Protocol for the Heart Failure Clinical Research Network

**Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients:
EXACT-HF**

Compiled by:
The Heart Failure Network Research Group
June 30, 2010
Amendment 1

Distributed by:
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1. EXECUTIVE SUMMARY

Background: Oxidative stress may contribute to ventricular and vascular remodeling, and disease progression in patients with heart failure. Xanthine oxidase (XO) is a potential source of oxidative stress in heart failure, and may be an important target for therapy. Allopurinol is an XO inhibitor, which reduces serum uric acid levels, and may be useful in the treatment of patients with systolic heart failure (HF).

Hypothesis: In patients with symptomatic heart failure due to left ventricular systolic dysfunction and elevated serum uric acid levels, treatment with allopurinol for 24 weeks will improve clinical outcomes compared to treatment with placebo.

Study Design: Randomized, double-blind, placebo-controlled, 26-week trial, including:

> **Screening Phase:** Patients will have an initial screening evaluation, including baseline laboratory tests and echocardiogram, at which time preliminary patient eligibility will be determined. Those who meet inclusion and exclusion criteria and are interested in study participation will return within 7-14 days for randomization.

> **Study Drug Phase:** Patients will be randomized (1:1) to XO inhibition or placebo and undergo double-blind treatment for 24 weeks. Patients will return for evaluations at 4, 12 and 24 weeks. Drug tolerability and compliance will be assessed by phone contacts at 1, 8 and 18 weeks.

> **Follow-up Phase:** Patients who have completed 24 weeks of study drug will be contacted by phone 2 weeks after withdrawal from study drug to assess safety and HF symptoms.

Study Population: Approximately 250 patients meeting eligibility criteria will be enrolled.

Selected inclusion criteria
1. NYHA class II-IV heart failure due to ischemic or non-ischemic cardiomyopathy.
2. Heart failure symptoms for 3 months despite standard treatment.
3. Left ventricular ejection fraction ≤ 40% by echocardiography.*
4. Serum uric acid level $\geq$ 9.5 mg/dl.†
5. At least one of the following additional markers of increased risk:
   a. Hospitalization, ER visit or urgent clinic visit for heart failure requiring IV diuretics within the previous 12 months
   b. Left ventricular ejection fraction ≤ 25%
   c. B-type natriuretic peptide level > 250 pg/ml

*Determined at or within 4 weeks of screening evaluation.
†Determined at the time of screening evaluation.

Selected exclusion criteria

1. Hypertrophic or restrictive cardiomyopathy, constrictive pericarditis, biopsy-proven myocarditis, severe stenotic valvular disease, or complex congenital heart disease.
2. Acute coronary syndrome, PCI or CABG within 3 months.
3. Current ventricular assist device or ventricular assist device or heart transplant likely within the next 6 months.
4. Uncontrolled hypertension (i.e., SBP > 170 mm Hg or DBP > 110 mm Hg)
5. Serum creatinine > 3 mg/dL or estimated GFR < 20 ml/min.
6. Evidence of active hepatitis with ALT and AST greater than 3x normal.
7. Any condition other than HF which could limit the ability to perform a 6-minute walk test
8. Any diseases other than HF which are likely to alter the patient's global perception of status or quality of life over a period of 6 months.
9. Receiving treatment with allopurinol currently or within 30 days, or having symptomatic hyperuricemia which requires treatment with allopurinol.

Study Drug: Allopurinol (vs. matching placebo) 300 mg daily for one week, then 600 mg daily (in divided doses of 300 mg) to complete 24 weeks.

Concomitant Medications: Standard oral therapy for heart failure, including ACE inhibitors or ARBs, beta-blockers and diuretics will be continued and adjusted as medically indicated.

Primary Endpoint: A composite clinical endpoint (CCE) that classifies subject's clinical status as improved, worsened, or unchanged at 24 weeks. The classification will follow sequential rules based on the outcomes of the following items: 1) Death; 2) hospitalization, ER visit or emergent clinic visit for worsening HF; 3) medication change for worsening HF; and 4) Patient Global Assessment.

Principal Secondary Endpoints:

1. Change in quality of life (KCCQ) at 12 and 24 weeks.
2. Change in submaximal exercise capacity (6-MWT) at 12 and 24 weeks.

Tertiary Endpoints:

1. Individual components of the primary composite endpoint.
2. NYHA functional class at 12 and 24 weeks.
3. Echo measures: LV volumes, stroke volume, ejection fraction and mass.
4. HFN biomarker panel: BNP, ET-1, TnT, hs-CRP, PIIINP, CITP, uric acid.
5. Renal function: serum creatinine, cystatin C and estimated GFR.*
6. Markers of oxidative stress: malondialdehyde (MDA), myeloperoxidase (MPO), nitrotyrosine, allantoin, ST2, IL33.*
7. Markers of insulin resistance: plasma insulin, glucose and free fatty acid (FFA) levels; and substrate utilization by metabolic cart test.*
8. Increased diuretic requirement (defined as an increase in outpatient diuretic dose by at least 50% for more than one week).

9. Total number of hospitalizations for any cause.
10. Total number of hospital days.
11. Time to first hospitalization for heart failure.
12. Cardiovascular death.

*Change from baseline to 24 weeks for patients enrolled in Ancillary Study.

Safety: Safety will be evaluated by comparing the occurrence of adverse events and changes in laboratory values in the two treatment arms.

Statistical Analysis: All analyses will be conducted using an intention to treat (ITT) principle. Analysis of the primary efficacy CCE will utilize the Cochran-Mantel-Haenszel row mean score test with modified ridit scores to compare the distributions.

Potential Ancillary Studies: The mechanisms underlying the anticipated clinical benefits of XO inhibition in hyperuricemic heart failure patients are incompletely understood. Ancillary studies that could help to elucidate these mechanisms may include assessment of change in:
1. Vascular endothelial function
2. Diastolic function
3. Skeletal muscle structure and function
4. Exercise chronotropic and contractile "reserve"

Future Directions: If we demonstrate that chronic XO inhibition is safe and improves clinical outcomes in patients with systolic heart failure, this finding would provide a strong rationale to perform a similar study in patients with diastolic heart failure. If we demonstrate secondary improvements in renal function, this would suggest the need for a proof of concept study of acute XO inhibition in hospitalized patients with cardiorenal syndrome.

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2. HYPOTHESES AND OBJECTIVES

Primary Objective: To determine whether chronic inhibition of xanthine oxidase produces clinical benefits in hyperuricemic heart failure patients with left ventricular systolic dysfunction.

Hypothesis: In patients with symptomatic heart failure due to left ventricular systolic dysfunction and elevated serum uric acid levels, treatment with allopurinol for 24 weeks will improve clinical outcomes compared to treatment with placebo.

