Tolvaptan Treatment to Reverse Worsening Outpatient Heart Failure: Possible Role of Copeptin in Identifying Responders (TROUPER)

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Study Protocol

Tolvaptan Treatment to Reverse Worsening Outpatient Heart Failure: Possible Role of Copeptin In Identifying Responders (TROUPER)

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1. Protocol Synopsis

Title:	Tolvaptan Treatment to Reverse Worsening Outpatient Heart Failure: Possible Role of Copeptin In Identifying Responders
Indication:	Heart Failure
Location:	Approximately 4-6 clinical centers in U.S.
Rationale:	Patients with worsening heart failure presenting in the outpatient setting represent a unique opportunity for novel approaches to decongestion that may more rapidly improve fluid status and symptoms as well as reduce the risk of hospitalization. In these patients with less severe congestion, combining the vasopressin antagonist tolvaptan with loop diuretic may represent a more effective strategy for decongestion. In addition, profiling copeptin may help identify patients in this unique population who are more likely to respond to tolvaptan.
Hypothesis:	This study is designed to test two related hypotheses 1) that the addition of oral tolvaptan to loop diuretic therapy will produce better decongestion than augmentation of loop diuretic therapy in patients presenting with worsening heart failure in the outpatient setting 2) that prespecified post hoc stratification on baseline copeptin level will be a predictor of the degree of superiority of oral tolvaptan plus loop diuretic compared to augmentation of loop diuretic.
Study Design:	This study will be a randomized, double blind, positive control, multi-center clinical trial enrolling patients who present in the outpatient setting with signs and symptoms consistent with worsening congestive heart failure. The sample size for the study is 40 patients. Candidates for the study will be identified by screening outpatients presenting with worsening heart failure. Patients who qualify for the study will be enrolled within 24 hours of identification. Patients will initiate study medication in a hospital setting and will be observed for a period of time that will depend upon their baseline serum sodium and response to study drug. In most cases patients will be observed for 8 hours. Following this observational period, patients will leave the hospital setting and the remainder of the study will consist of follow-up by outpatient visits or by telephone.
Primary Objectives:	The primary objectives of this study are to compare the effects of oral tolvaptan plus augmented loop diuretic versus augmented loop diuretic on short term changes in body weight and indices of congestion in patients presenting with worsening congestive heart failure in the outpatient setting with and without prespecified post hoc stratification based on baseline copeptin level.

Tolvaptan Treatment to Reverse Worsening Outpatient Heart Failure
STUDY FLOW CHART

SCREENING
Patients presenting with worsening heart failure in the outpatient setting will be considered for the study. Patients who meet study inclusion and exclusion criteria will be consented and enter the study.
RANDOMIZATION
Patients will be randomized in a 1:1 fashion to Augmentation of current daily dose of oral loop diuretic + 30 mg of oral Tolvaptan daily OR Augmentation of current daily dose of oral loop diuretic + placebo for tolvaptan. The last day of study drug administration will be Day 8 of the study.
BASELINE VISIT
• History and physical examination, vital signs, and review of current cardiovascular medications • Serum pregnancy test • Assessment of degree of congestion present • Blood sampling for routine clinical labs and copeptin determination • Blood sampling for optional biobank for future study of biomarkers, DNA and RNA • Urine sample for future analysis Patients without baseline hyponatremia (serum sodium <135 mEq/L) will be observed for 8 hours in a hospital setting after dosing with study medication for assessment of vital signs and adverse events. Patients with baseline hyponatremia will be observed in a hospital setting and have repeat determination of serum sodium 6 hours after their dose of study drug. Patients with overcorrection of serum sodium (increase in serum sodium of > 6 mEq/L from baseline) will be receive D5W and have serum sodium monitored for a minimum of 24 hours (details in study protocol). Hyponatremic patients without overcorrection of serum sodium will complete observation at 8 hours.
FOLLOW-UP VISITS
Day 3 Visit, Day 8 Visit • History and physical examination, vital signs, current cardiovascular medications • Blood sampling for routine clinical labs and copeptin determination • Blood sampling for optional biobank for future study of biomarkers, DNA and RNA • Urine sample for future analysis • Changes in cardiovascular medications • Assessment of degree of congestion present • Assessment for occurrence of events related the morbidity index • Assessment for adverse events **Day 30 Telephone Follow-up** • Days of hospitalization and cause of hospitalization • Days of ED visit and reason for ED visit • Days of clinic visits and reasons for clinic visits

- Changes in cardiovascular medications
- Assessment for adverse events

2. Background and Rationale

Problem and Target Population. Worsening heart failure due to fluid overload remains a vexing problem in congestive heart failure (CHF) despite the use of evidenced-based medications dictated by guideline directed therapy. Acute decompensated heart failure is one manifestation of this general syndrome of worsening heart failure that has attracted increasing attention. Acute decompensated heart failure is on the severe end of the spectrum of the worsening heart failure syndrome and has emerged as a major public health problem associated with frequent hospitalization and a poor prognosis post discharge. However, patients presenting with worsening heart failure in the outpatient setting are also an important part of the overall decompensated heart failure syndrome. We are proposing that these patients comprise a novel clinical subset that has not been well investigated to date. Often patients presenting to the outpatient clinic with decompensated heart failure have less congestion and fluid overload than patients with acute heart failure who require hospitalization. Patients in this less ill group can often be managed as outpatients but they are at risk of developing more severe congestion and progressing to hospitalization. As efforts to reduce hospitalization for heart failure continue to intensify, the aim will be to identify interventions that more effectively relieve fluid overload and allow outpatient management without hospitalization.

The pathophysiology of the process that leads to congestion in outpatients who present with worsening heart failure is not fully delineated. However, congestion caused by sodium and water retention appears to be the major pathophysiological process underlying their decompensation. It is also well recognized these patients decompensate despite the administration of chronic diuretics including loop diuretics. Current treatment typically involves augmenting existing loop diuretic therapy and, less commonly, the addition of non-loop diuretics. However, this approach is often ineffective; hospitalization may ensue or the patient may have a poor response characterized by persistent symptoms and a slow recovery to euvolemia. Despite poor outcomes with current approaches, there has been little clinical investigation of potential therapeutic strategies to improve care in this important clinical subset.

Tolvaptan Therapy. Vasopressin antagonists are a potential adjunct to current strategies for the treatment of worsening heart failure seen in the outpatient setting. Tolvaptan, a selective oral V2 vasopressin receptor antagonist, has been well studied in acute and

chronic congestive heart failure. This agent is well known to produce substantial water loss that is accompanied by a significant reduction in body weight that is especially prominent early in the treatment period. This study will test the hypothesis that acute water loss and weight reduction induced by tolvaptan will be an effective strategy, when combined with loop diuretic therapy, to reverse the volume expansion occurring in outpatients with worsening heart failure. This tolvaptan based strategy, may be an effective way to reset the patient's volume status to euvolemia and thereby reduce symptoms and prevent progression to hospitalization. If this concept is correct, the addition of tolvaptan may be short-term and yet still effective.

Copeptin Guided Therapy. In addition to testing the possible novel role of tolvaptan as effective therapy in outpatients with worsening heart failure, this trial is also designed to investigate the potential role of the biomarker, copeptin, to guide patient selection for tolvaptan therapy. Copeptin or c-terminal pre-provasopressin is tightly coupled to vasopressin secretion. So this biomarker provides a reliable estimate of the extent of vasopressin activation in patients presenting with worsening heart failure. Greater activation of vasopressin could result in more water retention and promote expansion of intravascular volume; leading to more advanced congestion than that promoted by sodium retention alone. Given that the major mechanism of action of tolvaptan appears to be inhibition of vasopressin, it is possible that this drug may be more pharmacologically active in patients where greater vasopressin activation is present.

In the current study design, assessment of the association of copeptin with the therapeutic response to tolvaptan will be done post hoc. Samples for analysis of copeptin will be obtained throughout the study but assays will not be performed until after the study is completed. The proposed principal analysis of the predictive role of copeptin for tolvaptan response will be based on post hoc stratification of the study population by baseline copeptin level. The current plan is to base this post hoc stratification on the results of a recently completed pilot study of the association of pre-treatment copeptin level with the effect of tolvaptan on change in body weight in patients with chronic stable heart failure due to reduced ejection fraction.

Results from this pilot study by our group provide preliminary data to suggest that copeptin may indeed be an effective way to identify patients with heart failure who have greater response to tolvaptan. A total of 20 outpatients with chronic stable symptomatic heart failure and history reduced left ventricular ejection fraction (≤40) were enrolled in the pilot study. Patients were selected for later enrollment by targeting those with upper or

lower quartile copeptin levels determined during an outpatient screening period (n=10 each). Patients received a single dose of 30 mg of tolvaptan and body weight, fluid intake and urine output were monitored in a clinical research unit for 24 hours. For analysis, patients were divided into two groups using a prespecified cut point based on their baseline copeptin level determined during their study hospitalization (≥10 versus <10 pmol/L). Results comparing key study variables based on this prespecified cut point approach are shown in Table 1. These findings demonstrate that change in body weight, reflecting the net aquaretic response to tolvaptan, was greater in the subgroup of patients with baseline copeptin levels ≥ 10 pmol/L.

