

# Rationale and study design for a multicenter, randomized, double-blind, placebo-controlled study of the effects of tolvaptan on the acute and chronic outcomes of patients hospitalized with worsening congestive heart failure

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Hospitalizations for patients presenting with worsening heart failure are occurring with increasing frequency, but few strategies for treating these patients are supported by evidence from randomized clinical trials. Exacerbations of chronic heart failure are associated with significant rates of morbidity and mortality,<sup>1</sup> and hospitalizations related to heart failure are the primary cause for admissions in patients aged >65 years. In 1998, hospital discharges with a diagnosis of heart failure were reported to be 978,000, which represents a 160% increase since 1979.<sup>1</sup> Recent clinical trials for patients with advanced heart failure have reported 60-day mortality rates as high as 10%.<sup>2,3</sup> In the recent Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME CHF)<sup>3</sup> trial, 35% of the patients were rehospitalized or had died within 60 days after enrollment. These striking figures underscore the fact that, despite the proven benefits of angiotensin-converting enzyme (ACE) inhibitors,  $\beta$ -blockers, and spironolactone in the treatment of chronic heart failure, exacerbations are common, and morbidity and mortality rates in the heart failure population remain unacceptably high. Clearly, new therapies to improve clinical outcomes in the acute setting of heart failure are needed.

No treatment strategies tested in well-controlled, prospective trials have been shown to improve rates of morbidity and mortality in patients hospitalized with

exacerbations of chronic heart failure. Typically, these patients are treated with therapies targeted at resolving volume overload and improving hemodynamic function. Improvements in hemodynamic measures, however, have not consistently correlated with decreased rates of morbidity or mortality. Aggressive diuresis is often the first therapeutic modality employed in this population, and although such an intervention may translate into an improvement in the disease symptoms, it is not without risk. Patients with heart failure who receive high doses of diuretics are susceptible to hypotension, arrhythmias due to hypokalemia, and further neurohormonal activation.<sup>4</sup> Thus, novel agents that can achieve the goals of therapy—namely, symptomatic improvement, the prevention of hospital readmissions, and reduced rates of morbidity and mortality—are needed.

The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial was a randomized, double-blind, placebo-controlled study designed to evaluate the effect of tolvaptan, a novel antagonist of the vasopressin receptor subtype  $V_2$ , in patients hospitalized with acute exacerbations of chronic heart failure. This article discusses the rationale supporting  $V_2$  antagonism and presents the design of the first large trial of tolvaptan to investigate clinical end points in this population.

## Rationale for $V_2$ -receptor antagonism

Arginine vasopressin (AVP) is a neurohormone synthesized, stored, and released in the central nervous system. The physiologic actions of vasopressin in the setting of heart failure are problematic. The neurohormone is released in response to several factors, primarily an increase in plasma osmolality, severe hypovolemia, and hypotension. Its release is regulated by osmoreceptors throughout the nervous system and is also stimulated by other neurohormones, including

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**Table I.** Location and biologic effects of vasopressin receptors

Receptor type	Location	Biologic effects
V <sub>1a</sub>	Vascular smooth muscle, myometrium, bladder, adipocytes, hepatocytes, platelets, renal medullary interstitial cells, vasa recta in renal microcirculation, epithelial cells in renal cortical collecting duct, spleen, testis, multiple CNS structures	Vasoconstriction, glycogenolysis, platelet aggregation, ACTH release, growth of vascular smooth muscle cells
V <sub>1b</sub>	Adenohypophysis	
V <sub>2</sub>	Principal cells of renal collecting duct	Increased water permeability of collecting duct

CNS, Central nervous system; ACTH, adrenocorticotropic hormone.

angiotensin II, which has been shown to stimulate neurons responsible for the release of vasopressin, both centrally and peripherally. The stimulation of vasopressin release by angiotensin II may be one explanation for the elevated vasopressin levels observed in patients with heart failure. Data from the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment studies demonstrated that heart failure patients had elevated levels of AVP compared with control groups.<sup>5</sup>