Secondary Objectives: Other secondary objectives of this protocol will be:
- To evaluate the effects of xanthine oxidase inhibition on quality of life and submaximal exercise capacity in hyperuricemic patients with systolic heart failure.
- To evaluate the effects of xanthine oxidase inhibition on left ventricular structure and function in hyperuricemic patients with systolic heart failure.
- To determine the effects of xanthine oxidase inhibition on biomarkers of oxidant stress and ventricular remodeling in patients with heart failure.
- To determine the safety and tolerability of chronic xanthine oxidase inhibition in patients with heart failure.

3. BACKGROUND AND SIGNIFICANCE

Heart Failure. Heart failure (HF) is a common disease in the United States with significant associated morbidity and mortality. It is estimated that 2% of the U.S. population carries the diagnosis of HF, with a prevalence greater than 10% in patients over the age of 75.[1] Despite recent advances in therapy, the overall 5-year mortality remains around 50%, and the 1-year mortality in patients with New York Heart Association (NYHA) functional class III-IV heart failure on maximal medical therapy is 35-40%. Many aspects of the pathophysiology of heart failure are incompletely understood, and there is a clear need for improved medical therapies.

Oxidant stress and progression to heart failure. Reduced myocardial antioxidant activity and increased oxidant damage have been demonstrated in animal models of heart failure, and markers of oxidative stress are increased in HF patients.[2] These data have led to the thesis that reactive oxygen species (ROS) may contribute to the progression of myocardial failure. Xanthine oxidase (XO) is among the potential sources of ROS in heart failure, and may be an important target for therapy.[3] Current evidence supports the hypothesis that heart failure is associated with an increase in the activity of the XO, which in turn increases production of superoxide and uric acid (UA). Other contributors to hyperuricemia include activation of pro-inflammatory cytokines, impaired vascular function and renal insufficiency. In patients with heart failure, there is a strong relationship between elevated UA levels and increased mortality.[4]

Superoxide decreases nitric oxide signaling and also decreases myofilament sensitivity to calcium and contractility. Decreased contractility leads to hypoperfusion of the heart

and other organs, increases anaerobic metabolism, and leads to depletion of ATP and the accumulation of hypoxanthine (the substrate of XO). Allopurinol can reverse these processes, ultimately increasing cardiac contractile efficiency and reducing myocardial oxygen consumption.

Acute xanthine oxidase inhibition in heart failure. Heart failure is characterized by an imbalance between left ventricular (LV) performance and myocardial energy consumption. Experimental models suggest that oxidant stress resulting from XO activation contributes to mechanoenergetic uncoupling, and that XO inhibition with allopurinol may improve LV efficiency.[5] Cappola et al.[6] instrumented patients with idiopathic dilated cardiomyopathy to assess myocardial oxygen consumption (MVO_2), contractility (dP/dt_{max} and E_{es}) and efficiency (SW/MVO_2) before and after intracoronary infusion of allopurinol. Allopurinol caused a significant decrease in MVO_2 (-16 $\pm$ 5%, p<0.01) without a parallel decrease in dP/dt_{max} or E_{es}. The net result was a significant increase in myocardial efficiency (+40 $\pm$ 7%, p<0.05).

Chronic xanthine oxidase inhibition in heart failure. Impaired endothelium-dependent relaxation contributes to symptoms and exercise intolerance in heart failure. An important mechanism underlying endothelial dysfunction is increased oxidative stress, due in part to vascular XO activity. To determine if chronic XO inhibition would improve endothelial function in heart failure, Farquharson et al.[7] randomized 11 patients with mild-moderate heart failure in a double-blind, crossover study to receive allopurinol 300 mg once daily or placebo for one month. Allopurinol significantly improved endothelium-dependent vasodilation and reduced markers of oxidative stress. In a subsequent study, George et al.[8] demonstrated a steep dose-response relationship between allopurinol and its effect on endothelial function. In 30 subjects with chronic heart failure, allopurinol 600 mg once daily increased forearm blood flow in response to acetylcholine compared to both allopurinol 300 mg once daily and placebo, and was well tolerated.

4. PRELIMINARY STUDIES

Oxypurinol is the primary metabolite of allopurinol, and therefore a potent XO inhibitor. Numerous studies have documented the potential benefits of oxypurinol in experimental and clinical conditions involving oxidative stress. The OPT-CHF Trial was designed to test whether oxypurinol produces clinical benefits in patients with NYHA functional class III or IV heart failure due to systolic dysfunction receiving optimal medical therapy.[9] In this study, 405 patients with a mean age of 65 years and LVEF of 26%, who were well treated with ACE inhibitor/ARB (96%) and beta-blocker (92%), were randomized to receive oxypurinol 600 mg once daily or placebo for 24 weeks. Efficacy was assessed using a composite end point comprising heart failure morbidity, mortality and quality of life.[10] Oxypurinol reduced serum uric acid by ~2 mg/dl (p<0.001, figure 1), but did not improve clinical status in unselected patients with moderate-severe heart failure. In a subgroup analysis, patients with elevated UA levels ($\geq$ 9.5 mg/dl, n = 108) responded favorably to oxypurinol, whereas patients with UA < 9.5 mg/dl exhibited a trend towards worsening (figure 2). In addition, UA reduction to oxypurinol correlated with favorable

clinical response.

Based on these data, we hypothesize that in patients with symptomatic heart failure due to LV systolic dysfunction, who have elevated serum uric acid levels, treatment with allopurinol for 24 weeks will improve clinical outcomes compared to treatment with placebo.
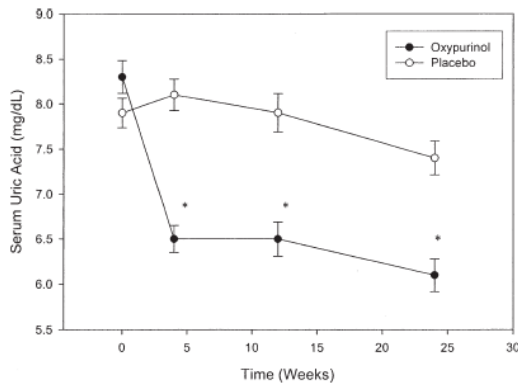
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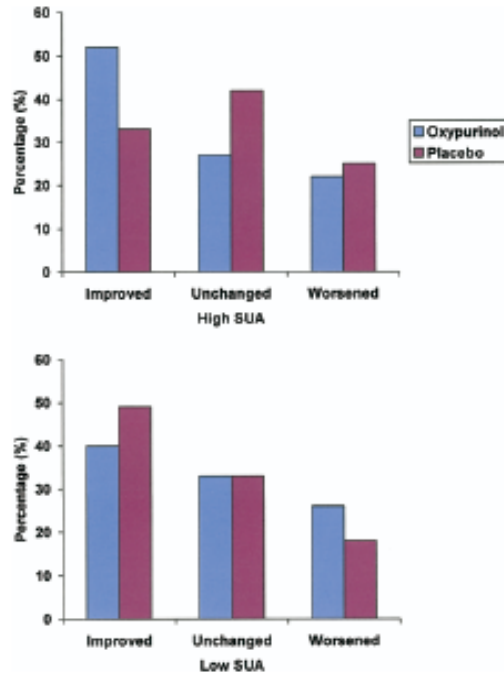
Figure 2