Table 1. Changes in body weight and fluid status after tolvaptan by baseline copeptin

Study Group	All Patients	Copeptin ≥ 10 pmol/L	Copeptin < 10 pmol/L	*P value
N	20	10	10	
Baseline Copeptin (pmol/L)	13.1 ± 9.7	20.5 ± 8.7	5.7 ± 1.9	<0.001
Change in Body Weight (Kg)	-0.8 ± 1.1	-1.3 ± 1.0	-0.4 ± 1.0	0.035
Net Output (mL)	1360 ± 1881	2091 ± 1662	630 ± 1876	0.089
Total Output (mL)	6141 ± 2072	6498 ± 2328	5784 ± 1835	0.853
Total Input (mL)	4780 ± 1664	4406 ± 1398	5154 ± 1893	0.393

Values are mean ± SD. *P Values are for comparison of copeptin groups by nonparametric analysis.

One potential implication of these pilot study results is that the contribution of water retention to the worsening chronic heart failure seen in the outpatient clinic may vary significantly. Patients with low vasopressin activation can be hypothesized to have less water retention and so that water overload may play less of a pathophysiological role than sodium retention in these patients. In contrast, if the patient's heart failure is associated with an elevation in vasopressin, there may be a greater role for water overload and therefore a better clinical response to tolvaptan therapy.

Assessment of Other Potential Markers.

The study will collect serial blood samples to allow future investigation of other potential biomarkers and Omic markers (including DNA and RNA) that may inform understanding of the decompensated heart failure state and heart failure patient response to tolvaptan therapy.

Assessment of Congestion. One of the key design features of this protocol is the choice of the primary efficacy endpoint. Years of acute heart failure research have established the difficulty of identifying a sensitive method to detect important changes in fluid status during treatment for acute decompensation. Although some have questioned the role of objective assessments of congestion like change in body weight, the work of Pang et al. shown below (Figure 1) suggests reconsideration of this measurement as a useful surrogate marker. These investigators report data from the EVEREST trial that shows a very strong link between the degree of acute weight loss and the magnitude of dyspnea relief reported by the patient after 24 hours of inpatient therapy. These findings strongly support using change in body weight as the primary efficacy endpoint for the current study.

Figure 1. Pang et al. Change in Weight versus Change in Patient Reported Dyspnea

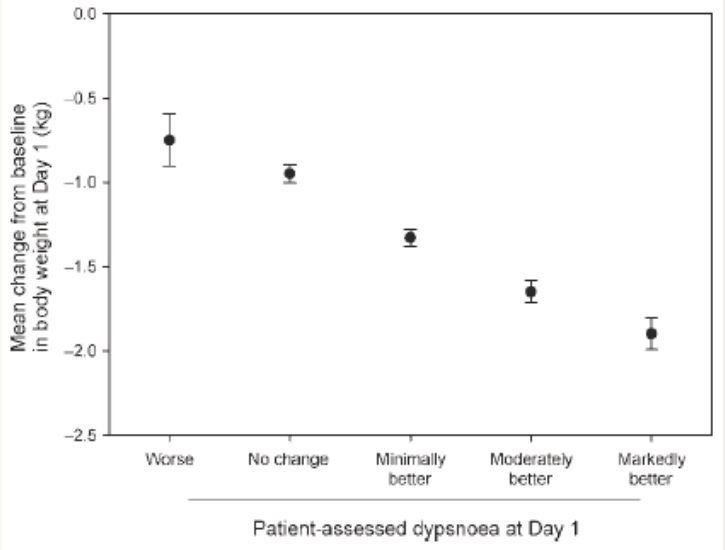

Figure 5 Association between patient-assessed dyspnoea status and body weight change at inpatient Day 1. Note: worse includes minimally worse, moderately worse, and markedly worse. For association between weight change and treatment: $P < 0.0001$ for dyspnoea status adjusted for treatment; $P < 0.0001$ adjusted for dyspnoea status; and $P = 0.3008$ for dyspnoea–treatment interaction.

Visual Analog Scales (VAS) for Patient Assessment. Additionally, it is necessary to consider other approaches to assess fluid status that are more clinically oriented. There continues to be substantial controversy surrounding the accuracy of a number of clinical assessments to document improvement in worsening heart failure. Both the nature of the

symptom and sign assessment as well as the type of measurement used remains in dispute. However, scales that measure symptomatic dyspnea remain a major tool to quantify the effect of treatment strategies to reverse worsening heart failure. Documenting improvement in patient reported dyspnea by the 10-point VAS is generally well accepted as evidence of clinical effectiveness of an intervention. This scale has been used in a number of acute heart failure trials. Therefore changes in the VAS dyspnea scale from baseline to Visit 2 is designated as the highest priority secondary endpoint in this trial. It important to note that due to measurement variability, VAS and Likert scales are relatively insensitive ways to determine changes in patient symptoms and substantial sample sizes are needed to have power to detect significant differences especially between placebo and drug groups. The present study sample size is not adequate for this purpose. However, observed changes may be compared to those seen in larger acute heart failure trials to give hypothesis generating signals of tolvaptan efficacy.

Changes in Loop Diuretic to Reflect Clinical Status. Recent work with tolvaptan has documented that background loop diuretic therapy does not remain the same in tolvaptan and placebo groups throughout the study period. Although well recognized to be a confounder of the interpretation of the efficacy of tolvaptan therapy in addition to loop diuretics, studies to date have not been well designed to capture detailed information on changes in loop and other diuretics during the study period. In contrast, the present study is designed to collect detailed information on type of diuretic as well as dose in conjunction with extensive clinical assessments at specific visits during the study. This will assist in correlation of clinical findings with changes in diuretic dosing in the study arms.

In addition, our extensive clinical experience with outpatients treated for worsening heart failure since the inception of the TROUPER study has clearly demonstrated the clinical relevance of changes in loop diuretics during treatment for decompensation. This experience strongly suggests that increases in loop dose during Visit 2 would reflect worsening congestion while a decision to reduce loop dose during Visit 2 would indicate improvement in volume status and less congestion. Therefore, assessments of change in loop diuretic dosing at Visit 2 are designated as key secondary endpoints in this trial. Three assessments of change in loop diuretic will be made during analysis of study results: 1) change from baseline to 48 hours in loop diuretic dose (with loop diuretic dosing standardized on milligrams (mg) of furosemide equivalent), 2) whether loop diuretic dose was changed at 48 hours using a dichotomous approach and 3) changes in loop diuretic which account for whether loop diuretic was decreased, increased or unchanged. Details

of this analysis and the respective priority of these key secondary endpoints related to changes in loop diuretic at Visit 2 are presented later in the statistical analysis plan section of this protocol.

Heart Failure Clinical Status Assessments. This study also affords the opportunity to collect a substantial amount of information on various indices of heart failure status in this unique clinical population. Data remain limited on the clinical characteristics and clinical course of patients with outpatient worsening of heart failure. The study will use a novel version of the 10-point VAS scale for patient reported congestion based on the patient's self report of their perception of the extent of fluid overload present. The study investigator also will complete a VAS congestion scale based on their perception. Finally, reported changes in fluid status will also be assessed by the Likert scale method with data collected from patients and as observed by study investigators. A substantial amount of information was collected on a variety of signs and symptoms of heart failure status including detailed assessment of congestion and physical limitation during the follow-up period. Future analyses of these data will help to better understand the clinical picture and course of patients with outpatient worsening of heart failure.

Clinical Outcomes. Assessment of the effect of study treatments on occurrence of worsening heart failure as reflected by extra clinic visits, increases in diuretic treatment and hospitalization is of interest in this unique study population. The small sample size of this pilot trial makes it unlikely that this issue could be adequately addressed by the current study. However, information on these adverse clinical outcomes will be collected as part of the protocol.

Modifications to Original Study Statistical Analysis Plan. A number of modifications were made to the original statistical analysis plan for the study. Secondary efficacy endpoints were revised to reflect 1) knowledge gained since the design of the study concerning the assessment of worsening heart failure, 2) the results of analyses of blinded, aggregate study data related to clinical metrics of worsening heart failure collected in the trial and 3) refinement of the analysis of the primary endpoint related to baseline copeptin and clarification of the analysis of the association of change in body weight with baseline copeptin in the two randomized arms of the study. In addition, to reduce the effect of multiple testing, a limited number of secondary endpoints were specified. These finalized secondary outcomes were ordered according to their clinical importance. Blinded review of adverse outcomes revealed that events related to worsening heart failure were uncommon during the treatment period. Thus the tertiary endpoint, clinical composite of morbidity, was

removed due to lack of power to address between group differences. Finally, the approach to exploratory endpoints was refined to emphasize future aggregate analyses of detailed data collected on heart failure characteristics and the clinical course of this unique population of heart failure patients. The primary endpoint of the study was unchanged. Changes to the original statistical analysis plan were made before the study was unblinded. All changes were made in consultation and agreed upon by the statistician conducting study data analysis.

3. Study Objectives and Hypotheses

Hypotheses. This study is designed to test two related hypotheses 1) that the addition of oral tolvaptan to augmented loop diuretic therapy will produce better decongestion than augmentation of loop diuretic therapy alone in patients presenting with worsening heart failure in the outpatient setting and 2) that prespecified post hoc stratification based on baseline copeptin level will be a predictor of the degree of superiority of oral tolvaptan plus augmented loop diuretic compared to augmentation of loop diuretic alone.