Vasopressin exerts its effects through interactions with vasopressin receptors, 2 types of which have been identified: V<sub>1</sub> and V<sub>2</sub>, with V<sub>1</sub> receptors being further divided into V<sub>1a</sub> and V<sub>1b</sub>. The location and effects of these receptors and their subtypes are displayed in Table I. In general, vasopressin promotes vasoconstriction via cyclic adenosine monophosphate (cAMP)—independent V<sub>1a</sub> receptors on the vascular wall and water resorption in the kidneys via cAMP-dependent V<sub>2</sub> receptors. The most significant effects of vasopressin are mediated via the V<sub>2</sub> receptor, where vasopressin increases water permeability of the renal collecting duct. In addition, V<sub>2</sub> receptor-mediated effects are observed with lower vasopressin concentrations than those required to elicit effects mediated by V<sub>1</sub>. Thus, the V<sub>2</sub> receptor stimulation that promotes water resorption likely occurs early in patients with heart failure, when plasma vasopressin levels begin to rise.<sup>6</sup> Inhibition of AVP at the V<sub>2</sub> receptor induces a pure water diuresis (aquaresis) without causing a depletion of electrolytes or the activation of neurohormonal systems. Patients in whom such inhibition has occurred lose free water, which may lower their potential for the adverse effects typically associated with loop diuretics, such as hypotension, hypokalemia, and activation of the renin-angiotensin-aldosterone system. Two vasopressin receptor blockers that have been used in patients with heart failure are conivaptan and tolvaptan.<sup>7</sup> Acute IV administration

of conivaptan, a nonspecific V<sub>1a</sub> and V<sub>2</sub> receptor antagonist, has been shown to produce favorable hemodynamic changes as well as to increase urine output in patients with advanced heart failure.<sup>8</sup> Compared with placebo, this agent significantly reduced PCWP and right-atrial pressure; however, it did not affect cardiac index, systemic or pulmonary vascular resistance, BP, or heart rate. Chronic therapy with tolvaptan, an oral V<sub>2</sub> receptor antagonist, when used in patients with mild heart failure in addition to standard therapy including diuretics, has resulted in increased urine output and decrease in body weight and edema.<sup>9</sup> Tolvaptan has also been shown to normalize serum sodium in patients with heart failure and hyponatremia.<sup>10</sup>

### Design of the ACTIV in CHF trial

ACTIV in CHF was a prospective, randomized, double-blind, placebo-controlled, parallel-group trial that studied the use of 3 doses of tolvaptan, an oral non-peptide vasopressin V<sub>2</sub>-receptor antagonist, given once a day to patients hospitalized for worsening heart failure. The study was sponsored by Otsuka. Candidates for the trial were required to have New York Heart Association (NYHA) class III or IV heart failure, left ventricular ejection fraction (LVEF) of <40% within the previous 12 months, and at least 2 signs of heart failure. (The specific eligibility criteria are displayed in Table II.) The patients who met the entry criteria were informed of the study's purposes, procedures, risks, and potential benefits, and were asked to provide informed consent. Those who entered the trial were then randomized in a 1:1:1:1 fashion to treatment with placebo or with 30 mg, 60 mg, or 90 mg of tolvaptan; those randomized to the study medication received it at 9 AM, within 1 hour of the time of randomization.

Patients treated with tolvaptan received the therapy daily for the duration of their hospitalization, provided

**Table II.** Eligibility criteria for patients in the ACTIV in CHF trial

**Inclusion criteria**

- Age  $\geq 18$  years
- NYHA class III or IV cardiac disease at screening
- Two of the following signs of heart failure: elevated JVD, rales, chest x-ray with signs of radiographic congestion, pedal edema, increased abdominal girth, weight gain  $>10$  pounds above baseline
- Admission to hospital for heart failure within 96 hours of screening

**Exclusion criteria**

- Women of child-bearing potential without acceptable method of contraception
- Pregnancy or lactation
- Cardiac surgery within 60 days except for percutaneous intervention
- History of myocardial infarction within 30 days
- History of sustained ventricular tachycardia or ventricular fibrillation within 30 days unless automatic implantable cardioverter defibrillator was present
- CHF related to tachyarrhythmias or bradyarrhythmias
- Angina at rest or with slight exertion and/or unstable angina
- Hemodynamically significant primary cardiac valvular disease
- Hypertrophic cardiomyopathy
- History of cerebrovascular accident within the previous 6 months
- Significant hepatic, renal, or hematologic disorder or dysfunction beyond that which could be expected from CHF alone
- CHF due to uncorrected thyroid disease, active myocarditis, or known amyloid cardiomyopathy
- Systolic arterial blood pressure  $<110$  mm Hg
- Use of the following inhibitors of the CYP 3A4 enzyme within 7 days: ketoconazole, troleandomycin, miconazole, cimetidine, clotrimazole, danazol, dexamethazone, diltiazem, erythromycin, fluconazole, gestodene, indinavir, itraconazole, triacetyl oleandomycin, quinidine, quinine, ritonavir, saquinavir, verapamil, zafirlukast, azithromycin
- Ingestion of grapefruit or grapefruit juice while on study drug
- Use of amiodarone within 10 weeks
- History of hypersensitivity and/or idiosyncratic reaction to benzazepine derivatives
- Requirement for treatment with nonsteroidal anti-inflammatory agents or aspirin at a dose  $>700$  mg/day
- History of drug or medication abuse within the past 12 months, or current alcohol abuse
- Serum potassium level  $<3.5$  mEq/L or  $>5.3$  mEq/L
- Uncontrolled diabetes mellitus
- Urinary tract obstruction
- Morbid obesity
- Presence of malignancy
- Participation in another clinical drug trial within 30 days
- Previous participation in any tolvaptan clinical trial
- Terminally ill or moribund condition with little chance of short-term survival
- The donation of blood or plasma within 30 days before study enrollment

