorenal and CVCT. P.K., G.S and W.D. are employees of Bayer AG. P.C is an employee of Bayer LLC. J.E.U. has received personal fees from Bayer AG for the AVANTI trial, grants from Cardurion and Cyclorion, and personal fees from Cyclorion, Merck/Pfizer, Edwards/CRF, Cytokinetics, Imbria, and Abiomed.

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Figures

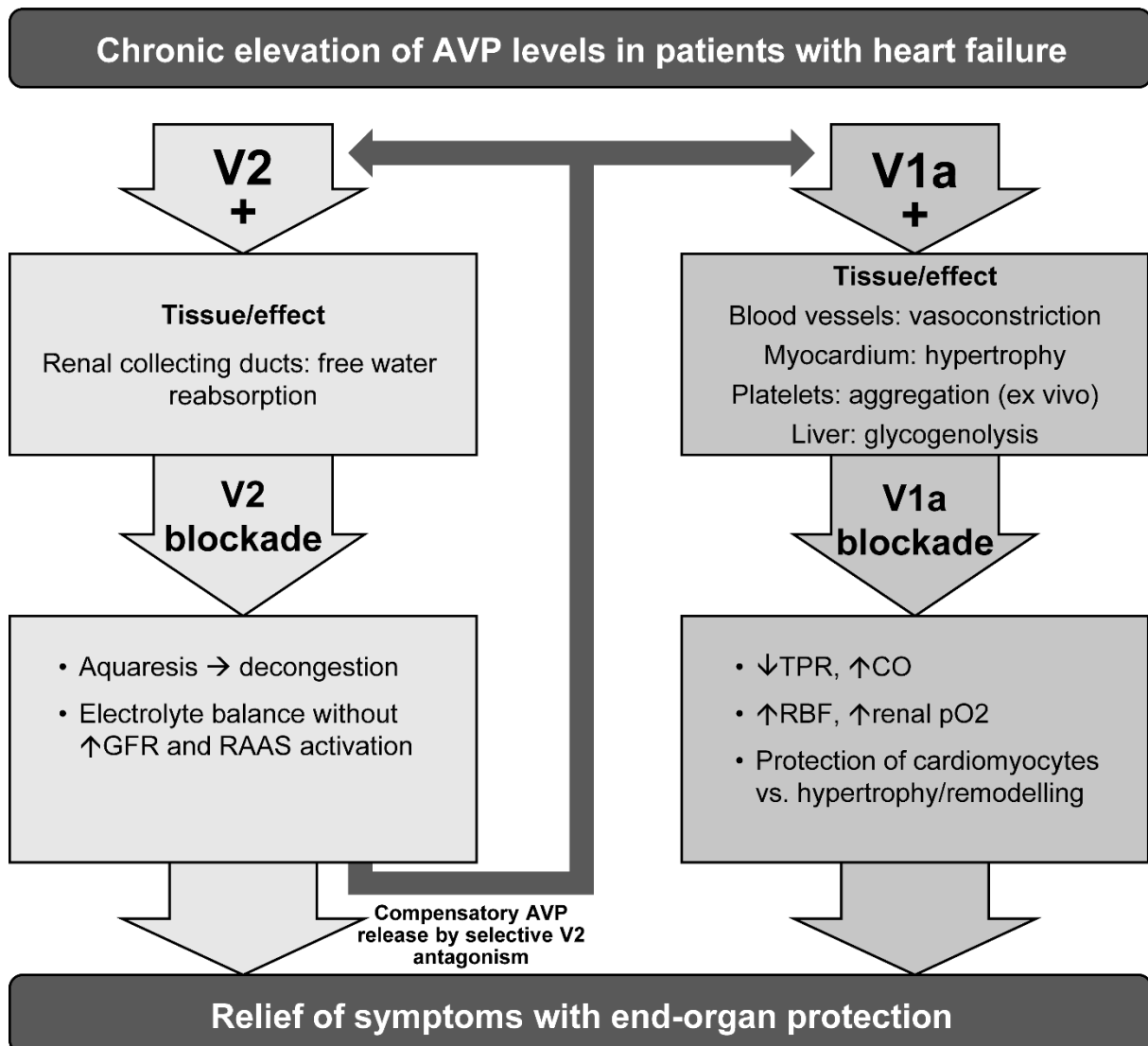


Figure 1. Vasopressin receptor antagonist profile in congestive heart failure. Chronic elevation of AVP levels in patients with heart failure leads to activation of both the V1a and the V2 receptor.⁸ Selective blockade of the V2 receptor has been shown to improve decongestion without RAAS activation or worsening renal function¹³ but results in compensatory AVP release leading to V1a receptor activation.³⁸ 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, cardio output; GFR, glomerular filtration rate; pO_2 , 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]