5. BASIC STUDY DESIGN

Study Design: This study is a multi-center, randomized, double-blind, placebo-controlled, 24-week trial of allopurinol in patients with symptomatic heart failure due to LV systolic dysfunction (LVEF ≤ 40%) and elevated serum uric acid levels (UA ≥ 9.5 mg/dl). A total of 250 patients will be enrolled. The study includes the following phases as shown in Figure 3:

Screening Phase: Patients will have an initial screening evaluation, including baseline laboratory tests and echocardiogram, at which time preliminary patient eligibility will be determined. Those who meet inclusion criteria and are interested in study participation will return within 7-14 days for randomization.

Study Drug Phase: Patients will be randomized (1:1) to XO inhibition or placebo and undergo double-blind treatment for 24 weeks. Active therapy will consist of allopurinol 300 mg uptitrated to 600 mg daily (in divided doses of 300 mg), with dose adjustment

for renal dysfunction. Patients will return to clinic for evaluations at 4, 12 and 24 weeks.

<u>Follow-up Phase</u>: Patients who have completed 24 weeks of study drug will be contacted by phone 2 weeks after withdrawal from study medication to assess safety and HF symptoms.

STUDY FLOW DIAGRAM (Figure 3)

Screening Visit -1
-7 to -14 Days

↓

Visit 0
Baseline Evaluation
and Randomization

Day 0

↓

Begin 300 mg/day*
Days 0 to 6

↓

Visit 1 - Phone Follow-up
Days 7 to 10; Up-titrate
to 600 mg (300 mg bid)

*Dosage will be adjusted
based on renal dysfunction
(see section 7.8)

↓

Visit 2
4 Weeks*

Visit 3 - Telephone
Compliance Check
8 Weeks

↓ ←

Visit 4
12 Weeks*

Visit 5 - Telephone
Compliance Check
18 Weeks

↓ ←

Visit 6
24 Weeks

Withdrawal from
Study Drug

↓

Visit 7 - Telephone Check
26 Weeks

Safety Follow-up

6. STUDY POPULATION AND ELIGIBILITY CRITERIA

6.1 Study Population
It is anticipated that approximately 250 patients meeting eligibility criteria listed below will be enrolled in the study.

6.2 Inclusion Criteria
1. Males or females age 18 years or older.
2. NYHA functional Class II-IV heart failure due to ischemic or non-ischemic cardiomyopathy.
3. HF symptoms for 3 months despite standard heart failure treatment with an ACE inhibitor or ARB, and beta-blocker (if tolerated).
4. Left ventricular ejection fraction $\leq$ 40% by echocardiography.*
5. Serum uric acid level $\geq$ 9.5 mg/dl.†[4,9,11]
6. <u>At least one</u> of the following <u>additional</u> markers of increased risk:*
   a. Hospitalization, ER visit or urgent clinic visit for heart failure requiring IV diuretics within the previous 12 months
   b. Left ventricular ejection fraction ≤ 25%
   c. B-type natriuretic peptide level > 250 pg/ml

*Determined at or within 4 weeks of screening evaluation.
†Determined at the time of screening evaluation.

6.3 Exclusion Criteria
1. Female who is pregnant, nursing, or of childbearing potential not practicing effective birth control.
2. Hypertrophic or restrictive cardiomyopathy, constrictive pericarditis, biopsy-proven myocarditis, severe stenotic valvular disease, or complex congenital heart disease.
3. Acute coronary syndrome, PCI or CABG within 3 months.
4. Current ventricular assist device or ventricular assist device or heart transplant likely within the next 6 months.
5. Uncontrolled hypertension (i.e., blood pressure consistently greater than 170 mm Hg systolic or 110 mm Hg diastolic).
6. Active hyperthyroidism or untreated hypothyroidism.
7. Serum creatinine > 3 mg/dL or estimated GFR < 20 ml/min (modified MDRD).
8. Evidence of active hepatitis with ALT and AST greater than 3x normal.
9. Any condition other than HF which could limit the ability to perform a 6-minute walk test (e.g., peripheral arterial disease, orthopedic or neurological conditions).
10. Any diseases other than HF which are likely to alter the patient's global perception of status or quality of life over a period of 6 months.
11. Any condition, which in the opinion of the investigator would jeopardize the evaluation of efficacy or safety.
12. Receiving treatment with allopurinol or oxypurinol currently or within 30 days, or having symptomatic hyperuricemia which requires treatment with these agents.

13. Hypersensitivity to allopurinol and oxypurinol.
14. Clinically significant neutropenia (i.e., white-cell count < 3000 or absolute neutrophil count < 1000 per mm^3).
15. Concomitant treatment with azathioprine or ampicillin.
16. Unwillingness or inability to comply with study requirements.

7. TREATMENT INTERVENTIONS

7.1 Intervention

The therapeutic intervention is double-blind treatment with allopurinol or placebo. Study drug will be given for 24 weeks starting with 300 mg by mouth once daily for 1 week. If that dose is well tolerated, the dose will be increased to 600 mg daily (in divided doses of 300 mg) for the remaining 23 weeks of the study. Patients unable to tolerate the 600 mg dose will be maintained on the 300 mg dose. Patients with a serum creatinine level > 2.0 mg/dl at screening will be started on 100 mg daily, and titrated to 300 mg daily. The active and placebo study drug will appear identical to preserve the double-blind study design. Patients should be instructed to take the study drug as prescribed.

7.2 Study Drug Supplies

At clinic visits, the patient will receive study bottle(s) providing enough study drug to last at least until the next scheduled clinic visit. Patients will be instructed to take the medication as required by the protocol, and compliance will be assessed by phone contact (see below). Patients will be instructed to return unused drug supplies at each visit. The patient must return all bottles dispensed, even if they are empty.

