CLINICAL PROTOCOL

AQUARESIS UTILITY FOR HYPONATREMIC ACUTE HEART FAILURE (AQUA-AHF) STUDY

Protocol #: HS-13-00705
Phase IV

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Protocol Synopsis

AQUARESIS UTILITY FOR HYPONATREMIC ACUTE HEART FAILURE (AQUA-AHF) STUDY **Protocol #** HS-13-00705	
Study Type	Prospective, randomized, open-label, parallel-group
Hypothesis	Volume management of acute congestive heart failure complicated by hyponatremia with a vasopressin-receptor antagonist-based aquaretic regimen is more effective and with fewer adverse events than a loop diuretic-based regimen.
Objectives	1. Compare urine output and length of hospital stay between a vasopressin receptor antagonist-based regimen to a loop diuretic-based regimen for hyponatremic heart failure patients hospitalized with evidence of volume overload. 2. Compare the safety (renal function, electrolyte abnormalities, and hemodynamics) of vasopressin receptor antagonist-based to a loop diuretic-based regimen for hyponatremic heart failure patients hospitalized with evidence of volume overload.
Interventions	1. Tolvaptan (with rescue loop diuretic or metolazone). 2. Furosemide (with rescue metolazone) Eligible patients will be randomized within 48 hours of presentation to the hospital. Tolvaptan will be dosed initially at 30mg daily, with the option to titrate up to a maximum of 60mg daily. Furosemide will be initiated as a continuous infusion at 5mg/h, with the option to titrate higher. Monotherapy with the study medication must be continued for at least the first 24 hours. If after 24 hours the diuretic response is deemed inadequate, the dose of study medication may be increased and/or the use of additional diuretic agents may be initiated at the discretion of the treating physician. Physicians will be encouraged to increase the primary study drug before the use of additional diuretic agents as clinically acceptable.
Patient Population	N=50 Requiring hospitalization for acute heart failure with evidence of volume overload, and a serum sodium concentration of < 135 mEq/L documented within the first 48 hours of the admission. Initial treatment with diuretics prior to randomization is allowable. A maximum of 25 patients will be enrolled with serum sodium concentrations between 130 to 134 mEq/L as the inclusion.
Inclusion Criteria	Acute HF with signs or symptoms of volume overload (i.e. elevated JVP, rales, edema) Serum sodium < 135 mEq/L at time of or within first 48 hours of hospitalization Randomized within 48 hours of presentation to hospital ≥ 18 years of age Informed consent

Exclusion Criteria	Severe symptomatic hyponatremia requiring acute treatment (Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms e.g. any seizure activity or any neurologic impairment deemed to require immediate treatment by the primary treating physician) Severe renal impairment upon admission (creatinine clearance < 20 mL/min) Renal replacement therapy dependent, or requiring upon admission Acute coronary syndrome on admission Evidence of cardiogenic shock or requiring intravenous vasopressors VAD Pregnancy Patient requiring concomitant use of strong CYP3A4 inhibitors (clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and telithromycin)
Primary Endpoints	Primary efficacy endpoint: Mean urine output at 24 hours post randomization Primary safety endpoint: Mean change in serum creatinine at 24 hours post randomization
Secondary Endpoints	<u>Efficacy:</u> Urine output at 8, 48, 96 hours post-randomization, total at discharge Mean hourly urine output at 24 hours Serum sodium change at 8, 24, 48, 96 hours, and at discharge Weight change at 24, 48, 96 hours, and at discharge Cumulative furosemide dose at 48, 96 hours, and at discharge Cumulative use of metolazone at 48, 96 hours, and at discharge Self-rated change in dyspnea (Likert Scale) at 24 and 96 hours <u>Safety:</u> GFR change at 24, 48, 96 hours, and at discharge (estimated from Scr) Acute worsening of kidney function (increase in Scr 0.3 mg/dL or 25% above baseline) Electrolyte abnormalities (hypokalemia, hypomagnesemia, hyper/hyponatremia) Hypotension Changes in plasma renin activity, copeptin, cystatin C concentrations, NT-proBNP In-hospital mortality Hospital length of stay (ICU and total)
Statistical Plan	A total of 50 patients (25 in each group) would provide 93% power to detect a difference of 50% in urine output at 24 hours between treatments, alpha=0.05. The power was calculated based on the magnitude of difference in urine output seen in the ACTIV-CHF (24 hour mean urine output for tolvaptan was approximately 4100±2100mL vs 2300±1100mL compared to placebo when added to standard therapy) and in the Udelson et al study (24 hour mean increase in urine output with tolvaptan monotherapy 2600±1500mL vs 900±850mL with furosemide). Based on our previous data demonstrating poor response to loop diuretics in the hyponatremia acute HF population, we believe