ACTIV in CHF, Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure; NYHA, New York Heart Association; CHF, chronic heart failure; JVD, jugular venous distention; CYP, cytochrome  $P_{450}$ .

the length of stay after randomization did not exceed 10 days; those remaining in the hospital after 10 days of therapy were counted as treatment failures and the drug was discontinued. Patients in the tolvaptan group continued to receive the agent for 7 weeks of out-patient therapy. They returned for follow-up visits at weeks 1, 3, 5, and 7 after hospital discharge to undergo a repeat of study procedures, which included the following: physical examination; heart failure and cardiovascular assessments; measurement of vital signs and weight; the performing of 12-lead electrocardiograms (ECGs); tests for urine sodium creatinine and osmolality; clinical and pharmacokinetic laboratory tests; completion of physician- and patient-assessed clinical and symptom scales; recording of concomitant medications; and the assessment of adverse events related to the study treatment.

ACTIV in CHF was designed with 2 primary end points. The primary end point for the in-patient phase was the change in body weight at 24 hours after the first dose of tolvaptan. The primary end point for the 7-week out-patient phase was the clinical worsening of heart failure as defined by the following events: the requirement for rehospitalization; an unscheduled visit for the treatment of heart failure to an emergency department or an out-patient clinic; a  $<24$ -hour stay in an observation unit associated with the need for either increased therapy or a new therapy for heart failure; or death. All clinical events were adjudicated by physicians in an independent end point committee. Secondary end points included NYHA classification, dyspnea, orthopnea, body weight at discharge, edema, rales, jugular venous distension, hepatomegaly, fluid intake, daily urine output, daily serum electrolytes, length of

hospital stay, diuretic usage, physician-assessed clinical scales, and patient-assessed symptoms scales. Another objective of the trial was to demonstrate the safety of tolvaptan therapy in patients hospitalized for worsening heart failure. Each patient remained in the study until its completion, unless the patient's serum sodium level measured  $\geq 146$  mEq/L or potassium level measured  $\geq 6$  mEq/L. The safety of participants was evaluated by monitoring adverse events and vital signs and by conducting safety laboratory tests, ECGs, and physical examinations.

ACTIV in CHF enrolled 320 patients from 50 centers in the United States and South America. The study's sample size was based on the assumption that 50% of the participating patients would experience the events specified as the primary outcome measures at the end of 7 weeks. It was expected that treatment with tolvaptan would reduce the occurrence of these events by 22%. The sample size of 320 patients (80 per arm) was estimated to have an 80% power ( $\alpha = 0.05$ ) to detect this difference in clinical outcomes, and a  $>80\%$  power to detect a 1.5 kg mean change from baseline body weight at 24 hours between patients in any of the 3 tolvaptan-treated groups compared with the placebo group. An intention-to-treat analysis will be conducted and will include all patients receiving at least 1 dose of the study drug.

## Summary

The identification of novel approaches for the treatment of volume overload in patients with heart failure is urgently needed. The current standard of care for this population involves the administration of loop diuretics. It is well documented that high doses of these agents increase the activity of the renin-angiotensin system; in addition, the use of loop diuretics in the setting of heart failure may increase the risk of arrhythmic death caused by electrolyte depletion, and decrease the patient's tolerability of life-saving therapies such as ACE inhibitors.

The introduction of the mechanism of  $V_2$  antagonism holds promise for the treatment of exacerbations of chronic heart failure and provides a rational approach to therapy in the acute setting of this disease. This treatment approach, however, must be supported by data from controlled clinical trials that demonstrate the safety of  $V_2$  antagonism as a therapeutic measure and its association with improvements in clinical outcomes. In this regard, the ACTIV in CHF trial makes an important contribution to heart failure research, and its findings will offer insight into the future role of vasopressin antagonism in the treatment of heart failure.

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## Appendix

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