7.3 Randomization, Stratification and Blinding

At the Baseline Visit (Visit 0) patients who qualify will be randomized to treatment using a permuted block randomization scheme stratified by clinical site. Study drug or matching placebo should be started within 12 hours of completing Baseline Visit 0. Following randomization, all patients will receive treatment for 1-week at a dose of 300 mg daily before up-titrating the dose to 600 mg daily (in divided doses of 300 mg) for the remainder of the study. Patient's with a serum creatinine > 2.0 mg/dl at screening will receive treatment for 1 week at a dose of 100 mg daily before up-titrating to 300 mg daily for the remainder of the study.

In order to randomize a patient, the center must access the automated web-based system coordinated by the Data Coordinating Center (DCC) and Almac Clinical Services. The system will confirm that eligibility criteria have been met, and will subsequently assign a unique patient number and study drug.

Blinding of the study, with respect to treatment groups, will be preserved by the use of matching placebo capsules of allopurinol. Investigators are requested NOT to measure serum uric acid levels during this study. In the event that a serum uric acid level is measured, the investigator may be asked at the end of the trial if they had obtained any information which may have led to the unblinding of treatment.

7.4 Unblinding

The investigative sites will be given access to the treatment code for their patients for emergency un-blinding ONLY by calling the DCC. Given the well-known safety profile of allopurinol and given the lack of a specific antidote, it is anticipated that there should be no need to un-blind the study drug for any reason. Any suspected study drug-related events should be treated as though the patient received active therapy. Nevertheless, in the rare event of necessary un-blinding, the DCC medical monitor must be contacted to discuss a given case.

Randomization data are kept strictly confidential, accessible only to authorized persons, until the time of un-blinding.

7.5 Packaging, Labeling and Drug Accountability

Each study bottle will contain enough capsules to assure at least an extra 7 days of treatment beyond a 12-week interval. The bottle number dispensed will be recorded on the Study Drug Accountability Log page in the Case Report Form. Each bottle dispensed to the patient will include labeling with the contents of the bottle, standard investigational product warning (on label for Canadian sites), dosing instructions, storage conditions, study name, bottle number, sponsor name, and manufacturing date. The patient number will be written on the bottle once it is assigned. All study drugs will be kept in a secure place. Study drug should be stored at room temperature and protected from light.

The number of capsules dispensed, used, and returned by each patient at each visit after randomization will be recorded on the Drug Accountability CRF. This will enable the full accountability for investigational drug. An estimate of patient compliance will also be made at each clinic visit. Patients not fully compliant with their study drug regimen must be encouraged to take medication as prescribed. Reasons for lack of compliance relating to adverse events must be described in the patient medical record and captured in the CRF.

7.6 Concomitant Medication

Patients should be receiving a stable treatment regimen for heart failure for at least 2 weeks prior to randomization. Patients receiving beta-blockers should have been receiving these for at least 3 months prior to the screening visit. Regular intermittent use of supplemental diuretic doses (oral or IV) are permitted if used as part of a regular diuretic treatment regimen at baseline. Patients may not be included in the trial if they are taking allopurinol or oxypurinol or have taken one of these agents within 30 days of randomization. Patients with a history of gout may enter the trial as long as they are not currently treated with these agents nor is there a strong likelihood of the need for these agents during the study.

It is likely that some patients will require adjustments of background therapy for heart failure during the trial. Any change in dose regimen of a cardiovascular active drug during the trial must be recorded in the CRF. Information about concomitant medication will be collected from the Screening visit until the end of the trial.

7.7 Risks of Treatment

Chronic treatment with allopurinol is generally safe. Uncommon side effects are described in section 8.3.4. As there is no prospective, controlled evidence of the long-term benefits of XO inhibition in heart failure, randomization to placebo does not represent withholding of established medical therapy.

7.8 Dose Adjustment with Renal Dysfunction

The following table provides study plan for dose adjustment in patients with renal dysfunction.

Doses outlined below are total daily doses.

Visit (Time)	SCr ≤ 2 mg/dl	SCr > 2, but ≤ 3 mg/dl	SCr > 3, but < 5 mg/dl	SCr ≥ 5 mg/dl
0 (Baseline)*	300 mg	100 mg	Excluded	Excluded
1 (7-10 Days)*†	600 mg	300 mg	---	---
2 (4 Weeks)	600 mg	300 mg	100 mg	Discontinue
4 (12 Weeks)	600 mg	300 mg	100 mg	Discontinue

SCr, serum creatinine level.
*Screening laboratories will be used to determine dosing at baseline and Visit 1.
†Laboratories will not be checked at this visit, which is a telephone call.

Note if renal function improves at visit 2 or 4, subjects will remain at the established dose (i.e. no up-titrations).

8. RECRUITMENT AND SCREENING PROCEDURES

8.1 Common Recruitment Procedures

All subjects will be recruited from patients who are referred to the heart failure programs at the Regional Clinical Centers (RCC) or satellites for outpatient management of heart failure, LV dysfunction or both. No specific ethnic groups will be selected; however attention will be paid to the recruitment of women and minorities. These patients will have heart failure as the result of several etiologies (e.g., idiopathic, ischemic, hypertensive, valvular). Inclusion will require that the LVEF be ≤ 40% by echocardiography. While this measurement is made routinely as part of the HF evaluation, blinded measurements of the screening and 24-week studies will be made by the echo core laboratory.

Recruitment will start by the investigators reviewing the patients' charts and selecting likely candidates. The primary physician will be contacted with full explanation of the protocol and consultation regarding the suitability of the patient. If the primary physician agrees, patients will be approached for participation at the time of their screening visit to the heart failure clinic. Informed consent will be obtained as required by the RCC institutional review boards. There can be no changes in the protocol without the prior agreement of the Heart Failure Network (HFN) Steering Committee.

8.2 Estimated Enrollment Period

The study will enroll 250 patients with chronic heart failure at 9 RCCs and associated satellite centers in the U.S. and Canada. It is anticipated that 14 patients will be enrolled per month (1.5 patients per RCC/satellites) for a total planned enrollment period of 18 months.

8.3 Informed Consent Procedures

8.3.1 Informed Consent

Patients will typically be recruited in the outpatient setting, but may be initially identified as a potential study subject during an inpatient admission for heart failure. If the patient meets inclusion/exclusion criteria, the process of informed consent will include description of the study purpose, interventions and evaluations, potential risks and benefits, alternative treatments, the right to withdraw and confidentiality. All questions will be answered, and if the subject is willing to participate, the informed consent form (ICF) will be signed. The patient will then undergo screening tests, which include laboratories and a transthoracic echocardiogram*. If the patient meets criteria for participation based on these studies (e.g., uric acid level $\geq$ 9.5 mg/dl, LVEF $\leq$ 40%, one additional marker of increased risk), the patient will be randomized and begin study drug.

*Echocardiogram may have been performed within 4 weeks of screening.