	a 50% difference (standard deviation of 25%) is a reasonable and conservative estimate of what the difference will likely be. Descriptive statistics will be computed for each treatment group. For all comparative analyses between the two treatment groups, independent samples t-test and Chi-Square test (or Fisher's exact test) will be performed for continuous variables or categorical variables, respectively. If either the normality or equal-variance assumptions underlying the traditional t-tests are violated, a non-parametric test will be used. *Amendment August 9, 2017:* *Due to slow enrollment, we anticipate not achieving our desired sample size of 50 subjects. Our revised power calculation reveals that if we achieve a mean difference with the same magnitude standard deviation between groups (e.g. mean difference is 1000±1000mL), our power will be between 80-90% with a sample size between 34-46 subjects. Based on current rate of enrollment, it is likely that we will achieve a sample of at least 34 subjects, which should allow the results to be meaningful despite early termination of enrollment.*
Study Duration	18 months

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List of Abbreviations

CRF – case report form
CYP450 – cytochrome P-450 oxidative enzymes
GFR – glomerular filtration rate
HF – heart failure
HIPAA – Health Insurance Portability and Accountability Act
ICU – intensive care unit
JVP – jugular venous pulsation
LVSD – left ventricular systolic dysfunction
NYHA FC – New York Heart Association Functional Classification
PRA – plasma renin activity
RAAS – Renin-Angiotensin-Aldosterone System
Scr – serum creatinine concentration
UO – urine output

1. Introduction

1.1 Hyponatremia in Hospitalized Patients

Hyponatremia is one of the most commonly encountered electrolyte abnormalities in hospitalized patients.[1-5] In clinical practice, hyponatremia is usually defined as serum sodium of ≤ 135 mmol/L (mEq/L). Although hyponatremia is commonplace in the hospitalized setting, the true incidence of this condition remains poorly characterized. Zilberberg and colleagues in a retrospective cohort study of over 190,000 patients reported a 5.5% incidence of hyponatremia at the point of hospital admission.[6] However, other studies suggest that the incidence may be as high as 15%.[1]

Extensive literature suggest that hyponatremia in the hospitalized setting is associated with an increase in mortality. Uncontrolled trials have reported mortality in hyponatremic patients ranging from 5-51% depending on study design and serum sodium cut- offs. One prospective observational, case controlled study found that mortality of hospitalized patients with hyponatremia was 27% compared to 9% in normonatremic patients.[7] This study also found that patients with hyponatremia had higher serum creatinine concentrations and longer length of hospital stays as compared to controls. Zilberberg et. al. also found a higher in-hospital mortality rate in hyponatremic patients (5.9%) compared to normonatremic patients (3%).[6] In addition, even mild hyponatremia (serum sodium concentration between 130-134 mEq/L) may be detrimental, increasing in-hospital mortality by 37% compared to those with normonatremia.[2] It remains unclear why hyponatremia is associated with increased mortality. It is hypothesized that hyponatremia may be a signal for important physiologic abnormalities in patients with cardiovascular diseases, or a predictor of other severe consequence associated with sodium irregularities such as cerebral edema.[2]

1.2 Hyponatremia and Heart Failure Outcomes

Heart failure (HF) patients are especially prone to developing hyponatremia. Several retrospective analyses have reported the prevalence of hyponatremia in the chronic HF population to be 19.7-27% based on admission serum sodium concentrations.[8-12] Heart failure patients often develop hypervolemic hyponatremia due to water retention which is associated with excessive neurohormonal stimulation.[13] However, hyponatremia may also persist in HF patients who are euvolemic.

Hyponatremia is frequently regarded as a marker for the severity of HF. Several studies have suggested that hyponatremia in HF is associated with increased length of stay, morbidity, and mortality.[8-12] In the OPTIMIZE-HF registry, lower admission sodium (<135 mmol/L) was associated with higher in-hospital mortality (6.0% vs. 3.2%), longer length of stay (6.4 days vs. 5.5 days), and 60-90 day mortality (12.4% vs. 7.1%) compared to normal admission sodium. For each 3 mmol/L decrease in admission sodium below 140 mmol/L, the risk of in-hospital mortality was increased by 19.5% in patients with left ventricular systolic dysfunction (LVSD) and by 8.6% in patients with non-LVSD.[9] Similarly, in the OPTIME-CHF trial, patients with the lowest baseline serum sodium (median < 134 mmol/L) experienced longer length of hospital stays, and higher in-hospital and 60-day mortality. Consistent with the results from OPTIMIZE-HF, each 3 mmol/L decrease in admission sodium values was associated with an 18% relative increase in the probability of death within 60 days.[8] In a study of HF patients with preserved left ventricular ejection fraction, Rusinaru et. al. demonstrated hyponatremia was a powerful predictor of 7-year mortality.[12] One limitation of all the above studies was that the assessment of hyponatremia was made based solely on admission serum sodium concentrations. Results from the ESCAPE trial suggest that a significant proportion of normonatremic patients on admission also developed hyponatremia during the hospitalization. This study found a 15.9% incidence of acute hyponatremia, although the association

to patient outcomes was not assessed.[11] However, we recently demonstrated that acute hyponatremia has the same prognostic value as hyponatremia detected upon admission.[14] There is now mounting evidence that hyponatremia is more than just a marker of disease severity. The ACTIV in CHF trial suggested that correction of hyponatremia was associated with a survival advantage. The 60-day mortality among patients with serum sodium levels that improved was 11.1% compared to 21.7% in those with persistent hyponatremia.[10]