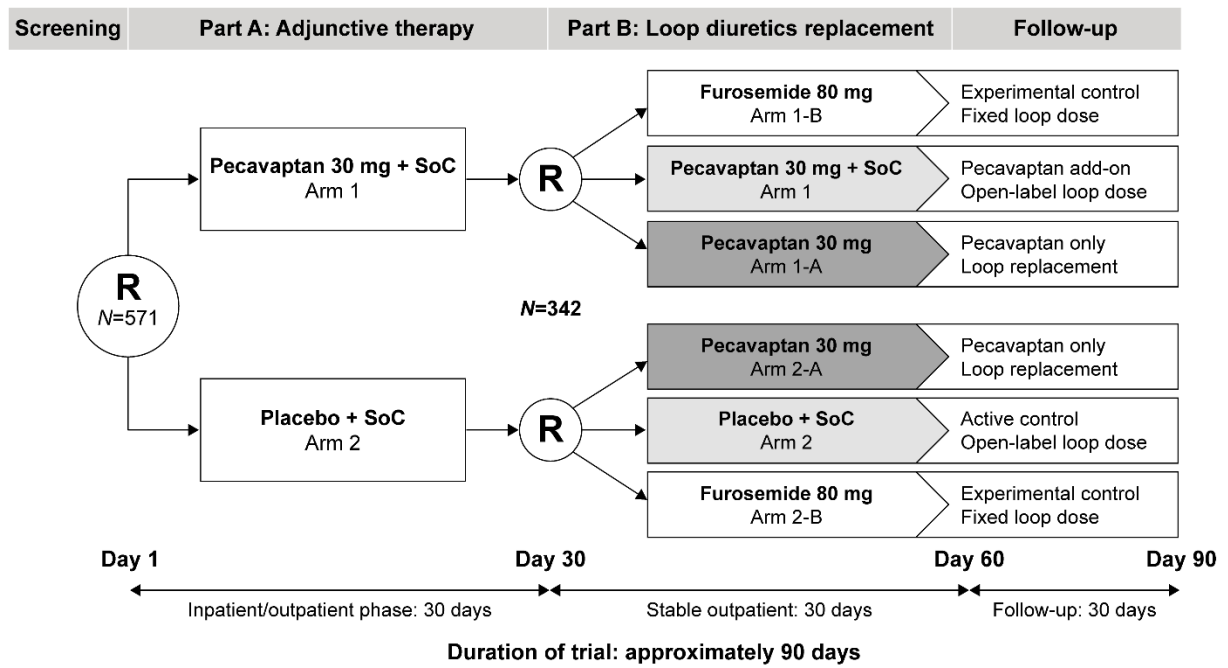


Figure 2. Study design

SoC, standard of care.

[2 column width; greyscale in print]

Tables

Table 1. Objectives

Primary objective	<ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• 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	<ul style="list-style-type: none">• Further evaluation of efficacy, safety, and patient-reported outcomes with pecavaptan when added to loop diuretics vs. loop diuretics alone in the 30–60-day period post-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 30–60-day period post-hospitalization• Further evaluation of the pharmacodynamics and pharmacokinetics of pecavaptan• Further evaluation of the effect of pecavaptan on exploratory biomarkers

HF, heart failure.

Table 2. Key inclusion and exclusion criteria.