8.3.2 Confidentiality and HIPAA Requirements

All information collected on study participants will be stored in a confidential manner using procedures in place at each participating RCC and satellite site. Only approved study personnel will have access to data collected as part of this study. Study participants will be identified by a unique Subject ID # on all study documents and tests. Plasma samples, echocardiograms, and exercise, clinical and quality of life data will be collected specifically for the research protocol, and identifying information will be removed before transfer to the DCC or core laboratories. Existing clinical or demographic data will be collected from the patient's record for the purposes of the research protocol, and all data will be de-identified before submitting to the DCC. All data will be transmitted in a secure manner, and stored securely at the DCC using standard Duke Clinical Research Institute (DCRI) operating procedures.

8.3.3 Protections of Human Subjects

Protections for human subjects of research are required under Department of Health and Human Services (HHS) regulations at 45 CFR 46. Subpart A of the HHS regulations constitutes the Federal Policy (Common Rule) for the Protection of Human Subjects, which has been adopted by an additional 16 Executive Branch Departments and Agencies. Each institution engaged in (non-exempt) HHS-supported human subjects research must provide a written Assurance of Compliance, satisfactory to the Office for Protection from Research Risks (OPRR), that it will comply with the HHS human subjects' regulations. – 45 CFR 46.103(a)

8.3.4 Summary of the Risks and Benefits

This study will evaluate the safety and tolerability of allopurinol in hyperuricemic heart failure patients with reduced LV systolic function. Allopurinol is a commonly used, FDA-approved medication for the treatment of gout. The dose being evaluated in this study (600 mg orally in divided doses of 300 mg) is within the current standard of care for patients with gout, and the side effect profile is well characterized. This dose has also been studied in patients with mild-moderate heart failure,[8] and shown to be well tolerated.

Uncommon side effects include pruritus (3%), rash (1.5%), nausea or vomiting (1.3%), and renal failure (1.2%). Rare, serious adverse effects (less than 1%) include Stevens-Johnson syndrome, agranulocytosis, anemia, myelosuppression, and hepatotoxicity.

The Allopurinol Hypersensitivity Syndrome (AHS), which involves progression of skin rash to exfoliative lesions, generalized vasculitis and/or irreversible hepatotoxicity, occurs in less than 0.5% of patients, with a case fatality rate of up to 25%. Study drug should be held in a patient developing a new rash until a clinical assessment is made.

Given the co-existence of chronic heart failure and chronic kidney disease in some patients with advanced heart disease, a schedule of dose adjustments for patients with renal impairment will be used (see section 7.8).

There are minimal risks associated with other study-related procedures including echocardiography, 6-minute walk test, quality of life survey, biomarker blood collection and metabolic cart used in the ancillary study. The potential benefits of study participation include improved clinical status and contributing to improved treatment of hyperuricemic heart failure patients.

9. BASELINE EVALUATION AND RANDOMIZATION

See Appendix A for complete schedule of assessments throughout the study (Study Flow Chart).

9.1 Screening Visit (Visit -1)

Patients who are medically stable and receiving established doses of standard HF therapy will be evaluated for potential eligibility for enrollment during a screening visit to the RCC or satellite. The trial procedures will be explained to the patient, and informed consent will be obtained as described in section 8.3. Routine procedures during the screening visit will include:

- Medical history, including history of HF hospitalization, ER visit or urgent clinic visit requiring IV diuretics within 12 months. Variables to be recorded for study purposes include age, sex, etiology, duration of heart failure, NYHA class (see Appendix D) and co-morbidities (e.g., diabetes)
- Medication review with focus on dose and duration of HF therapy
- Complete physical exam, including height and weight
- Clinical chemistry* and hematology-CBC (including UA level and BNP)
- Serum pregnancy test for women of child-bearing potential

- Transthoracic echocardiogram to be read locally for qualifying LVEF, and then sent to core lab for complete baseline analysis (see section 11.3.1)**

* Laboratories to include: sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, total protein, albumin, ALT, AST, alkaline phosphatase and total bilirubin.

**Qualifying echocardiogram may be obtained at or within 4 weeks of screening visit.

Patients who meet all inclusion and exclusion criteria and who are interested in study participation will return within 7-14 days for randomization.

9.2 Baseline/Randomization Visit (Visit 0)

The minimum interval between screening and baseline visits is 7 days, and patients must remain clinically stable during this period. At the baseline visit (Visit 0, Day 0), the following procedures will be performed:

- Medication review
- Interim history to confirm stability
- Cardiovascular exam (HR, BP, body weight and cardiopulmonary exam)
- 12-lead electrocardiogram (ECG)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)[12]
- 6-minute walk test (6-MWT)[13] (see Appendix C)
- Blood sampling for HFN biomarkers
- Metabolic cart assessment of substrate utilization with markers of insulin resistance and markers of oxidative stress (part of Ancillary Study, see Appendix E)

Patients will then be randomized (1:1) to allopurinol or placebo to be taken with food once daily. Initial dose of study drug will be 300 mg of allopurinol or matched placebo daily. After 1 week, the dose will be increased to 600 mg daily (in divided doses of 300 mg). For patients with a screening creatinine level > 2.0 mg/dl, the starting dose of allopurinol will be 100 mg, and this will be increased to 300 mg daily after 1 week. Study drug, including matched placebo, will be provided by Almac Clinical Services. Randomization codes will be provided by the DCC through a web-based enrollment system, and the patient and physician investigator will be blinded to assigned therapy.

10. FOLLOW-UP EVALUATIONS

10.1 Follow-up Phone Contacts (Visits 1, 3, 5 and 7)

10.1.1 Follow-up Contact for Drug Titration (Visit 1 - 7 to 10 days after randomization)

Seven to ten days after the baseline visit, the investigator or research coordinator will contact the patient by telephone to ascertain if the study medication is well tolerated. If so, the patient will uptitrate the study medication to 600 mg daily (in divided doses of 300 mg) of allopurinol or matched placebo.* If the study drug is not well tolerated, the investigator will evaluate the nature of the intolerance and take appropriate action including temporarily or permanently discontinuing the dosage for drug-related adverse events or continuing study drug at the lower dose of 300 mg once daily.

*As described above, patients with a screening creatinine > 2.0 mg/dl will uptitrate study medication to 300 mg of allopurinol or matched placebo, or in the case of drug intolerance will continue at the lower dose of 100 mg once daily or discontinue study medication.

10.1.2 Follow-up Compliance Checks (Visits 3 and 5)
The Site Investigator or research coordinator will contact the patient by telephone at 8 and 18 weeks ($\pm$ 7 days) to assess compliance with study drug and inquire about adverse events. The patient will be encouraged to take study drug as prescribed and to report any concerns related to side effects or ongoing participation in the study.