Objectives. This study is designed to address the following objectives:

The objectives of this study will be to compare the effects of oral tolvaptan plus augmented loop diuretic versus augmented loop diuretic on 1) short term changes in body weight with and without stratification for baseline copeptin and 2) indices of congestion in patients presenting with worsening congestive heart failure in the outpatient setting with and without prespecified post hoc stratification based on baseline copeptin level.

4. Study Overview and Patient Cohort

This study will be a randomized, double blind, positive control, multi-center clinical trial enrolling patients who present in the outpatient setting with signs and symptoms consistent with worsening congestive heart failure. The sample size for the study is 40 patients. Candidates for the study will be identified by screening outpatients presenting with worsening heart failure. Patients who qualify and consent for the study will be enrolled within 24 hours of identification. Patients will be observed in a hospital setting following the initial administration of randomized therapy as outlined in detail below. Assuming they tolerate study treatment during this observation period, patients will leave the hospital setting and the remainder of the study will consist of observation during outpatient visits or telephone follow-up to assess response to randomized therapy. Patients will receive study medication through Day 8 of the study.

4.1 Inclusion and Exclusion Criteria

Inclusion Criteria

- ≥ 18 years of age
- Presenting to clinic with worsening heart failure due congestion (fluid overload)
    - Patient reported worsening fluid overload based on perception of edema and/or weight gain

  With at least one of the following symptoms
    - Worsening dyspnea on exertion or fatigue
    - Worsening orthopnea or PND
    - Perception of abdominal and/or lower extremity edema
    - Early satiety and/or decreased appetite

  And at least one of the following signs
    - Lower extremity edema
    - Ascites
    - Elevated JVD
    - Pulmonary rales
- Daily oral dose of loop diuretic
- Prior history of heart failure with this diagnosis for at least 1 month with preserved or reduced left ventricular ejection fraction
- Signed informed consent

Exclusion Criteria

- Patients with symptomatic hyponatremia will be excluded from the study.
- Patients with severe hyponatremia, defined as serum sodium < 125 mEq/L at the time of screening, will be excluded regardless of whether they are symptomatic or not.
- Patients with the following predisposing factors for osmotic demyelinating syndrome (ODS), assessed by the study investigator judgment, will be excluded: chronic alcoholism at the time of study, severe liver disease, marked malnutrition, and risk for chronic hypoxia.
- Patients currently undergoing renal replacement therapy
- Planned hospitalization for acute heart failure
- History of primary significant liver disease or acute hepatic failure, as defined by the investigator

- Hemodynamically significant arrhythmias
- ACS or acute myocardial infarction within 4 weeks prior to study entry
- Active myocarditis
- Hypertrophic obstructive, restrictive, or constrictive cardiomyopathy
- Severe stenotic valvular disease amendable to surgical treatment
- Complex congenital heart disease
- Constrictive pericarditis
- Clinical evidence of digoxin toxicity
- History of adverse reaction or clinical contraindication to tolvaptan
  - Concomitant use of strong CYP3A4 inhibitors
  - Inability of patient to sense and/or respond to thirst
  - History of hypersensitivity to tolvaptan
  - Patient is anuric
- Enrollment or planned enrollment in another randomized clinical trial during the study period
- Pregnant or breast-feeding
- Inability to comply with planned study procedures

5. Study Design

5.1 Overview

Patients will be randomized in a 1:1 fashion to one of two treatment arms:

- Augmentation of current daily dose of oral loop diuretic + 30 mg of oral Tolvaptan daily
- Augmentation of current daily dose of oral loop diuretic + placebo of oral Tolvaptan daily

The study oral treatment regimen will begin on the day of randomization and continue for a total of 8 days. Patients will have study medication initiated in a hospital setting and will undergo monitoring during their baseline visit according to the presence or absence of hyponatremia and change in serum sodium from baseline during their baseline visit. Patients will return two days after randomization for their first follow-up visit on Day 3. At this time they will undergo follow-up evaluation of their heart failure state including determination of body weight, vital signs and assessment of clinical evidence of congestion. Patients will return again on Day 8 for their second and final follow-up visit. Following study assessments at that the visit, the randomized treatment period will end and the patient will

be continued on appropriate diuretic therapy alone with the specific type and dosing of these agents being determined by the treating physician.

All patients will have a Day 30 follow up phone call to establish vital status, determine occurrence of hospitalizations and ED visits, assess adverse events, review heart failure symptoms, and review changes in cardiovascular medications since Visit 3.

5.2 Randomization

All patients will be randomized using a block design to ensure roughly equal distributions of patients into each arm of the trial. Randomization will be stratified by clinical site.

5.3 Blinding

This study will be double blinded. Tolvaptan or matching placebo will be supplied by Otsuka America Pharmaceutical, Inc. The pharmacist at each institution will be unblinded to assure dispensation of the correct treatment following the stratified (by site) block design.

5.4 Treatment Arms

Patients will be randomized in a 1:1 fashion to one of two types of treatment:

- Augmentation of current dose of loop diuretic + 30 mg of oral tolvaptan daily

  Or

- Augmentation of current dose of loop diuretic + placebo for tolvaptan

Doses of loop diuretics will be standardized to mg equivalents of furosemide based on 40 mg of furosemide for each 1 mg of bumex and 2 mg of furosemide for each 1 mg of torsemide. Augmentation of current dose of loop diuretic will be defined as doubling the current dose of oral loop diuretic if the total daily dose of loop diuretic is ≤ 120 mg furosemide equivalents. If the total current oral dose of loop diuretic is > 120 mg then the augmented dose of will be 50% of the current oral dose of loop diuretic + the current oral dose of loop diuretic in furosemide mg equivalents.

5.5 Patient Safety

5.5.1 General Considerations.

Investigators should follow the randomized treatment strategy for the 8 days of treatment. However, as always, the patient's safety, as assessed by clinical evaluation of the study investigators, will take priority over treatment assignment and management based on adherence to the study protocol. Patients who are experiencing inadequate treatment response in terms of relief of congestion may have unscheduled visits as required. They may be treated with more aggressive measures including additional diuretic and may be hospitalized according to investigator judgment. Patients will also be evaluated for excessive decongestion and volume

depletion during the study and may have changes in study medication and augmented loop diuretic as a result. Patients with this possibility may also have additional laboratory assessment and follow-up visits as needed. Patients may continue to be seen for face to face visits after their Day 8 study visit based on investigator judgment of volume status and clinical course.

The study drug (Tolvaptan or placebo) will be stopped prior to the 8 days of planned therapy as per the study protocol or if the study investigator believes in their judgment that the rate of rise of serum sodium is inappropriately rapid or if serum sodium increases to >145 mEq/L in the setting of volume depletion.

5.5.2 Patient Monitoring after Initial Administration of Study Drug

All patients will be observed for at least 8 hours in a hospital setting following the initial administration of randomized therapy. As part of this monitoring they will be observed for adverse neurological events including dysarthria, dysphagia, behavioral disturbance, and muscle weakness.

5.5.3 Monitoring Serum Sodium after Initial Dosing of Study Drug

To aid in monitoring the safety and clinical response following the first dose of study drug, patients will be divided into those with and without hyponatremia based on results from blood samples collected at baseline before receipt of study drug. Serum sodium levels at screening will be evaluated to help identify patients likely to have this degree of reduction in serum sodium at baseline. Hyponatremia will be defined as a serum sodium < 135 mEq/L as measured at the baseline/randomization visit (Visit 1). Hyponatremic patients will be more closely monitored during the baseline visit for possible overcorrection of serum sodium as described below

Patients with No Hyponatremia.

At Visit 1, patients without hyponatremia will be observed for the occurrence of any adverse events for 8 hours in a hospital setting after initial administration of study drug (Figure 2). Patients free of adverse events and clinically stable from a volume standpoint will leave the facility and return for follow-up as outlined below.

Baseline Visit Safety Assessment

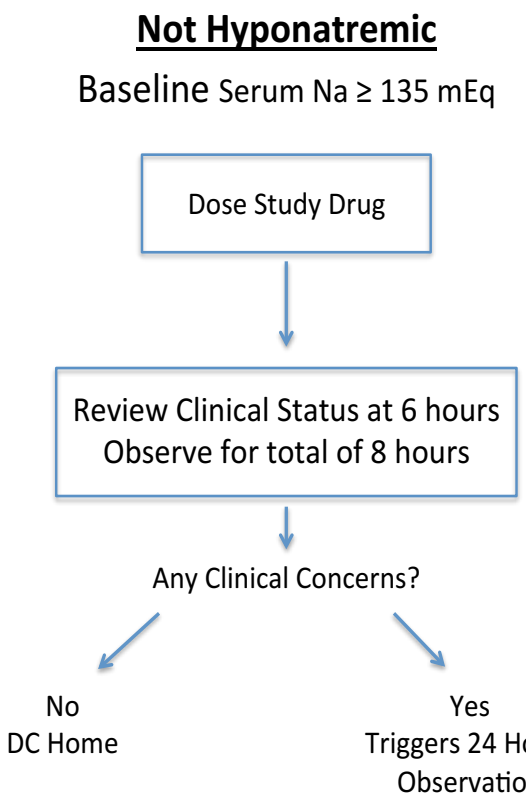

Figure 2

Patients with Hyponatremia. At Visit 1, patients with hyponatremia will have a repeat determination of serum sodium performed from a blood sample taken 6 hours post initial study drug administration (Figure 3). Patients with an increase in serum sodium > 6 mEq/L at 6 hours will require additional monitoring of serum sodium for 24 hours, they will also receive D5W as outlined in detail in Section 6.2. Patients with an increase in serum sodium > 6 mEq/L will not receive additional doses of study medication but will otherwise complete the study as planned.