Key inclusion criteria	Key exclusion criteria
<ul style="list-style-type: none"> • Age ≥ 18 years and ≤ 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 at least 12 weeks prior to 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 ≥ 40 mg of furosemide or equivalent, within 4 weeks prior to index hospitalization • At least one of the following parameters must be present on any day during Days 3–7 of the index hospitalization: <ul style="list-style-type: none"> – Natriuretic peptides (BNP/NT-proBNP): <ul style="list-style-type: none"> • Drop in BNP or NT-proBNP 	<ul style="list-style-type: none"> • Acute de novo HF • Stroke or carotid angioplasty within 3 months prior to screening • Implantation of a cardiac resynchronization therapy device within 3 months prior to 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 (e.g. nitrates) or IV inotropic support within 24 hours prior to randomization • Estimated glomerular filtration rate of < 30 mL/min/1.73 m² determined by the Modification of Diet in Renal Disease equation at screening; reassessments allowed as clinically needed • Serum potassium ≥ 5.5 mmol/L or ≤ 3.3 mmol/L at screening; reassessments allowed as clinically needed • Serum sodium ≥ 146 mmol/L or ≤ 130 mmol/L at screening; reassessments

<p>≤30% from admission values (if measured during index hospitalization) or</p> <ul style="list-style-type: none"> • BNP ≥500 pg/mL or NT-proBNP ≥1800 pg/mL at screening (Days 3–7 of index hospitalization) <p>– Body weight loss <0.4 kg per 40 mg furosemide at Day 4 of index hospitalization</p> <p>– Composite congestion score ≥3</p> <p>– Hypervolemic hyponatremia defined as serum sodium <136 mmol/L</p> <p>– In-hospital worsening renal function defined as increased serum creatinine ≥0.3 mg/dL compared to index hospitalization admission values and at least one of the following:</p> <ul style="list-style-type: none"> • Jugular venous pressure ≥10 cm on physical examination • Inferior vena cava diameter >21 mm • Inferior vena cava collapse with sniff <50% • ≥2 peripheral edema or pulmonary edema or pleural effusion on chest X-ray or 	<p>allowed as clinically needed</p> <ul style="list-style-type: none"> • Syndrome of inappropriate antidiuretic hormone secretion • Diabetes insipidus <p>Exclusion from Part B only</p> <ul style="list-style-type: none"> • 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 re-hospitalization 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
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clinical exam	
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A complete list of eligibility criteria can be found in online **Supplementary Table S1**.

BNP, brain natriuretic peptide; EF, ejection fraction; ER, emergency room; HF, heart failure;

IV, intravenous; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 3. Endpoints

Primary endpoints	<ul style="list-style-type: none">• Part A:<ul style="list-style-type: none">– Changes in body weight and serum creatinine (Day 1 vs. Day 30)• Part B:<ul style="list-style-type: none">– Changes in body weight and BUN/creatinine ratio (Day 30 vs. Day 60)
Secondary endpoints	<ul style="list-style-type: none">• Treatment-emergent adverse events (including serious adverse events)• Pharmacodynamics measured by change in augmentation index
Main exploratory endpoints	<ul style="list-style-type: none">• Efficacy endpoints:<ul style="list-style-type: none">– Composite of CV death, non-fatal myocardial infarction, and non-fatal stroke– Changes in the New York Heart Association 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 score²⁷• Safety endpoints:<ul style="list-style-type: none">– Number of subjects with worsening renal function, hypo- or hyperkalemia, or hyper- or hyponatremia– Urinary sodium/potassium ratio and urinary sodium concentration

	<ul style="list-style-type: none">• Patient-reported outcomes:<ul style="list-style-type: none">– Symptom frequency as measured by the Kansas City Cardiomyopathy Questionnaire• Pharmacokinetics and pharmacodynamics:<ul style="list-style-type: none">– Trough and peak concentrations of pecavaptan– Changes in thoracic fluid content (measured by ReDS™ device)– Changes in body weight– Pulse wave analysis• Biomarkers (e.g. NT-proBNP, aldosterone, renin, copeptin, KIM-1)
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BUN, blood urea nitrogen; CV, cardiovascular; KIM-1, kidney injury molecule 1; NT-proBNP, N-terminal pro-brain natriuretic peptide; ReDS, remote dielectric sensing.