1.3 Hyponatremia and Treatment Response

In addition to its prognostic value, hyponatremia may have importance during the acute management of HF i.e. influencing responses to treatment. One concern related to the pharmacologic management of acute HF is the development of hypotension. Data from ADHERE, a registry of acute HF patients, demonstrated that low systolic blood pressure is an independent predictor of in-hospital mortality.[15] Hyponatremia may predispose patients to hypotension. In the OPTIME-CHF study, sustained hypotension defined as a low systolic blood pressure for > 30 minutes requiring intervention, was more common in patients within the lowest quartile of serum sodium (132-135 mEq/L).[8] We also demonstrated that hyponatremia was associated with an increased risk of sustained hypotension in our acute HF patient population.[14]

Another major concern in the management of acute HF is diuretic resistance. Patients on chronic loop diuretic therapy may fail to respond to escalating doses of diuretics. One proposed mechanism is the routine use of diuretics, which promotes the excretion of sodium, leads to the development or exacerbation of hyponatremia.[13,16] Decreased sodium delivery to the kidney as a result of the decreased plasma sodium concentration would stimulate the macula densa to release renin, thereby activating the renin-angiotensin-aldosterone system (RAAS). This increase in RAAS activation may lead to further vasoconstriction and water retention, essentially counteracting the desired diuretic effect. In support of this contention, we've recently shown that acute or chronic hyponatremia, especially <130 mEq/L, was associated with higher loop diuretic dose requirements and more frequent need for escalation of the diuretic regimen to achieve the same level of diuresis as normornatremic HF patients.[14] Severity of hyponatremia was also associated with a greater than two-fold increase in the incidence of diuretic resistance, acute worsening renal function, sustained hypotension, increased length of stay, and in-hospital mortality. Our study results raised two important questions: 1) whether correction of hyponatremia can prevent or lower the risk of complications with conventional diuretics and 2) whether alternative treatments such as aquaretics (i.e. vasopressin receptor antagonists) represent a superior treatment modality for these patients.

1.4 Tolvaptan and Volume Management in Heart Failure

Aquaresis with tolvaptan represents a potentially advantageous approach to the management of volume overload in HF, especially in patients presenting with concomitant hyponatremia. Several prospective, randomized, controlled trials have clearly demonstrated the efficacy of tolvaptan for augmenting diuresis when administered in combination with furosemide for the management of congestive HF symptoms.[17-22] In addition, tolvaptan was also associated with a favorable safety profile, devoid of significant effects on serum electrolytes and incidence of acutely worsening renal function. The potential for tolvaptan to be used as an alternative to furosemide was recently considered in a study by Udelson et al.[23] Eighty-three patients with stable NYHA FC II-III systolic HF and evidence of congestive symptoms were randomized to tolvaptan 30mg, furosemide 80mg, or the combination for 7 days. Tolvaptan was associated with a significantly greater daily urine output (approximately 1700mL/24h greater than furosemide monotherapy) and decrease in body weight compared to furosemide or the combination. Importantly, this study did not evaluate patients in an acute

decompensated state, included only systolic HF patients, did not allow titration of diuretic doses, and was limited to comparison with furosemide administered orally. Our data indicating poor outcomes with loop diuretics in hyponatremic acute HF patients, along with the Udelson study, suggest that tolvaptan may be a superior treatment modality for patients presenting in acute HF complicated by hyponatremia. These are clinically challenging patients to manage due to their poor response to loop diuretics and their propensity for adverse effects. Hence they represent an important niche for alternative diuretic strategies. Therefore, there is a **critical need to evaluate the role of tolvaptan monotherapy as a first-line option** for the treatment of these clinically complex patients. The purpose of the current study is to prospectively evaluate the comparative efficacy and safety of a tolvaptan-based diuretic regimen compared to conventional diuresis with a furosemide-based regimen on short-term clinical and treatment outcomes in hyponatremic acute HF patients.