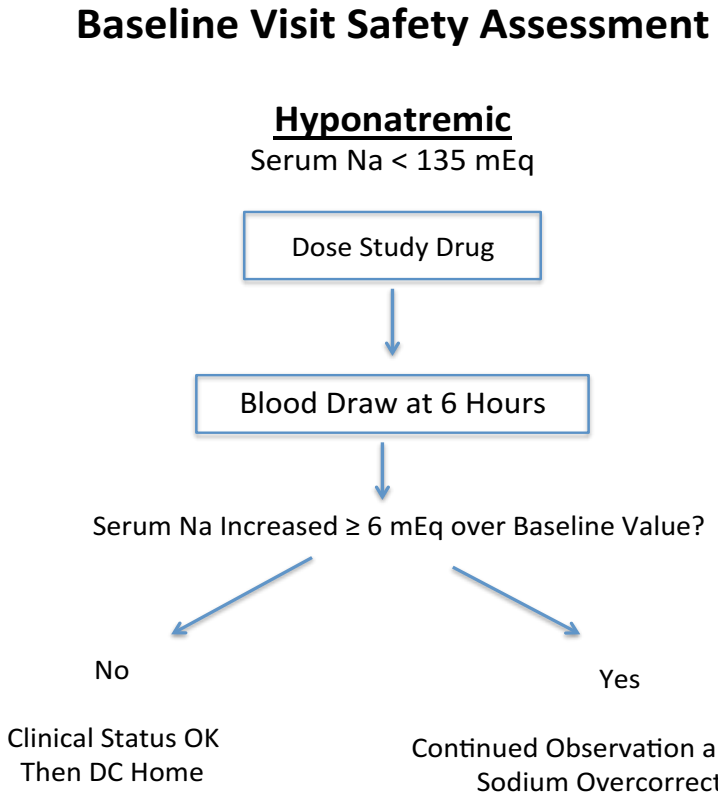

Figure 3

5.6 Additional Monitoring of Serum Sodium During the Study.

All study patients will have follow-up at 48 hours (Visit 2) with clinical assessment of volume status including evaluation for volume depletion. All patients will have follow-up determination of serum sodium, other electrolytes and renal function at this visit to complement their clinical evaluation and to address the possibility of overcorrection of serum sodium.

All patients will return for a final follow-up visit at 8 days (Visit 3). At this visit all patients will have clinical assessment of volume status including evaluation for volume depletion. All patients will also have determination of serum sodium, other electrolytes and renal function at this visit to complement their clinical evaluation.

6. Study Methodology - See Appendix A

6.1 Screening and Enrollment

6.1.1 Study Screening

Outpatients seen at the participating centers with signs and symptoms consistent with worsening chronic heart failure will be screened by site study personnel for possible entry into the trial. Patients found to meet eligibility criteria will be approached regarding the study and consented for enrollment if they agree to participate. Patients are expected to be enrolled and randomized within 24 hours of informed consent.

6.1.2 Study Enrollment and Estimated Enrollment Period

The sample size for the study is 40 patients. The projected timeline for enrollment is approximately 12 months.

6.2 Baseline Procedures

6.2.1 Randomization

All study subjects will be randomized in a 1:1 fashion to one of the two treatment groups.

6.2.2 Baseline Assessments

At the time of randomization, all study subjects will undergo:

- History and physical examination focused on signs and symptoms of congestion
- Assessment of the degree of congestion and dyspnea present
- Vital signs (including blood pressure and body weight)
- Documentation of current cardiovascular medications
- Measurement of Creatinine, BUN, electrolytes, and serum osmolarity
- Serum pregnancy test for women of child bearing potential

6.2.3 Baseline Blood Sampling

- Blood samples will be obtained prior to the patient receiving study drug/placebo
- A blood sample (20 mL) will be collected for assay of routine clinical labs and copeptin determination
- An optional blood sample (30 mL) will be collected for potential future biomarker and Omic analysis (including DNA and RNA)
- A urine sample (5 mL) will be collected for later measurement of biomarkers, electrolytes and osmolarity and other analytes

6.2.4 Follow-up Observation at Baseline Visit

All patients will initiate study drug tolvaptan/placebo in a hospital setting.

6.2.5 Observation at Baseline Visit - Patients without Hyponatremia

- Patients who are not hyponatremic at baseline will be monitored for 8 hours for adverse effects and changes in vital signs suggestive of potential volume

depletion (orthostatic decline in blood pressure and increases in heart rate) and intake and output. Review of these findings will aid in identification of patients who may be more likely to have overcorrection of serum sodium due to excess aquaresis and inadequate per oral intake. Any patient without hyponatremia at baseline who is clinically suspected to have overcorrection of serum sodium will have repeat determination of serum electrolytes and renal function at 6 hours post initial dose of tolvaptan/placebo. Results of these labs will be reviewed prior to their discharge from the hospital setting. Any patient subsequently found to have an increase in serum sodium > 6 mEq/L will be managed as indicated below for patients with baseline hyponatremia and a similar increase in serum sodium.

6.2.6 Observation at Baseline Visit - Patients with Hyponatremia

- Patients who are hyponatremic at baseline will have repeat determination of serum sodium 6 hours after their initial dose of study drug. Any patient found to have a rise in serum sodium of > 6 mEq/L at the 6 hour time point will receive treatment with intravenous D5W. Intravenous D5W will administered at the rate of 3 mL/kg per hour (210 mL for a 70 kilogram patient) which is expected to reduce serum sodium from 1 to 2 mEq/L per hour.
- Patients with this degree of early increase in serum sodium will have repeat serum sodium and other electrolytes plus BUN and Creatinine determined at 2 hour intervals during D5W administration. Administration of D5W will stop when the patient is at least 14 hours post their initial dose of study drug and the serum sodium is < 8 mEq/L above their baseline value.
- Patients with this degree of early increase in serum sodium will be observed for a minimum of 24 hours after their initial dose of study medication. They will also have repeat determination of serum sodium and other electrolytes plus BUN and Creatinine 20 hours after their initial dose of study medication and these values will be reviewed prior to their discharge from the hospital setting. If their serum sodium remains < 12 mEq/L above baseline at the 20 hour blood draw and they are clinically stable, they will be discharged from the hospital setting at the 24 hour point. In the rare event that the patient is found to have a 20 hour serum sodium that is ≥ 12 mEq/L from their baseline, they will receive additional D5W as above with repeat determinations of serum sodium until their value is <

12 mEq/L above their baseline. At that time if they are clinically stable then they will be discharged from the hospital setting.

- Patients found to be hyponatremic will also be monitored for development of symptoms during the study related to reduced serum sodium. As a precaution, patients with symptomatic hyponatremia are excluded from the study, Patients with heart failure who present with hyponatremia are very commonly asymptomatic and the condition is chronic and does require therapy to reverse the hyponatremia per se. Patients with heart failure and chronic hyponatremia rarely become symptomatic. Patients enrolled in the study with asymptomatic hyponatremia will be cautioned to monitor for changes in mental status, nausea, and lethargy between their baseline visit and follow-up visits. Patients will be instructed to contact the study investigators should these symptoms develop and they will be seen for follow-up evaluation as needed.

6.2.7 Follow-up of Patients with Overcorrection of Sodium

Once discharged, any patient with overcorrection of sodium will be followed in the study as planned except they will not be treated further with study medication. They will be treated with augmented loop diuretic and other diuretics as appropriate. They will return for study visit 2 (Day 3) where they will have repeat determination of serum electrolytes, including serum sodium, as well as BUN and Creatinine. In the unlikely event that they are found to have serum sodium > 18 mEq/L at this visit, they will be considered for per oral hydration or administration of additional intravenous D5W at the discretion of the clinical investigator. They will be seen at Day 8 for evaluation as planned per protocol including repeat determination of serum sodium. They will also have 30 day follow-up as planned.

6.3 Evaluation During Follow-up

6.3.1 Day 3 at 48 hours post study drug administration

Patients will return on study Day 3 at 48 hours after initial administration of study drug. This follow-up evaluation is expected to occur within ± 2 hours of initial study drug administration on Day 1.

All patients will undergo the following assessments at this time point:

- Directed history and physical examination, focused on signs and symptoms of congestion
- Assessment of the degree of congestion and dyspnea present

- Vital signs (including blood pressure and body weight)
- A blood sample (20 mL) will be collected for assay of routine clinical labs and copeptin determination
- An optional blood sample (30 mL) will also be collected for potential future biomarker and Omic analysis (including RNA)
- A urine sample (5 mL) will be collected for later measurement of biomarkers, electrolytes and osmolarity and other analytes
- Changes in cardiovascular medications
- Assessment for occurrence of heart failure events
- Assessment for adverse events

6.3.2 Day 8 Follow-up

Patients will return on study Day 8 for their last face-to-face visit in the study. This follow-up evaluation is expected to occur within ± 2 hours of initial study drug administration on Day 1.