10.2 Follow-up Clinic Visits (Visits 2, 4 and 6)
Patients will return to the RCC or satellite for study visits at 4, 12 and 24 weeks ($\pm$ 7 days). At each visit, interim history including review of medications, Patient Global Assessment (PGA)[10] (see Appendix B), NYHA class and adverse experiences, and cardiovascular exam will be performed. In addition, any hospitalizations or unscheduled ER visits will be recorded. Blood samples for routine chemistry* and hematology (CBC) will be collected and processed locally, with every attempt made to avoid checking serum UA level. At 12 and 24 weeks, all patients will undergo repeat 12-lead ECG, 6-minute walk test, KCCQ and measurement of HFN biomarkers that include serum UA. In addition at the 24 week visit, repeat transthoracic echocardiography and metabolic cart† testing will be performed. At each clinic visit, study drug compliance will be assessed and medication bottles returned.

*Laboratories to include: sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, total protein, albumin, ALT, AST, alkaline phosphatase and total bilirubin.

†For patients enrolled in Ancillary Study.

In the event that a patient withdraws from study treatment, every effort will be made to obtain a set of observations at each specified time point through 24 weeks. At a minimum, the primary outcome variable parameters should be assessed at these visits.

10.3 Follow-up Safety Check (Visit 7)
Two weeks ($\pm$ 1 week) after the last dose of study drug, patients who have completed 24 weeks of study drug will be contacted by phone for a safety evaluation to include interim history (e.g., ER visit or hospitalization) and HF symptom assessment (e.g., fatigue, shortness of breath, weight gain or edema).

11. OUTCOME DETERMINATIONS

11.1 Primary Endpoint
The primary endpoint of this study will be a composite clinical endpoint (CCE) that classifies the subject's clinical status as improved, worsened, or unchanged at 24

weeks, similar to that reported by Packer,[14] with a slight modification as previously described.[10] The classification will follow sequential rules based on the outcomes of the following items: 1) Death; 2) hospitalization, emergency room visit or emergent clinic visit for worsening HF; 3) medication change for worsening HF; and 4) Patient Global Assessment.

IMPROVED	WORSENED	UNCHANGED
Patient Global Assessment moderate or markedly improved	Death	Neither improved or worsened
	Hospitalization, ER visit or emergent clinic visit for worsening HF	
	Medication change for worsening HF	
	Patient Global Assessment moderate or markedly worse	

11.1.1 Deaths
All-cause mortality will be used in the composite analysis. To understand further the impact of XOI on advanced heart failure, the cause of death will be adjudicated by the physician investigator and classified as due to HF, other cardiac cause, or non-cardiac cause. In addition, they will be classified as sudden or non-sudden deaths.

11.1.2 Hospitalizations, Emergency Room Visits or Emergent Clinic Visits
Occurrence of hospitalizations, ER visits or emergent clinic visits for HF at any time in the trial will be counted when they meet the criteria outlined for such visits. The cause of these events will be adjudicated by the physician investigator and classified as due to HF, other cardiac, or non-cardiac. Importantly, hospitalizations for HF will be reported only as an efficacy endpoint and will not be reported as a serious adverse event.

11.1.3 Global Patient Assessment
The 7-point Patient Global Assessment instrument (Appendix B) will be evaluated at 4,12 and 24 week time points and will be utilized in the composite score assessment.

11.1.4 Medication Change for Worsening Heart Failure
The investigator must either prescribe or concur with: 1) the addition of a new drug class for worsening heart failure, or 2) an increase in diuretic dose or an increase or decrease in beta-blocker or renin-angiotensin system inhibitor dose by at least 50% for more than one week. A newly added drug class is defined as the addition of a new pharmacologic agent specifically indicated for heart failure therapy, or generally recognized as effective in the management of heart failure within current treatment guidelines, and NOT in the same pharmacological class as the therapy composing the patient's current drug regimen.

In the event that the investigator does not concur with a change in therapy initiated by another physician, the investigator may, using his/her medical discretion, terminate this

therapy. In the event that the patient is seen by another physician who adds medication to their heart failure regimen, the patient is to be specifically advised to inform the investigator of this immediately, before starting such therapy, if at all possible.

11.2 Secondary Endpoints
The following parameters will be designated as the principal secondary efficacy criteria in this study:
- Change in quality of life as assessed by Kansas City Cardiomyopathy Questionnaire (Appendix B) at 12 and 24 weeks.
- Change in submaximal exercise capacity as assessed by 6-minute walk test (Appendix C) at 12 and 24 weeks.

11.3 Tertiary Endpoints
The following efficacy measures will be considered as additional parameters for evaluation:
- Individual components of the primary composite.
- NYHA functional class (using criteria outlined in Appendix D).
- Echocardiographic measures: LV volumes, stroke volume, ejection fraction and mass (see section 11.3.1).*
- HFN biomarker panel: BNP, ET-1, TnT, hs-CRP, PIIINP, CITP, uric acid.*
- Renal function as assessed by serum creatinine, cystatin C and estimated GFR.*
- Markers of oxidative stress: malondialdehyde (MDA), myeloperoxidase (MPO), nitrotyrosine, allantoin, ST2 and IL33. (see section 11.3.2 and Appendix E).*
- Markers of insulin resistance: plasma insulin, glucose and free fatty acid (FFA) levels following overnight fast; and measurement of substrate utilization with metabolic cart (see section 11.3.2 and Appendix E).*
- Increased diuretic requirement (defined as an increase in outpatient diuretic dose by at least 50% for more than one week).
- Total number of hospitalizations for any cause.
- Total number of hospital days.
- Time to first hospitalization for heart failure.
- Cardiovascular death.

*Change from baseline to 24 weeks for patients enrolled in Ancillary Study using metabolic cart and blood markers.

11.3.1 Echocardiographic Technique
Standard images and Doppler flow studies will be recorded, and analyzed off-line by the HFN core lab.* Measurements will be obtained at screening and 24 weeks and include left ventricular:
- End-diastolic and end-systolic volumes: calculated using the modified Simpson's rule. All volumes will be normalized to body surface area (m^2).
- Stroke volume: calculated as end-diastolic volume - end-systolic volume.
- Ejection fraction: calculated as stroke volume/end-diastolic volume.
- Mass: calculated as $1.04*0.8[(IVS+PW+LVEDD)^3-(LVEDD)^3]+0.6$., where IVS

and PW = interventricular septal and posterior wall thickness, respectively; and LVEDD = left ventricular end-diastolic diameter.

*As noted in section 9.1, the screening echocardiogram will be read locally for qualifying LVEF before being sent to the core lab for complete analysis.