2. Study Rationale and Objectives

Hyponatremia is the most common electrolyte abnormality in the hospital setting.[1,3] Hyponatremia, based on admission values, has been associated with higher in-hospital mortality, 60-day mortality, longer length of hospital stay, and requirement for hospital readmissions.[2,4,5] Similar findings are applicable to hospitalized HF patients as well.[8-11] However despite these associations, the importance of hyponatremia to influence acute treatment decisions in acute HF remains equivocal due to a lack of data. Importantly, we've recently shown that moderate to severe hyponatremia, especially <130 mEq/L, was associated with higher loop diuretic dose requirements and more frequent need for escalation of the diuretic regimen to achieve the same level of diuresis as normornatremic patients.[14] Severity of hyponatremia was also associated with a greater than two-fold increase in the incidence of diuretic resistance, acute worsening renal function, sustained hypotension, increased length of stay, and in-hospital mortality. Our study results raised two important questions: 1) whether correction of hyponatremia can prevent or lower the risk of complications with conventional diuretics and 2) whether alternative treatments such as aquaretics (i.e. vasopressin receptor antagonists) represent a superior treatment modality for these patients? Data from small subgroups of hyponatremic patients in the EVEREST and ACTIV-CHF studies indicated that tolvaptan is effective at raising serum sodium and urine output in these patients.[20,21] In addition, tolvaptan monotherapy was shown to exert a greater effect on urine volume and weight loss than a fixed dose of furosemide in stable NYHA FC II-III systolic HF patients.[23] However, these were not acutely decompensated patients, and a fixed dose of tolvaptan was being compared to fixed dose oral furosemide. Therefore, there is a **critical need to evaluate the role of aquaresis with tolvaptan as an acute treatment modality for acute HF complicated by hyponatremia**. These patients pose a particularly difficult challenge when attempting to gain effective diuresis with loop diuretics. The **purpose** of the current study is to prospectively evaluate the comparative efficacy and safety of a tolvaptan-based diuretic regimen compared to conventional diuresis with a furosemide-based regimen on short-term clinical and treatment outcomes in hyponatremic acute HF patients. Both reduced and preserved left ventricular systolic function patients will be studied.

The following are the study objectives:

1. Compare urine output and length of hospital stay between a vasopressin receptor antagonist-based regimen to a loop diuretic-based regimen for hyponatremic heart failure patients hospitalized with evidence of volume overload.
2. Compare the safety (renal function, electrolyte abnormalities, hemodynamics, neurohormonal activation) of vasopressin receptor antagonist-based to a loop diuretic-based regimen for hyponatremic heart failure patients hospitalized with evidence of volume overload.

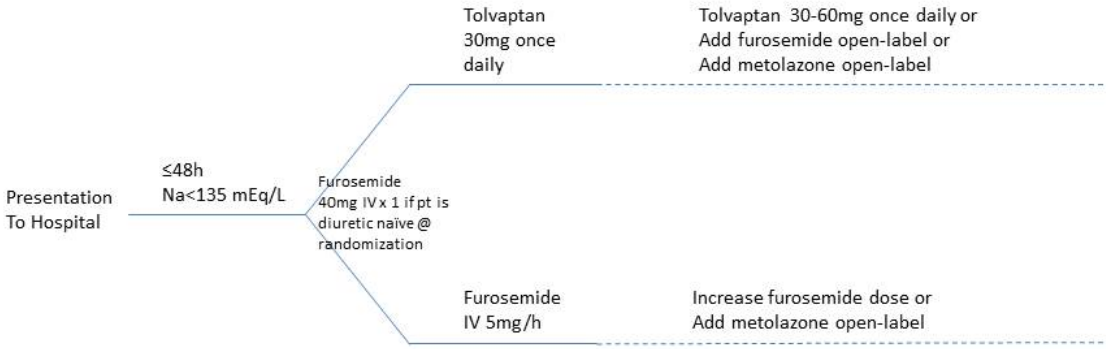
3. Study Design

3.1 Trial Design

3.1.1 Design

This will be a prospective, open-label, parallel-group, randomized study comparing a tolvaptan-based aquaretic regimen to a conventional continuous infusion loop diuretic-based regimen of furosemide. The initial 24 hours of study treatment will compare tolvaptan monotherapy to furosemide monotherapy. After the initial 24 hours, treatment regimens may be altered to achieve desired clinical goals.

3.1.2 Study Procedures Overview



	≤48h	Randomization	8 hours	24 hours	48 hours	72 hours	96 hours	Discharge
Inclusion / Exclusion	X							
Vitals		X	X	X	X	X	X	X
Labs		X	X	X	X	X	X	X
Cystatin C		X		X			X	
PRA/copeptin /BNP		X		X			X	
UO		X	X	X	X	X	X	X
Weight		X		X	X	X	X	X
Furosemide dose eq.		X	X	X	X	X	X	X
Dyspnea scale				X				X

3.1.3 Study Duration

Study subject enrollment to occur over a 12-18 month period. Data analysis will occur simultaneously once the final subject has been discharged from the hospital since no long term follow-up is planned.