- Directed history and physical examination, focused on signs and symptoms of congestion
- Assessment of the degree of congestion and dyspnea present
- Vital signs (including blood pressure and body weight)
- A blood sample (20 mL) will be collected for assay of routine clinical labs and copeptin determination
- An optional blood sample (30 mL) will also be collected for potential future biomarker and Omic analysis (including RNA)
- A urine sample (5 mL) will be collected for later measurement of biomarkers, electrolytes and osmolarity and other analytes
- Changes in cardiovascular medications
- Assessment for occurrence of heart failure events
- Assessment for adverse events

6.3.3 Telephone contact (Day 30)

All study patients will be contacted by telephone on study day 30 (+/- 2 days).

- Review of heart failure symptoms
- Review of changes in cardiovascular medication
- To determine vital status and occurrence of hospitalizations and ED visits.

Completion of this 30 day telephone follow-up will end the patient's participation in the study.

6.3.4 Core Lab Blood Sample Processing

At each study visit, in addition to sending a blood sample to the local site laboratory, plasma, serum, and whole blood samples and a urine sample will be processed and shipped to the UNITE-HF Biomarker and Genomics Core laboratory at UNC. These samples will undergo additional processing as needed and will be stored long-term according the Manual of Operations that will be developed for the study. Whole blood will be processed at the core lab to isolate DNA and RNA which will be stored appropriately for potential long-term analysis. The blood biomarker copeptin will be measured to assess the association with the therapeutic response to tolvaptan after the completion of study enrollment and patient follow-up. The remainder of the samples will be used by study investigators to evaluate the role of specific biomarkers (plus genetic and Omic markers) in the biology and pathophysiology of heart failure and the response to heart failure medications including tolvaptan.

7. Study Endpoints

7.1 Primary Endpoint

The primary endpoint for the study will be change in body weight between patients randomized to tolvaptan versus placebo from baseline to 48 hours with and without stratification for baseline copeptin level.

7.2 Secondary Endpoints – Congestion Indices and Body Weight.

7.2.1 Change in the patient reported visual analog scale for dyspnea from baseline to 48 hours.

7.2.2 Change in loop diuretic dose (mg furosemide) at 48 hours.

7.2.3 Loop Diuretic Adjustment defined as decrease versus no change or increase in loop diuretic dosing at 48 hours.

7.2.4 Change in Loop Diuretic Score defined based on change in loop diuretic dosing.

7.2.5 Change in body weight from baseline to 8 days.

7.3 Exploratory Endpoints

7.3.1 Association of change in Body Weight with Baseline Copeptin by Randomized Study Arm. Correlation between copeptin concentration at baseline and the change in body weight from baseline to 48 hours in the study patients stratified by randomization to tolvaptan or placebo.

7.3.2. Other Exploratory Endpoints. Planned exploratory endpoints include longitudinal changes in copeptin, renal function, and serum sodium. In addition, other areas of interest that may warrant future analyses include investigation of interrelationships between clinical characteristics and change in the pattern of worsening heart failure during treatment in the study patients.

8. Statistical Analysis of Study Endpoints

8.1 General Aspects of the Study Analysis

8.1.1 Intention to Treat. The primary analysis will be done on an intention-to-treat basis, with patients analyzed as being in the treatment group to which they were randomized.

8.1.2 Missing Data. No imputation will be made for missing study data points.

8.2 Primary Endpoint.

8.2.1 Priority Analysis of Primary Endpoint

The two components of the Primary Endpoint will be ordered by their importance. The priority analysis of the primary study endpoint will be change in body weight between treatment groups at 48 hours **without stratification** for baseline copeptin.

8.2.2 Second Analysis of the Primary Endpoint

The second analysis of the primary study endpoint will be change in body weight between treatment groups at 48 hours **with stratification** for baseline copeptin. This approach will stratify study patients into subgroups based on their baseline copeptin level. Change in body weight will be compared between tolvaptan and placebo stratified according to baseline copeptin levels into low and high groups, in a similar manner to that described above for the primary analysis of the primary endpoint. A single prespecified cut point for baseline copeptin will define low and high copeptin in the randomized subgroups. Originally, this cut point was defined as < 10 pmol/L based on the previous pilot study of the relationship of baseline copeptin to tolvaptan response described in the background section of the protocol. However, recent studies in patients with volume overload, suggest that few patients in the current protocol would have values < 10 pmol/L. Therefore, the prespecified cut point will be determined based on blinded analysis of the baseline copeptin levels in the current study. This cut point will be determined taking into consideration the distribution of copeptin levels present in the study population at baseline. Additional cut points may be proposed based on the unrestricted correlation analysis of the changes in body

weight related to baseline copeptin in the randomized subgroups as described below (8.5.4.1). The copeptin guided hypothesis predicts that patients with elevated baseline copeptin who are treated with tolvaptan will have a significantly greater weight loss than placebo treated patients.

Table 2. Analysis of Treatment Effect by Baseline Copeptin

	Tolvaptan + Augmented current loop	Augmented current loop	Change in Body Weight
Baseline Copeptin Level	Low	Low	Weight change will be similar in 2 treatment groups
	High	High	Weight change will be > in Tolvaptan + Augmented current loop

8.3 Secondary Endpoints: Ordered by Clinical Importance.

8.3.1 VAS Score. The highest priority secondary endpoint will be based on the patient reported VAS dyspnea score with comparison of the change in this scale from Visit 1 to Visit 2 by treatment group. Based on previous experience with this scale, the current study will not have statistical power to determine if there is a difference between the tolvaptan and placebo group in VAS dyspnea results. However, this dyspnea score has been widely used in previous trials of acute heart failure and may provide a signal of potential benefit of tolvaptan.

8.3.2 Change in Loop Diuretic Dose at Visit 2. The next highest priority secondary endpoint will be based on changes in loop diuretic dosing in the study patients at Visit 2. Doses of loop diuretic will be converted as necessary to milligram (mg) equivalents of furosemide dose by the following definitions: 1 mg of bumetanide = 40 mg of furosemide and 1 mg of torsemide = 20 mg of furosemide. The difference of interest will be the dose of loop diuretic at the end of Visit 2 minus the dose at the start of Visit 2 (expressed as mg equivalents of furosemide).

8.3.3 Categorical Assessment of Loop Diuretic Use at Visit 2 – Loop Diuretic Adjustment. Clinical experience strongly suggests that changes in dosing of loop diuretics during the trial would be a strong indicator of changes in congestion status. Specifically, a decision to increase loop diuretic dose during Visit 2 would equate to

worsening congestion while a decision to reduce loop dose during Visit 2 would reflect improvement in volume status and less congestion.

During the development of this aspect of the analysis plan (still in the blinded period of the study), the investigators assumed that the pattern of changes in loop dose use would be similar to that of patients with acute heart failure where increases in doses of loop diuretic are typical. Thus, the initial analysis for loop dose adjustment was based on increases in loop dose at Visit 2 or the addition of metolazone. However, when blinded aggregate study results were reviewed, the opposite pattern was found. The aggregate blinded data revealed that loop doses on the whole decreased rather than increased at Visit 2 and no additional diuretics were added. These observations led to a final analytical approach, where dichotomous response was characterized as favorable when loop doses were decreased and unfavorable when loop doses stayed the same or were increased.

8.3.4 Change in Loop Diuretic Score at Visit 2. A final response analysis based on changes in diuretic use at Visit 2, change in loop diuretic score, will be developed. This scoring system accounts for increases, decreases, and no change in loop diuretic dose to capture the overall pattern of loop diuretic use at 48 hours. This change in loop diuretic score endpoint will be calculated as follows: patients having an increase in loop diuretic dose at Visit 2 will be given a score of 2, patients with no change a score of 0, and patients with a decrease in loop dose at Visit 2 will be given a score of -1. Increases in loop diuretic dose will be given a higher weighting to account for their reflection of treatment failure. Scores for diuretic change will be compared between the two treatment groups as described below.

8.3.5 Change in Body Weight Visit 1 to Visit 3. This secondary endpoint will be change in body weight change from Visit 1 to Visit 3 by treatment group.

8.5 Statistical Analysis of Study Results

8.5.1 General Statistics. Descriptive statistics will be generated for a comprehensive set of study variables to determine measures of central tendency and dispersion, as well as to characterize the nature of their distributions and whether outliers existed in the data. Continuous values will be reported as mean ± standard deviation and categorical values as frequencies and percentages.

8.5.2 Analysis of the Primary Endpoint. The comparison of change in body weight from baseline to 48 hours between the two treatment groups constituted the primary endpoint. Hypothesis testing on this between-group change was performed by

nonparametric methods using the Wilcoxon rank-sum test via SAS PROC NPAR1WAY; a two-sided significance level of .05 was applied. This analysis of change in body weight was compared between all tolvaptan treated patients and all placebo treated patients on an intention-to-treat basis. Within-group changes over time were analyzed via the nonparametric Wilcoxon signed-rank test using SAS PROC UNIVARIATE under a two-sided significance level of .05. The second analysis of the primary study endpoint, comparison of change in body weight between treatment groups at 48 hours **with stratification** for baseline copeptin, will be conducted in the same manner as the priority comparison.

8.5.3 Analysis of Secondary Endpoints.

A two-sided significance level of .05 will also be applied to statistical testing of secondary endpoints with no adjustment for multiple comparisons.

8.5.3.1 Changes in VAS Scale. Changes in the VAS dyspnea scale will be analyzed via point estimates and corresponding standard deviations. Supportive between-treatment group comparisons will be conducted via the Wilcoxon rank-sum test.