11.3.2 Insulin Resistance and Substrate Utilization Ancillary Study (see also Appendix E)

The hypothesis of this ancillary study is that chronic XO inhibition will improve insulin sensitivity and energy substrate utilization in hyperuricemic HF patients. The homeostasis model assessment of insulin resistance (HOMA-IR), derived from fasting plasma insulin and glucose levels, will be used to measure insulin sensitivity.[15] Efficiency of energy substrate utilization will be assessed by a metabolic cart,[16] in addition to measurement of free fatty acid (FFA) levels. Assessment of insulin sensitivity and energy substrate utilization will be performed at baseline and 24 weeks.

- **HOMA-IR methodology.** After an overnight fast, venous blood will be drawn to measure plasma insulin and glucose levels. Patients taking long-acting insulin the evening prior or any insulin the morning of will be asked to withhold that dose. The HOMA-IR is calculated as insulin $[(\mu U/ml)*glucose (mmol/l)] / 22.5$. A value of < 1.0 is considered normal. Insulin sensitivity derived from the HOMA-IR correlates well with that from the gold-standard euglycemic clamp technique (r ~ 0.85).[15]
- **Metabolic cart.** A standard metabolic cart will be used to measure oxygen consumption (VO_2) and carbon dioxide production (VCO_2) at rest. The respiratory quotient (RQ) will be calculated as the ratio of VCO_2/VO_2. A higher RQ is indicative of a greater proportion of free fatty acid compared to carbohydrate metabolism and therefore inefficient energy substrate utilization.[16]

12. METHODS TO PROMOTE ADHERENCE

12.1 Adherence to Study Drug

Patients will be instructed to bring all used and remaining bottles of study drug to each study visit. Compliance will be assessed at the 4, 12 and 24 week visits by pill counts. In addition, between-visit compliance will be encouraged by direct telephone contact at 1, 8 and 18 weeks. Patients will return all bottles for inventory check at the final visit.

12.2 Adherence to Study Procedures

Adherence to study procedures will be enhanced by the following factors:
- At screening and baseline visits, the study will be carefully explained to the patient (and family member or friend if present) with particular attention to the required study visits and procedures. The potential subject will be asked to carefully consider his/her ability to participate fully in all aspects of the study.
- Patients with non-cardiac dyspnea or fatigue due to frailty, motivational factors, pulmonary disease or orthopedic problems will be identified and excluded as unable to perform 6-minute walk test.

- Allopurinol, the active study drug, has a long history of excellent safety and tolerability in patients with gout. It is anticipated that there will be few permanent study drug discontinuations due to adverse effects.
- Data completeness at each RCC will be monitored by the DCC. RCCs that have satellite sites will be responsible for monitoring the data originating from these satellite sites. Sites not providing complete data will be contacted by HFN leadership and strategies designed to enhance compliance.

13. PARTICIPANT SAFETY AND ADVERSE EVENTS

13.1 Institutional Review Boards
All HFN sites will submit the study protocol, informed consent form, and other study documents to their Institutional Review Board (IRB) for approval. A copy of the signed and dated IRB approval for each RCC will be stored at the DCC. Approval letters for satellite sites will be stored at their RCC. Any amendments to the protocol, other than minor administrative changes, must be approved by each IRB before they are implemented.

13.2 Adverse Events

13.2.1 Definitions
An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

A serious adverse event (SAE) is an adverse event that:
- Results in death.
- Is life-threatening.
- Requires hospitalization which is not specifically required by the protocol and is not elective, other than endpoint events.
- 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.
- Results in congenital anomaly or birth defect. See also Appendix F for guidance on the definition of an SAE

In this trial certain primary efficacy endpoints may meet these definitions of AE/SAE. These include hospitalizations for HF, which will not be reported on the AE record of the CRF.

The relation between an adverse event and study drug will be determined by the investigator on the basis of his/her clinical judgment and the following definitions:

Not a reasonable possibility: It is unlikely that the event was caused by the study drug. The temporal relationship of the AE 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.

Reasonable possibility: 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.

An **Unexpected Adverse Event** is when the nature or severity of the event is not consistent with the applicable product information (i.e., package insert).

13.2.2 Anticipated Adverse Events and Drug Effects
The following adverse events are anticipated, disease-related events in patients with heart failure due to LV systolic dysfunction:
- Arrhythmias
- Sudden death
- Acute coronary syndrome
- Unplanned hospitalization, ER visit or clinic visit for worsening HF
- Cerebrovascular event
- Venous thromboembolism
- Lightheadedness, presyncope or syncope
- Worsening renal function

Chronic treatment with allopurinol is generally safe. Uncommon side effects are described in section 8.3.4.

13.2.3 Recording and Reporting of Adverse Events
The Site Investigator is responsible for monitoring the safety of patients enrolled into the study at the study sites. All AEs (except those listed above) must be recorded in the AE Record of the patient's CRF and source supportive documentation must be provided to support the CRF data. All AEs should be monitored until stabilization or death.

If an adverse event results in death or if an SAE is assessed as related to study drug an Expedited Event (EE) Form should be filled out and faxed to the DCC at 1-866-668-7138 within 24 hours of knowledge of the event. The form includes details about the event to include onset date and time, seriousness, outcome and relatedness to study drug. Site personnel can provide a complete detailed description of the event. The DCC will provide medical review of the EE Form and forward to key trial personnel, the DSMB chair and NHLBI Project Officer.

Adverse events which meet the criteria of serious, study drug-related, and unexpected per the U.S. package insert, qualify for expedited reporting to the regulatory authorities. The Site Investigator will assess all SAEs occurring at his/her site and evaluate for "unexpectedness" and relationship to study drug (Appendix F). The Site Investigator is required to complete and submit a MedWatch Online Voluntary Reporting form (3500) for the events identified as serious, drug-related and unexpected at: https://www.accessdata.fda.gov/scripts/medwatch/. A copy of this report should be kept at the site and also forwarded to the DCC. Investigators are also responsible for promptly reporting AE/SAEs to their IRB in accordance with local requirements.

13.3 Management of Gout
The study excludes enrollment of patients with gout who are currently receiving treatment with allopurinol (or oxypurinol), or have symptomatic hyperuricemia which requires treatment with these agents. However, it is anticipated that enrollment of hyperuricemic heart failure patients will include those at risk for developing gout during the course of the study. If this occurs and the patient's physician recommends use of open-label allopurinol (or oxypurinol), the subject will be: 1) required to stop taking study drug, and 2) requested to return for all other observations at each specified time point through 24 weeks (see section 10.2).