3.2 Study Endpoints

3.2.1 Efficacy Endpoints

Primary efficacy endpoint:
Mean urine output at 24 hours post randomization

Secondary efficacy endpoints:
Urine output at 8, 48, 96 hours post-randomization, total at discharge
Mean hourly urine output at 24 hours
Serum sodium change at 8, 24, 48, 96 hours, and at discharge
Weight change at 24, 48, 96 hours, and at discharge
Cumulative furosemide dose at 48, 96 hours, and at discharge
Cumulative use of metolazone at 48, 96 hours, and at discharge
Change in self-rated dyspnea (Likert Scale) at 24 and 96 hours

3.2.2 Safety Endpoints

Primary safety endpoint:
Mean change in serum creatinine at 24 hours post randomization

Secondary safety endpoints:
GFR change at 24, 48, 96 hours, and at discharge (estimated from Scr)
Acute worsening of kidney function (increase in Scr 0.3 mg/dL or 25% above baseline)
Electrolyte abnormalities (hypokalemia, hypomagnesemia, hyper/hyponatremia)
Hypotension
Changes in plasma renin activity, copeptin, NT-proBNP, and cystatin C concentrations
In-hospital mortality
Hospital length of stay (ICU and total)

3.3 Study Population

3.3.1 Inclusion Criteria

- Requiring hospitalization for acute HF with signs or symptoms of volume overload (i.e. elevated JVP, rales, edema)
- Serum sodium <135 mEq/L at time of or within first 48 hours of hospitalization (A maximum of 25 patients will be enrolled with serum sodium concentrations between 130 to 134 mEq/L as the inclusion).
- Randomized within 48 hours of presentation to hospital
- ≥ 18 years of age
- Informed consent

3.3.2 Exclusion Criteria

- Severe symptomatic hyponatremia requiring acute treatment (Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms e.g. any seizure activity or any neurologic impairment deemed to require immediate treatment by the primary treating physician)

- Severe renal impairment upon admission (creatinine clearance < 20 mL/min)
- Renal replacement therapy dependent, or requiring upon admission
- Acute coronary syndrome on admission
- Evidence of cardiogenic shock or requiring intravenous vasopressors
- Pregnancy
- Patient requiring concomitant use of strong CYP3A4 inhibitors (clarithromycin, ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, nefazodone, and telithromycin)

3.3.3 Informed Consent
Signed written informed consent will be obtained prior to initiating any study procedure for each patient. A signed copy of the Right of Research Participants and the Informed Consent, will be provided to each study subject, one copy in the patient medical records, and one copy retained by the investigators.

3.4 Randomization

3.4.1 Randomization Procedure
If a patient is suitable to participate in the study and has given signed informed consent, the patient will be assigned a study number and randomized to one of the treatment arms. Randomization will occur using a computer generated randomization list prepared by the principal investigator using a 10-block scheme prior to enrollment of the first study subject. Randomization will also be stratified based on serum sodium at inclusion to 130-134 mEq/L and <130 mEq/L.

3.4.2 Study Drugs
Study drugs (and scheduled in-patient medications) will be administered in an open-label fashion.

Patients randomized to tolvaptan will receive the study medication orally once daily. Tolvaptan tablets will be administered at 24 hour intervals, scheduled based on when the initial dose is received.

Patients randomized to furosemide will receive the medication as a continuous infusion. The loop diuretic furosemide will be prepared as per standard procedures of the hospital pharmacy for administration via continuous intravenous infusion.

After the initial 24 hour monotherapy period, escalation of the treatment regimen for either study arm will be either based on a minimum urine output < 100 mL/h or otherwise at the discretion of the primary treating physician to achieve clinical goals (e.g. relief of dyspnea, improvement in peripheral edema, resolution of jugular venous distention, improvement in pulmonary congestion based on chest radiograph, etc.). Patients randomized to furosemide will not be eligible to receive tolvaptan as a mode to treatment escalation. Tolvaptan dose will not be increased if serum sodium rises > 8 mEq/8 hours or >12 mEq/24h.

3.5 Study Procedures

3.5.1 Screening
Patients eligible for enrollment will be screened for inclusion and exclusion criteria by one of the approved study investigators. This includes assessment and documentation of patient's past and current medical history, current admitting diagnosis, medications on admission, physical exam, and

laboratory tests. If the patient meets inclusion and exclusion criteria, signed written informed consent will be obtained. Pregnancy test will be obtained in women of childbearing age.

3.5.2 Randomization
Implementation and documentation of the following procedures:
Vital statistics
Laboratory tests obtained
Blood drawn for cystatin C, plasma renin activity, NT-proBNP, and copeptin A
Urine sample (for future analyses)
Fluid balance and urine output
Body weight
Study drug dispensed and initiation time recorded
Administer dyspnea survey (Likert Scale)

3.5.3 8 hours
Implementation and documentation of the following procedures:
Vital statistics
Laboratory tests obtained
Fluid balance and urine output
Recording of any patient or physician reported adverse events

3.5.4 24 hours
Implementation and documentation of the following procedures:
Vital statistics
Laboratory tests obtained
Blood drawn for cystatin C, plasma renin activity, NT-proBNP, and copeptin A
Urine sample (for future analyses)
Fluid balance and urine output
Body weight
Recording of any patient or physician reported adverse events
Study drug continued and/or adjustments to treatment regimen
Administer change in dyspnea survey (Likert Scale)