8.5.3.2 Change in Loop Dose. For this continuous variable (dose of loop diuretic in furosemide mg equivalents) between-group comparisons will be assessed via t-test.

8.5.3.3 Loop Diuretic Adjustment. The Fisher's exact test will be used to assess between-group comparisons for this dichotomous variable.

8.5.3.4 Change in Loop Diuretic Score. For this ordinal variable between-group comparisons will be assessed via t-test.

8.5.3.5 Change in body weight from Visit 1 to Visit 3. This endpoint will be analyzed in a similar fashion as the change in body weight from Visit 1 to Visit 2.

8.5.4 Analysis of Exploratory Endpoints.

8.5.4.1 Change in Body Weight with Baseline Copeptin by Randomized Study Arm. This endpoint will be evaluated using Spearman Correlation analysis. The correlation coefficient between copeptin concentration at baseline and the change in body weight from baseline to 48 hours in the study patients within each of the two randomized arms (tolvaptan or placebo) will be determined. The two-sided 95% confidence interval will also be constructed. The Spearman correlation approach will be used as it is rank-based and does not make distributional assumptions.

8.5.4.2. Other Exploratory Endpoints. Planned between-group comparisons of continuous variables (copeptin, serum creatinine, and serum sodium) will be assessed via the Wilcoxon rank-sum test or t-test as appropriate.

9. Sample Size and Rationale

9.1 Sample Size.

The study will have a sample size of 40 patients, equally allocated to the two study treatment groups.

9.2 Power Calculation. The study power calculation was based on the primary analysis of the primary endpoint: change in body weight from baseline to 48 hours between the randomized study groups. Using experience in the preceding pilot study (8), a sample size of 40 patients will have 79% power to detect a difference of 1 kilogram in change in body weight between the study treatment groups (augmented loop diuretic + tolvaptan versus augmented loop diuretic alone) at the two-sided .05 significance level.

10. Safety and Adverse Events

10.1 Summary of the Risks and Benefits

General Safety Considerations. This study targets patients with worsening outpatient heart failure. The study will evaluate the addition of tolvaptan to augmentation of oral furosemide versus augmentation of oral furosemide alone in patients with worsening outpatient heart failure. Augmentation of oral loop diuretic is considered standard therapy in this target patient population. A number of moderate and large scale clinical trials have demonstrated evidence of the safety of tolvaptan in the treatment of patients for hyponatremia and patients with heart failure with and without hyponatremia. Side effects have been noted, most commonly thirst and polyuria and these may lead to discontinuation. However reduction in renal function and blood pressure or elevation of potassium are not associated with drug use; a major finding since most evidence based therapy for heart failure can produce significant renal dysfunction, unwanted hypotension and elevation of potassium that can have serious consequences.

Safety in Heart Failure. Oral tolvaptan was previously studied in the acute heart failure population in the EVEREST study, in which acute and chronic tolvaptan administration was not associated with any evidence of harm over a median follow-up of 10 months (compared to 8 days in the current study). The EVEREST study provides extensive experience with the safety of tolvaptan in heart failure. In this trial, 4133 patients with acute decompensated heart failure were randomized to either placebo or tolvaptan. The overall

rate of in hospital serious adverse events with the combination of oral Tolvaptan and IV loop diuretics was approximately 5%, and was similar between Tolvaptan and placebo. Therefore it is not anticipated that study participation will be associated with increased risks beyond that of standard therapy for decompensated heart failure.

Recurrent volume overload, driven by sodium and water retention, remains a major clinical problem in heart failure despite the use of potent diuretics acting at multiple points within the nephron. All too often patients fail to be congestion free despite the potential potency of loop diuretics in particular. Therefore potential benefits to study participants include the possibility of improvements in clinical congestion and associated symptoms (if Tolvaptan proves to be efficacious).

Risk of Overcorrection of Serum Sodium. Although the target patient population of this study is decompensated heart failure rather than hyponatremia, it must be acknowledged that there is the real potential for overlap of these two conditions in a given patient. This possibility means that there is one risk that is unique to tolvaptan versus other medications for heart failure that must be addressed: overcorrection of serum sodium. Overcorrection of serum sodium is related to the primary mechanism of action of tolvaptan which leads to greater water excretion by the kidney and consequently an increase in serum sodium. In the great majority of patients with heart failure, the increase in serum sodium following administration of tolvaptan is appropriate. However, rarely patients may experience an overcorrection of serum sodium. Overcorrection has been most commonly defined as an increase in serum sodium from baseline of > 12 mEq/Liter in a 24 hour period after tolvaptan administration.

The risk of overcorrection of serum sodium is strongly associated with the degree of reduction in serum sodium present prior to therapy. Overcorrection is generally only a potential issue when patients with hyponatremia are treated with tolvaptan. The widely accepted definition of hyponatremia is presence of a reduction in serum sodium to < 135 mEq/L. Hyponatremia can be further characterized as mild (serum sodium from 130 to 134 mEq/L) or marked (serum sodium < 130 mEq/L). A serum sodium of less than 125 mEq/L has also been defined as sufficiently reduced to warrant tolvaptan therapy as treatment regardless of the presence or absence of symptoms. Although it remains uncommon, overcorrection of serum sodium is most likely to occur in cases where serum sodium is < 125 mEq/L.

Since hyponatremia is uncommon in acute or chronic heart failure, overcorrection of serum sodium has not been reported as an issue in these studies. Review of the experience in

the EVEREST trial helps provide a clinical context concerning the potential risk of overcorrection of serum sodium specifically in patients with heart failure. Despite studying a targeted patient population of acute decompensated heart failure, hyponatremia was uncommon in the patients enrolled in this trial. A total of 4133 patients were studied, randomized to tolvaptan and randomized to placebo with an initial dose of 30 mg of tolvaptan daily. The incidence of hyponatremia at baseline was 11.5% overall (475 patients) and as expected, was similar in groups receiving tolvaptan and placebo.

Experience in the SALT trials, which used the definition above for hyponatremia (serum sodium < 135 mEq/L) as an inclusion criteria and did include patients with heart failure, can help define the risk of overcorrection of serum sodium in patients with heart failure and hyponatremia. A total of 448 patients were randomized in the SALT studies with 225 patients treated with tolvaptan and 223 patients with placebo. The initial dose of tolvaptan in these trials was 15 mg daily but could be titrated to 60 mg daily depending upon therapeutic response. In these trials only 5 patients on active therapy (2.2%) experienced a rise in serum sodium of > 12 mEq/L during any 24 hour period of treatment.

Osmotic Demyelination Syndrome (ODS). Although an increase in serum sodium can be lifesaving in acute symptomatic hyponatremia, overcorrection of serum sodium may rarely result in severe neurological dysfunction referred to as ODS. This syndrome is the general term for central pontine and extrapontine myelinolysis. Clinically ODS is characterized by dysarthria, dysphagia, behavioral disturbance, and muscle weakness which may not resolve and the condition may be fatal. A number of predisposing factors for ODS following overcorrection of serum sodium have been identified: chronic alcoholism, severe liver disease, marked malnutrition and hypoxia. Review of clinical reports of ODS suggest that while the threshold for observing this syndrome may be 8 to 12 mEq/L increase of serum sodium, most cases have occurred in the setting of significantly larger increases in serum sodium, often in excess of 20 mEq/L.

While there is no question that overcorrection of serum sodium by the criteria of an increase of > 12 mEq/L of serum sodium may rarely occur with tolvaptan therapy, the frequency with which ODS occurs in association with tolvaptan therapy remains disputed. None of the 5 patients in the SALT trials who has an increase in serum sodium of > 12 mEq/L experienced ODS (nor did any other patient in the SALT trials). No cases of ODS have been reported in patients treated with tolvaptan in randomized clinical trials including approximately 2,000 patients with heart failure. The FDA Package Insert for tolvaptan indicates that cases of ODS have been reported post marketing but the exact language in

the text concludes that the anecdotal nature of these reports does not permit assignment of causal role for tolvaptan. One example of confounding that may occur in the post marketing data is concomitant therapy with hypertonic saline. Simultaneously treatment with both tolvaptan and hypertonic saline is contraindicated, would significantly increase the risk of overcorrection and will not occur in this study. It is important to note that clinical series have found that the development of ODS may be low in the setting of overcorrection.

Implications for the Present Study. Given the study sample size of 40 patients and the planned exclusion of patients with serum sodium < 125 mEq/L, approximately 3 to 4 patients could be expected to be enrolled with hyponatremia. The low rate of overcorrection observed in the SALT Trials suggests, that even in the setting of hyponatremia, the risk of a single study patients experiencing overcorrection of sodium in response to tolvaptan would be low.

Minimizing Risk of Overcorrection of Sodium. Although the risk of overcorrection of serum sodium is low in patients with heart failure, it is appropriate to take steps to reduce the risk of this potentially very serious and rarely fatal complication.

During Screening

1- Patients with symptomatic hyponatremia will be excluded from the study.

2- Patients with severe hyponatremia, defined as serum sodium < 125 mEq/L at the time of screening, will be excluded regardless of whether they are symptomatic or not.

3- Patients with the following predisposing factors for ODS, assessed by the study investigator judgment, will be excluded: chronic alcoholism at the time of study, severe liver disease, marked malnutrition, and risk for chronic hypoxia.