Supplementary material

Table S1. Full inclusion and exclusion criteria

Full inclusion criteria	Full exclusion criteria
<ul style="list-style-type: none"> • Written informed consent • Ability to understand and follow study-related instructions • Age 18–85 years • Men must agree to use condoms during intercourse; women can only be enrolled if not of child-bearing potential • History of chronic HF (HF with reduced, preserved, or mid-range ejection fraction) on individually optimized treatment with HF medications for ≥ 12 weeks prior to index hospitalization • Admission to hospital with a primary diagnosis of decompensated HF including symptoms and signs of fluid overload requiring IV diuretic therapy in the emergency room or at any time between Day 1–3 of hospital admission (index hospitalization) • Patients on an average/usual total daily dose of loop diuretic ≥ 40 mg of furosemide or equivalent, within 4 weeks prior to index hospitalization 	<ul style="list-style-type: none"> • BMI < 18.5 kg/m² or > 35 kg/m² • Known hypersensitivity to the study drugs or excipients • Participation in another interventional clinical study or treatment with investigational medicinal product 30 days or five half-lives of the investigational drug prior to screening • Any other condition or therapy that would make the subject unsuitable for this study and would not allow participation for the full planned study period in the judgment of the investigator • Malignancy or other non-cardiac condition limiting life expectancy to < 1 year, per physician judgment • Known current alcohol and/or illicit drug abuse that may interfere with the subject's safety and/or compliance at the discretion of the investigator • Close affiliation with the investigational site or the sponsor

<p>At least one of the required signs and symptoms between Day 3–7 of the index hospitalization (see Table 2)</p>	<ul style="list-style-type: none"> • Subject is in custody by order of an authority or a court of law • Acute de novo HF • Active or history of acute inflammatory heart disease, ≤ 3 months prior to screening • Acute coronary syndrome or major CV surgery ≤ 3 months prior to screening • Implantation of a cardiac resynchronization therapy device ≤ 3 months prior to screening • Stroke or carotid angioplasty ≤ 3 months prior to screening • History of heart transplant or need for urgent heart transplantation, or presence of left ventricular assist device • Any primary cause of HF scheduled for surgery or interventional therapy • Hemodynamically significant ventricular arrhythmias or therapeutic defibrillator shock ≤ 4 weeks prior to screening • Resting HR while awake of < 50 bpm or > 110 bpm (in case of atrial fibrillation > 120 bpm) at the time of screening or at randomization • Symptomatic hypotension with systolic
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	<p>BP <95 mmHg during screening or at randomization</p> <ul style="list-style-type: none"> • Any systolic BP <85 mmHg during screening or at randomization • Complex congenital heart disease • Sepsis or ongoing systemic inflammation • Hypertrophic obstructive or restrictive cardiomyopathy • Requirement of mechanical support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation, or any ventricular assist device) or ultrafiltration/hemodialysis • Use of IV vasodilators (e.g. nitrates) or IV inotropic support within 24 hours prior to randomization or tolvaptan at any time during index hospitalization • Estimated glomerular filtration rate <30 mL/min/1.73 m², serum potassium ≥5.5 mmol/L or ≤3.3 mmol/L, or serum sodium ≥146 mmol/L or ≤130 mmol/L • Hepatic insufficiency classified as Child–Pugh B or C • Syndrome of inappropriate antidiuretic hormone secretion
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	<ul style="list-style-type: none"> • Diabetes insipidus • Concomitant treatment with potassium-sparing diuretic (with the exception of mineralocorticoid receptor antagonist) that cannot be stopped prior to randomization and for the duration of the treatment period • Concomitant treatment with strong and moderate inducers or inhibitors of CYP3A4 • Concomitant treatment with probenecid <p>Patients with the following characteristics were excluded from Part B only:</p> <ul style="list-style-type: none"> • Daily doses of furosemide (or the equivalent loop diuretic dose) of <40 mg or >200 mg at the final visit of Part A • Re-hospitalization 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 judgment of the investigator
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BMI, body mass index; BP, blood pressure; bpm, beats per minute; CV, cardiovascular; CYP3A4, cytochrome P450 3A4; HF, heart failure; HR, heart rate; IV, intravenous.