3.5.5 48 hours
Implementation and documentation of the following procedures:
Vital statistics
Laboratory tests obtained
Urine sample (for future analyses)
Fluid balance and urine output
Body weight
Recording of any patient or physician reported adverse events
Study drug continued and/or adjustments to treatment regimen

3.5.6 72 hours
Implementation and documentation of the following procedures:
Vital statistics
Laboratory tests obtained
Blood drawn for cystatin C, plasma renin activity, NT-proBNP, and copeptin A

Urine sample (for future analyses)
Fluid balance and urine output
Body weight
Recording of any patient or physician reported adverse events
Study drug continued and/or adjustments to treatment regimen

3.5.7 96 hours
Implementation and documentation of the following procedures:
Vital statistics
Laboratory tests obtained
Blood drawn for cystatin C, plasma renin activity, NT-proBNP, and copeptin A
Urine sample (for future analyses)
Fluid balance and urine output
Body weight
Recording of any patient or physician reported adverse events
Study drug continued and/or adjustments to treatment regimen
Administer change in dyspnea survey (Likert Scale)

3.5.8 Discharge from hospital
Implementation and documentation of the following procedures:
Vital statistics
Laboratory tests obtained
Fluid balance and urine output
Body weight
Recording of any patient or physician reported adverse events

3.6 Removal of Patient from Study
If at any time the primary treating physician or the principal investigators feel it would be unsafe for the patient to continue on the study protocol, the patient will be discontinued from any further study procedures. The patient will continue to be followed for non-investigational related endpoints (vital statistics, daily weights, fluid balance, standard laboratory tests, and disposition) until discharge from the hospital.

4. Study Laboratory Assessments

4.1 Data Points

	Randomization	8 hours	24 hours	48 hours	72 hours	96 hours	Discharge
Vital Statistics	X	X	X	X	X	X	X
UO (Fluid Balance)	X	X	X	X	X	X	X
Weight	X		X	X	X	X	X
Serum Chemistries	X	X	X	X	X	X	X
Cystatin C	X		X			X	
PRA	X		X			X	

Copeptin	X		X			X	
NT-proBNP	X		X			X	

4.2 Study Laboratory Assessments

Neurohormonal activation has been implicated as a pathophysiologic mediator of acute worsening renal function and diuretic resistance in HF when conventional diuretics are utilized. However, vasopressin receptor antagonists do not appear to increase plasma renin activity, which provides a potential mechanism to support the safety of these agents over conventional diuretics. Copeptin is a marker for vasopressin activation and has been shown to have prognostic value in HF patients. In addition, it may be a useful marker to identify patients who may exhibit a greater response to vasopressin receptor antagonists. Cystatin C has been shown to have prognostic importance in acute HF and is a more stable marker of glomerular filtration rate compared to serum creatinine. These additional laboratory assessments will be obtained to provide a more complete pathophysiologic model for the safety comparison between the two treatment groups.

4.2.1 Assessments of Investigational Laboratory Parameters
Blood samples will be obtained for analysis of cystatin C, plasma renin activity, and copeptin A at baseline, 24 hours and 96 hours. Urine samples will be collected and stored for potential future analysis of renal injury markers.

4.2.2 Performance of Investigational Laboratory Parameter Assays
The investigational laboratory assessments (cystatin C and plasma renin activity) will be outsourced to Quest Diagnostics. Copeptin A will be determined using a commercially available immunoassay (Brahms Copeptin Immunoassay, Thermofisher Scientific, Middleton, VA).

5. Evaluation of Adverse Events

5.1 Definitions
Acute worsening of kidney function will be defined as an increase in Scr of 0.3 mg/dL or 25% above baseline (Scr at time of randomization).

Electrolyte abnormalities will be defined as an occurrence of a laboratory value beyond the upper or lower limit of normal as defined by the institution's laboratory standards (hypokalemia K^+<3.5 mEq/L, hypomagnesemia Mg^{2+}<1.7 mEq/L, hypernatremia Na^+>145 mEq/L)

Serum sodium overcorrection will be defined as the occurrence of an increase in serum Na^+ > 8 mEq/L in 8 hours or > 12 mEq/L in 24 hours. For each event, any new neurologic sequelae (dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death) of overcorrection will also be recorded, otherwise the subject will be noted to be asymptomatic.

Hypotension will be defined as a systolic blood pressure reading < 80 mmHg (confirmed by immediate repeat assessment) or a systolic blood pressure < 90 mmHg with symptoms.

In-hospital mortality will be defined as any study subject death during the hospitalization regardless of cause.

Safety Information will be collected in accordance with the current Code of Federal Regulations.