Randomization - Initial Dose of Study Drug

4. All patients will initiate study drug tolvaptan/placebo in a hospital setting.
5. Patients who are not hyponatremic at baseline will be monitored for 8 hours for adverse effects and changes in vital signs suggestive of potential volume depletion (orthostatic decline in blood pressure and increases in heart rate) and intake and output. Review of these findings will aid in identification of patients who may be more likely to have overcorrection of serum sodium due to excess aquaresis and inadequate per oral intake. Any patient without hyponatremia at baseline who is clinically suspected to have overcorrection of serum sodium will have repeat determination of serum electrolytes and renal function at 6 hours post initial dose of

tolvaptan/placebo and these labs will be reviewed prior to their discharge from the hospital setting. Any patient subsequently found to have an increase in serum sodium > 6 mEq/L will be managed as indicated in points 6 to 9 that follow.

6. Patients who are hyponatremic at baseline will all have repeat determination of serum sodium 6 hours after their initial dose of study drug. Any of these hyponatremic patients found to have a rise in serum sodium of > 6 mEq/L at the 6 hour time point will receive treatment with intravenous D5W designed to limit further increases in serum sodium. Intravenous D5W will administered at the rate of 3 mL/kg per hour (210 mL for a 70 kilogram patient) which is expected to reduce serum sodium from 1 to 2 mEq/L per hour.
7. Patients with this degree of early increase in serum sodium will have repeat serum sodium and other electrolytes plus BUN and Creatinine determined at 2 hour intervals of D5W administration. Administration of D5W will stop when the patient is at least 14 hours post their initial dose of study drug and the serum sodium is < 8 mEq/L above their baseline values.
8. Patients with this degree of early increase in serum sodium will be observed for a minimum of 24 hours after their initial dose of study medication. They will also have repeat determination of serum sodium and other electrolytes plus BUN and Creatinine 20 hours after their initial dose of study medication and these values will be reviewed prior to their discharge from the hospital setting. If their serum sodium remains < 12 mEq/L above baseline at the 20 hour blood draw and they are clinical stable they will be discharged from the hospital setting at the 24 hour point. Any patient that is found to have a 20 hour serum sodium that is > 12 mEq/L from their baseline will receive additional D5W as above with repeat determinations of serum sodium until their value is < 12 mEq/L above their baseline. At that time if they are clinically stable then they will be discharged from the hospital setting.
9. Once discharged hyponatremia patients with overcorrection of sodium will be followed in the study but not treated further with study medication. They will return for a study visit Day 3 where they will have repeat determination of serum electrolytes, including serum sodium, as well as BUN and Creatinine. In the unlikely event that they are found to have serum sodium > 18 mEq/L above their baseline value at this visit, they will be considered for per oral hydration or administration of additional intravenous D5W at the discretion of the clinical investigator.

10. Any patient found to have overcorrection (a rise in serum sodium of > 6 mEq/L at the 6 hour time point) will still continue to be followed in the study and treated with augmented loop diuretic and other medical approaches as needed. They will be seen at Day 8 for evaluation as planned for the protocol and continue to have 30 day follow-up as well as additional clinic visits at any point during the study.
11. Patients found to be hyponatremic will also be monitored for development of symptoms during the study related to reduced serum sodium. As a precaution, patients with symptomatic hyponatremia are excluded from the study. Patients with heart failure who present with hyponatremia are very commonly asymptomatic and the condition is chronic and does require therapy to reverse the hyponatremia per se. Patients with heart failure and chronic hyponatremia rarely become symptomatic. Patients enrolled in the study with asymptomatic hyponatremia will be cautioned to monitor for changes in mental status, nausea, and lethargy between their baseline visit and follow-up visits. Patients will be instructed to contact the study investigators should these symptoms develop and they will be seen for follow-up evaluation as needed.

Hepatic Toxicity. The FDA proposed label changed for tolvaptan in 2013. These changes concerning tolvaptan use indicated that the drug should not be used for longer than 30 days and should not be used in patients with underlying liver disease. These changes were made after 3 cases of suspected liver injury with Tolvaptan were identified in the TEMPO study. TEMPO studied a significantly higher tolvaptan dose (60 mg per day and titrated up to 120 mg per day) and a longer duration of treatment (36 months) than in the planned study (30 mg for 8 doses – with 8 days of exposure). The patient population in TEMPO (Autosomal Dominant Polycystic Kidney Disease) is different than the one proposed for this study. The liver abnormalities occurred after at least 3 months of treatment and all 3 patients improved following discontinuation of treatment. The study protocol for this trial will exclude patients with known underlying liver disease to be consistent with the revised FDA labeling.

10.2 Serious Adverse Events

10.2.1 Definitions

A "**Serious Adverse Event**" (SAE) is any adverse event that:

- Results in death
- Is life-threatening

- Requires inpatient hospitalization or prolongation of hospitalization which is not specifically required by the protocol nor is it elective.
- Results in permanent impairment of a body function or permanent damage to a body structure
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when they jeopardize the patient or require medical or surgical intervention to prevent one of the serious outcomes listed above. Example of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse. Medical and scientific judgment must be exercised when classifying events as serious.

10.2.2 Laboratory Test Abnormalities

For laboratory test abnormalities to meet the definition of an SAE for this protocol, they must require that the subject have their investigational product discontinued or interrupted or the study subject must receive specific corrective therapy for the laboratory abnormality observed. In the case of laboratory test SAEs, the clinical diagnosis rather than the laboratory term will be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

10.2.3 Assessment of Severity

The determination of adverse event severity rests on medical judgment of a medically-qualified investigator. The severity of SAEs will be graded using the following definitions:

Mild: awareness of sign, symptom, or event, but easily tolerated;

Moderate: discomfort enough to cause interference with usual activity and may warrant intervention;

Severe: incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

10.3 Assessment of Causal Relationship

A medically-qualified investigator must assess the relationship of any AE to the use of study drug, based on available information, using the following guidelines:

Possibly Related - There is a reasonable possibility that the adverse event may have been caused by the study drug. The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the observed event.

Not Possibly Related- It is unlikely that the event was caused by the study drug. The temporal relationship of the adverse event to the study drug administration makes causal relationship unlikely and other drugs, therapeutic interventions or underlying conditions provide a more likely explanation for the event.

Expectedness - The expectedness of an adverse event or suspected adverse reaction shall be determined according to the package insert for U.S. marketed furosemide and tolvaptan. Any AE that is not identified in nature, severity, or specificity in the current U.S. package insert is considered unexpected. Events described in the U.S. package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not specifically mentioned as occurring with the particular drug under investigation are considered unexpected.

10.4 Recording and Reporting

Recording. All serious adverse events occurring from randomization through the 30 day follow-up period will be collected. The Site Investigator is responsible for monitoring the safety of patients enrolled into the study at the study sites. The following adverse events are anticipated, disease related-events in patients with decompensated heart failure however they should still be reported on the Serious Adverse Event form of the CRF (some may require reporting as study endpoints):

- Atrial fibrillation
- Ventricular tachycardia
- Myocardial infarction
- Acute coronary syndrome
- Acute renal failure
- Worsening heart failure
- Death

All serious adverse events must be recorded in the Serious Adverse Event Record of the patient's CRF. All serious adverse events should be monitored until stabilization or resolution.

Reporting to Local IRB. Investigators are also responsible for promptly reporting adverse events (serious and non serious) to their reviewing IRB in accordance with local requirements.

Reporting to Study Coordinating Center. Sites will report all adverse events and serious adverse events, as well as unexpected evens, to the coordinating center at UNC. All the adverse events (serious and non serious) and unexpected events from all sites will be formally reviewed in aggregate by the UNC coordinating center. The UNC coordinating center will report all unanticipated problems and serious adverse events to the study sponsor for review. Sites will be updated concerning the status of the study based on this review as appropriate. Consideration will be given to modification of the study protocol and the study ICF as appropriate based on this review.

10.5 Study Termination. The study may be terminated based on review of serious adverse events and unexpected events by the UNC coordinating center and the Study Sponsor. If 5 unexpected events occur this will trigger a temporary halt to the study until additional review of these events is conducted by the UNC coordinating center and the Study Sponsor.

11. Regulatory Issues

11.1 Institutional Review Boards

All sites will submit the study protocol, informed consent form, and other relevant study documents to their Institutional Review Board (IRB) for approval.

11.2 Informed Consent

All patients will have the purpose of the study, the study interventions and evaluations, and the potential risks and benefits of participation explained to them and their questions answered. If they consent to participation in this study, they will review and sign the informed consent form (ICF).

11.3 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with standard clinical research methods and procedures. These procedures are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

12. Study Administration

12.1 Substudy Governance and Committees

The governance and management of the TROUPER study will be organized to facilitate successful conduct of the project.

12.2 Description of the TROUPER Study Cordinating Center

The UNITE-HF Coordinating Center (CC) housed at the University of North Carolina Chapel Hill will serve as the CC for the study. The UNITE-HF CC will function as the study operational center and will be responsible for coordinating all aspects of the study. The UNITE-HF CC will provide project management, development and preparation of study-related documents, and site management and education related to the execution of the trial.

The UNITE-HF CC will conduct initial start-up activities which will primarily involve development of the study protocol and in site identification. The UNITE-HF CC will be responsible for site contracting and monitoring the site IRB approval process. During the study, the UNITE-HF CC will be responsible for ongoing site education and retention, quality control of site conduct of the study, and site reimbursement.

The UNITE-HF CC will conduct the data management for the trial. Data related activities will include development of study specific CRFs and instructions; establishing data management methods; creating and maintaining the substudy database; and ensuring all data queries are addressed.

The UNITE-HF CC will also be responsible for analysis of the study data and take a leadership role in development of presentations and publications related to the results of the substudy as describe in section 12.4 below.

12.3 TROUPER Study Steering Committee

A Steering Committee will be constituted to assist the UNITE-HF CC in addressing matters related to the conduct of the trial. The Steering Committee will include the principal

investigator of each site enrolling patients in the study. The principal investigator for the overall study protocol will chair the Steering Committee. The Steering Committee will meet periodically as determined by the UNITE-HF CC by teleconference or face-to-face to review the progress of the substudy. On issues requiring a vote, one vote per member will be allowed.

12.4 TROUPER Trial Publications and Presentations Committee

There will be a Publications and Presentations Committee for the TROUPER study. The principal investigator of the overall trial will chair this committee. Other members of the Publications and Presentations Committee will include members of the study Steering Committee and the TROUPER study Project Manager. The Committee will review publication proposals and manuscripts and will assist in dissemination of trial results.

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Appendix A: Schedule of Study Assessments

Assessment or Procedure	Screen	Baseline	8 to 24 † hours	Day 3	Day 8	Day 30
Informed Consent	X					
Review of Inclusion and Exclusion Criteria	X					
Serum pregnancy test as applicable		X				
Screening electrolytes, renal and liver function tests	X					
Directed History and Physical Examination		X		X	X	
Vital signs		X	X	X	X	
Body Weight		X		X	X	
Current Cardiovascular Meds		X		X	X	X
Blood sampling for Serum Creatinine, BUN, electrolytes, serum osmolarity and copeptin		X	X*	X	X	
Blood Sampling – for Other biomarkers and Omics		X		X	X	
Blood Sampling – Whole blood		X				
Urine Sampling		X		X	X	
Adverse Events Assessment			X	X	X	X
Assessment of Congestion and Dyspnea		X		X	X	
Changes in Cardiovascular Meds			X	X	X	X
Morbidity Assessment				X	X	X

* Blood sampling will be dependent up baseline hyponatremia or change during observation. † It is possible that a rare patient may have to remain under observation for more than 24 hours before their serum sodium is < 12 mEq/L based on determinations from serial blood samples.

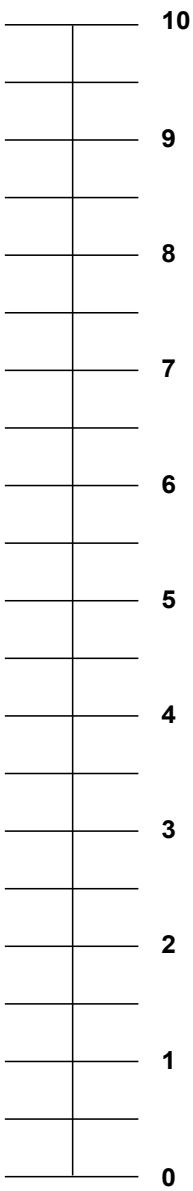
APPENDIX B

Baseline Visit (Day 1)

VISUAL ANALOG SCALE: PATIENT CONGESTION

VISIT 1 (Day 1) and Date: __ __ / __ __ __ / __ __ __ __
D D M M M Y Y Y Y

To be completed by patient. "Please draw a horizontal line on the scale to show how you think your fluid or congestion is right now. The number "0" equals the worst your fluid or congestion has ever felt and the number "10" equals the best your fluid or congestion has ever felt."



Best your fluid or congestion has ever felt

Worst your fluid or congestion has ever felt

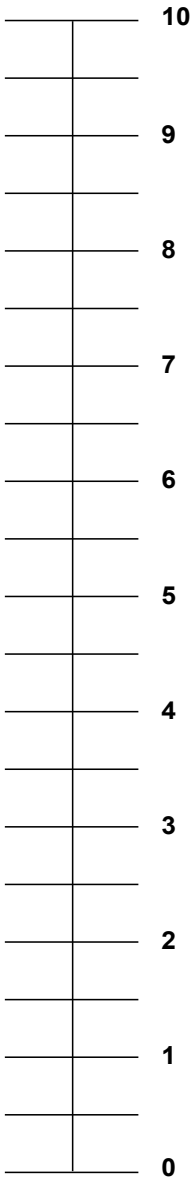
APPENDIX C

Baseline Visit (Day 1)

VISUAL ANALOG SCALE: PATIENT DYSPNEA

VISIT 1 (Day 1) and Date: __ __ / __ __ __ / __ __ __ __
D D M M M Y Y Y Y

To be completed by patient. "Please draw a horizontal line on the scale to show how you think your breathing is right now. The number "0" equals the worst your breathing has ever felt and the number "10" equals the best you have ever felt."



Best your breathing has ever felt

Worst your breathing has ever felt

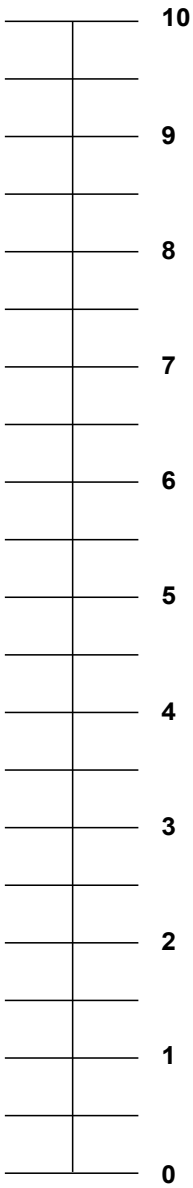
APPENDIX D

Baseline Visit (Day 1)

VISUAL ANALOG SCALE: INVESTIGATOR CONGESTION

VISIT 1 (Day 1) and Date: __ __ / __ __ __ / __ __ __ __
D D M M M Y Y Y Y

To be completed by Investigator. To indicate your opinion of how the patient feels, use the scale below which indicates the best possible state for the patient is a 10, and the worse state is 0. Please draw a line on the scale to show how you think the patient is now.



Best state patient could be in regarding fluid or congestion

Worst state patient could be in regarding fluid or congestion

APPENDIX E

Visit 2 (Day 3) versus Baseline Visit

LIKERT SCALE: PATIENT CONGESTION

VISIT 2 (Day 3) and Date: __ __ / __ __ __ / __ __ __ __
D D M M M Y Y Y Y

Patient will be presented with the following question:

"We would like to measure how you how your congestion is right now. Please circle the number next to the description that best indicates how you best your congestion is right now, compared to when you first started the study 48 hours ago"

3 = Markedly better

2 = Moderately better

1 = Minimally better

0 = No change

-1 = Minimally worse

-2 = Moderately worse

-3 = Markedly worse

APPENDIX F

Visit 3 (Day 3) versus Past Month

LIKERT SCALE: PATIENT CONGESTION

VISIT 2 (Day 3) and Date: __ __ / __ __ __ / __ __ __ __
D D M M M Y Y Y Y

Patient will be presented with the following question:

"We would like to measure how you how your congestion is right now. Please circle the number next to the description that best indicates how you best your congestion is right now, compared to your best compensated state in the past month"

3 = Markedly better

2 = Moderately better

1 = Minimally better

0 = No change

-1 = Minimally worse

-2 = Moderately worse

-3 = Markedly worse

APPENDIX G

Visit 2 (Day 3) versus Baseline

LIKERT SCALE: INVESTIGATOR CONGESTION

VISIT 2 (Day 3) and Date: __ __ / __ __ __ / __ __ __ __
D D M M M Y Y Y Y

Investigator is presented with the following question:

"We would like you to measure the degree of congestion in the patient. Please circle the number next to the description that best indicates how your assessment of the patient's degree of congestion right now, compared to when they first started the study 48 hours ago."

3 = Markedly better

2 = Moderately better

1 = Minimally better

0 = No change

-1 = Minimally worse

-2 = Moderately worse

-3 = Markedly worse

APPENDIX H

Visit 2 (Day 3) versus Baseline Visit

LIKERT SCALE: PATIENT DYSPNEA

VISIT 2 (Day 3) and Date: __ __ / __ __ __ / __ __ __ __
D D M M M Y Y Y Y

Patient will be presented with the following question:

"We would like to measure how you how your breathing is right now. Please circle the number next to the description that best indicates how you are feeling right now, compared to when you first started the study 48 hours ago"

3 = Markedly better

2 = Moderately better

1 = Minimally better

0 = No change

-1 = Minimally worse

-2 = Moderately worse

-3 = Markedly worse

APPENDIX I

Visit 2 (Day 3) versus Past Month

LIKERT SCALE: PATIENT DYSPNEA

VISIT 2 (Day 3) and Date: __ __ / __ __ __ / __ __ __ __
D D M M M Y Y Y Y

Patient will be presented with the following question:

"We would like to measure how your breathing is right now. Please circle the number next to the description that best indicates how you feel about your breathing right now, compared to your best compensated state in the past month "

3 = Markedly better

2 = Moderately better

1 = Minimally better

0 = No change

-1 = Minimally worse

-2 = Moderately worse

-3 = Markedly worse