Safety information is defined as "Any information from any source containing information" such as:

- Adverse event or suspicion thereof
- Lack of efficacy
- Overdose, abuse, misuse (even without resulting adverse reaction)
- Medication error
- Exposure during pregnancy or lactation (including uneventful) and reports where the embryo or fetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure)
- Counterfeit product
- Transfer of infectious disease by the medicinal product concerned
- Product complaint report which includes medically important information
- Pediatric use
- Occupational exposure
- Off-label use

5.2 Reporting

Study subjects will be continuously monitored during the trial for the development of all serious and non-serious adverse events which were not present at the time of randomization in accordance with the current Code of Federal Regulations. This information will be obtained through examination of the patient, laboratory work-up, and discussion with the patient and/or nursing staff. All adverse events will be recorded and assessed for severity. Serious adverse events will be reported within 24 hours to Otsuka (IRAE.Receipt@otsuka-us.com), and the Food and Drug Administration AERS via the Medwatch website (Form 3500).

Otsuka will be notified of any adverse events or other safety information arising out of or relating to your study in accordance with the following timeline:
(a) Twenty-four (24) hours from Date of First Receipt for Serious AE's. (defined below);
A serious adverse event includes any event that results in any of the following outcomes: death, is life-threatening (opinion of the investigator that the subject was at immediate risk of death), persistent or significant disability/incapacity, requires in-patient hospitalization or prolongs hospitalization, congenital anomaly/birth defect, other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; or
(b) Three (3) working days for pregnancy cases; or
(c) End of study for non-serious adverse events or during the study upon Otsuka's request.
(d) At least two (2) weeks prior to submission of an aggregate safety report.

A line-by-line listing of all serious adverse events will be sent once fifty percent (50%) enrollment is reached and at the end-of-study in order for Otsuka Safety & Pharmacovigilance to perform a reconciliation.

The estimated start date for this study is August 15th, 2013. Data collection will be considered complete once the final study subject has been discharged from the hospital. This event is estimated to occur January 15th, 2015. A study report will be finalized within one year of the end of data collection.

6. Statistical Analysis

6.1 Sample Size Calculation and Power Analysis

A total of 50 patients (25 in each group) would provide 93% power to detect a difference of 50% in urine output at 24 hours between treatments, alpha=0.05. The power was calculated based on the magnitude of difference in urine output seen in the ACTIV-CHF[20] (24 hour mean urine output for tolvaptan was approximately 4100±2100mL vs 2300±1100mL compared to placebo when added to standard therapy) and in the Udelson et al[23] study (24 hour mean increase in urine output with tolvaptan monotherapy 2600±1500mL vs 900±850mL with furosemide). Based on our previous data demonstrating poor response to loop diuretics in the hyponatremia acute HF population, we believe a 50% difference (standard deviation of 25%) is a reasonable and conservative estimate of what the difference will likely be.

Amendment August 9, 2017:
Due to slow enrollment, we anticipate not achieving our desired sample size of 50 subjects. Our revised power calculation reveals that if we achieve a mean difference with the same magnitude standard deviation between groups (e.g. mean difference is 1000±1000mL), our power will be between 80-90% with a sample size between 34-46 subjects. Based on current rate of enrollment, it is likely that we will achieve a sample of at least 34 subjects, which should allow the results to be meaningful despite early termination of enrollment.

6.2 Endpoint Analyses

Descriptive statistics will be computed for each treatment group. For all comparative analyses between the two treatment groups, independent samples t-test and Chi-Square test (or Fisher's exact test) will be performed for continuous variables or categorical variables, respectively. If either the normality or equal-variance assumptions underlying the traditional t-tests are violated, a non-parametric test will be used.

7. Risk Analysis

7.1 Data Safety Monitoring

The principal investigators will be responsible for monitoring adverse events which may occur during the course of the study, and determine if the benefit to risk of amending study procedures or continuing the study is appropriate in order to mitigate any unforeseen risks.

8. Drug Management

8.1 Drug Storage

All study medications will be stored by the Investigational Drug Service pharmacy.

8.2 Drug Dispensing and Tracking

The Investigational Drug Service pharmacy will maintain all records related to receipt, inventory, dispensing of the study medications.

9. Reports and Records Management

9.1 Source Documents

All source documents pertaining to the study will be maintained by the principal investigators. These include the screening log, case report forms (CRFs), informed consent forms, laboratory results, and other supporting documentation where appropriate or needed.

9.2 Data Collection

All data will be collected manually on standardized CRFs. Data from completed CRFs will be entered into a computer database.

9.3 File Management and Retention

All study documents will be retained by the principal investigators in a secured location for a minimum of 2 years after the study results have been published.

10. Ethics and Regulatory Issues

10.1 Institutional Review Board

The study will be conducted in compliance all applicable laws and regulatory requirements. The study will be submitted and approved through the Los Angeles County + University of Southern California Institutional Review Board.

10.2 Informed Consent and HIPAA

Signed written informed consent will be obtained prior to initiating any study procedure for each patient. A signed copy of the Right of Research Participants and the Informed Consent, will be provided to each study subject, one copy in the patient medical records, and one copy retained by the investigators. All study documents and procedures will be HIPAA compliant and use of protected health information will be minimized by encoding of the data.

10.3 Clinical Trials Registration

The study will be registered with www.clinicaltrials.gov through the Protocol Registration System.

11. Confidentiality

All data collected in the conduct of the study will be treated as confidential and will not be disclosed to any personnel not directly related to the study or authorized regulatory officials. All investigators will have completed HIPAA training. Each study subject will be assigned a study number, and this number will be the only identifier linking study data to the protected health information.

12. Investigator Listing

Tien M.H. Ng, Pharm.D., FCCP, BCPS (AQ-C)	Associate Professor of Clinical Pharmacy Director, PGY2 Residency in Cardiology University of Southern California Los Angeles, CA
Uri Elkayam, M.D., FACC	Professor Division of Cardiovascular Medicine USC Keck School of Medicine
Michael Fong, M.D., FACC	Associate Professor of Clinical Medicine Co-Director, Advanced Heart Failure and Cardiomyopathy Division of Cardiovascular Medicine USC Keck School of Medicine
Andrew Yoon, M.D.	Assistant Professor of Clinical Medicine Division of Cardiovascular Medicine USC Keck School of Medicine

13. References

1. Asadollahi K, Beeching N, Gill G. Hyponatraemia as a risk factor for hospital mortality. QJM : monthly journal of the Association of Physicians 2006;99:877-80.
2. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. The American journal of medicine 2009;122:857-65.
3. Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. Archives of internal medicine 2010;170:294-302.
4. Patel GP, Balk RA. Recognition and treatment of hyponatremia in acutely ill hospitalized patients. Clinical therapeutics 2007;29:211-29.
5. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. The American journal of medicine 2006;119:S30-5.
6. Zilberberg MD, Exuzides A, Spalding J, et al. Epidemiology, clinical and economic outcomes of admission hyponatremia among hospitalized patients. Current medical research and opinion 2008;24:1601-8.
7. Gill G, Huda B, Boyd A, et al. Characteristics and mortality of severe hyponatraemia--a hospital-based study. Clinical endocrinology 2006;65:246-9.
8. Klein L, O'Connor CM, Leimberger JD, et al. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. Circulation 2005;111:2454-60.

9. Gheorghiade M, Abraham WT, Albert NM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. European heart journal 2007;28:980-8.
10. Rossi J, Bayram M, Udelson JE, et al. Improvement in hyponatremia during hospitalization for worsening heart failure is associated with improved outcomes: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) trial. Acute cardiac care 2007;9:82-6.
11. Gheorghiade M, Rossi JS, Cotts W, et al. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. Archives of internal medicine 2007;167:1998-2005.
12. Rusinaru D, Buiciuc O, Leborgne L, Slama M, Massy Z, Tribouilloy C. Relation of serum sodium level to long-term outcome after a first hospitalization for heart failure with preserved ejection fraction. The American journal of cardiology 2009;103:405-10.
13. Goldsmith SR. Current treatments and novel pharmacologic treatments for hyponatremia in congestive heart failure. The American journal of cardiology 2005;95:14B-23B.
14. Ng TMH, Cao DX, Patel KA, Wong YM, Prasad M, Elkayam U. Hyponatremia is associated with diuretic resistance and a higher incidence of worsening renal function in patients with acute decompensated heart failure. Journal of the American College of Cardiology 2011;59:E105.
15. Fonarow GC, Adams KF, Jr., Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA : the journal of the American Medical Association 2005;293:572-80.
16. Rosner MH. Hyponatremia in heart failure: the role of arginine vasopressin and diuretics. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2009;23:307-15.
17. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation 2003;107:2690-6.
18. Udelson JE, Orlandi C, Ouyang J, et al. Acute hemodynamic effects of tolvaptan, a vasopressin V2 receptor blocker, in patients with symptomatic heart failure and systolic dysfunction: an international, multicenter, randomized, placebo-controlled trial. Journal of the American College of Cardiology 2008;52:1540-5.
19. Costello-Boerrigter LC, Smith WB, Boerrigter G, et al. Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure. American journal of physiology Renal physiology 2006;290:F273-8.
20. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA : the journal of the American Medical Association 2004;291:1963-71.
21. Konstam MA, Gheorghiade M, Burnett JC, Jr., et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA : the journal of the American Medical Association 2007;297:1319-31.
22. Matsuzaki M, Hori M, Izumi T, Asanoi H, Tsutamoto T. Effects of tolvaptan on volume overload in Japanese patients with heart failure: results of a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2011;25 Suppl 1:S19-31.
23. Udelson JE, Bilsker M, Hauptman PJ, et al. A multicenter, randomized, double-blind, placebo-controlled study of tolvaptan monotherapy compared to furosemide and the combination of tolvaptan and furosemide in patients with heart failure and systolic dysfunction. Journal of cardiac failure 2011;17:973-81.