14. STATISTICAL CONSIDERATIONS

14.1 Overview
All planned analyses will be prospectively defined for this study and approved by the DCC prior to unblinding. In addition, exploratory analyses will be performed to help explain and understand findings and further dissect results observed from the planned analyses. All analyses will be conducted using the intention to treat (ITT) principle with a minor modification as described below. Statistical tests with a two-sided p value < 0.05 will be considered statistically significant, unless otherwise stated. Analyses will be performed using SAS software (SAS Institute).

14.2 Analysis of the Primary Endpoint
The ITT population includes all patients who are randomized. This is the primary population for the efficacy analyses. Analysis of the primary efficacy CCE will utilize the Cochran-Mantel-Haenszel row mean score test with modified ridit scores to compare the distributions.

The study is designed to test whether allopurinol is significantly more effective than placebo in patients with NYHA class II-IV heart failure and LVEF ≤ 40% receiving standard background therapy for HF. The test for the superiority of allopurinol versus placebo will be based on a chi-square statistic which compares the two randomized arms with respect to differences in a linear trend in the proportions of patients that fall into the ordinal categories of the primary endpoint.[17]

Because the study is of short duration and relatively small size, no interim analysis for efficacy will be performed.

14.3 Analysis of Secondary and Tertiary Endpoints

Descriptive statistics (number of patients, medians, percentiles, ranges, means and standard deviations) will be summarized by treatment group for all continuous variables. Frequency distributions (the number and percentage of patients) will be tabulated for all categorical variables by treatment group. The analysis of variance (ANOVA) model will include the factor treatment for the analysis of continuous variables. For nominal categorical variables, a Chi-square test will be used. A Fisher's Exact test will be used when the Chi-square test is inappropriate. For ordinal categorical variables, a Wilcoxon rank sum test will be used. Analyses of the time-to-event endpoints will utilize the log-rank test to compare distributions between treatment groups, and a Cox proportional hazards regression model for estimation of the hazard ratios. The RCC/satellite is not included in the analysis models due to relatively small sample sizes per center. Analysis of the change from baseline in KCCQ score, 6-minute walk distance and serum UA levels will be conducted using a repeated measures mixed model, with baseline score as a covariate and treatment, time and the treatment by time interaction as fixed effects.

14.3.1 Missing Data

It is anticipated that all subjects will have complete information on all-cause mortality at the end of the study. Particular attention will be paid to maintaining low rates of missing data for the components of the primary endpoint. In the event that a patient withdraws from study treatment, every effort will be made to obtain a complete set of observations up to the 24 week assessment. Patients who are lost to follow-up will be evaluated for all endpoints using the last observation carried forward method.

14.4 Analysis of Safety

The safety population includes all patients who were randomized and received at least one dose of study medication. Safety will be evaluated by comparing the occurrence of adverse events and changes in laboratory values in the two treatment arms

Treatment emergent AEs are defined as all AEs that occurred, for the first time, on or after the first dose of study medication; or occurred on or after the first dose of study medication with a greater severity compared with the occurrences prior to the first dose. The number and percentage of patients experiencing treatment emergent AEs will be tabulated by treatment group, body system, and preferred term. The percentages between treatment groups will be compared using Fisher's Exact test. The number and percentage of patients experiencing treatment emergent AEs will also be tabulated by severity and relationship to the study medication.

Vital signs and laboratory evaluations will be descriptively summarized by treatment group and visit. Continuous variables will be compared between treatment arms using the analysis of variance methods described in section 14.3 above, and categorical variables will be compared using the chi-square test or Fisher's Exact test as appropriate.

14.5 Sample Size and Power Calculation

Based on previous data from the OPT-CHF study,[9] which used the same composite endpoint, it is assumed that the placebo arm will have approximately the following response rates for the primary endpoint: 33% improved, 42% unchanged and 25% worsened. We hypothesize that the outcome of the allopurinol arm will be improved, with response rates of approximately 52% improved, 37% unchanged, and 11% worsened. To estimate the statistical power under these assumptions, we randomly generated data sets to simulate the clinical trial, computed the Cochran-Mantel-Haenszel row mean score test statistic in each data set, and compared the resulting p-value to the 0.05 level of significance in order to assess the statistical power. Based on 2,000 replicate samples, we estimated that a sample size of 250 patients would provide 83% power to detect a statistically significant difference using the row mean score statistic under the assumptions above. Furthermore, if one were to consider simply the binary endpoint of improved response on the CCE scale and compare treatment arms using a conventional two group chi-square test, a total sample size of 250 subjects is sufficient to provide $\geq$85% power to detect a significant treatment difference under the assumptions above. Additional calculations confirmed that a sample size of 250 subjects will provide adequate power for other endpoints.

15. DATA MANAGEMENT PROCEDURES

15.1 Overview of Data Management and Publication

This study is a prospective, randomized, placebo-controlled trial where data will be collected, analyzed and interpreted by the DCRI, which functions as the DCC for the NIH/NHLBI Heart Failure Network. The DCC will provide data management, statistical analysis, and procedural consistency to produce high quality data. Specific goals will be to:

- Collaborate in the design of the case report forms (CRF). This is necessary to ensure that the data fields are properly defined and unambiguous, the instructions are clearly worded, and the precoded responses are positioned in order to facilitate accurate data entry. The CRF will be partitioned into 'booklets' according to the time points mandated by the protocol. At regular intervals, the different parts of the CRF will be forwarded to the DCC using a parcel-delivery system.
- Personnel at the clinical sites will record the data mandated by the protocol on the CRFs. The data will be abstracted from the participant's medical charts and other source documents. All CRFs will be completed according to the current Good Clinical Practice (GCP) guidelines. Training on completing the CRFs will be included in the training session described in the HF Network Manual of Operating Procedures.
- Construct the database management system. All CRFs will be entered into the study database. Double data entry by 2 different operators will be performed to ensure a high level of confidence in the data entered.
- A series of computerized validation checks (DCFs) will be programmed by the

DCC to check for missing data, inconsistencies in the data or data that is out of range. These DCFs will be forwarded to the clinical sites for investigation. The clinical site will return the DCFs with corrections and the database will be updated.
- Study drug will be packaged in bottles, foil sealed, and pre-labeled by the investigational pharmacy to guarantee blinding of therapy.

Data other than safety data cannot be used for publication or reporting outside of this study until the study is completed or discontinued by the DSMB or HFN Steering Committee. This is necessary since dissemination of preliminary information may inappropriately affect the objectivity of this study. For this reason, Site Investigators will not be allowed to perform subset analyses at any point before the conclusion of the study.

15.2 Data Security
Data will be captured and forwarded to the DCC from the RCC/satellite sites. Access to databases will be controlled centrally by the DCC through user passwords linked to appropriate privileges. This protects the data from unauthorized changes and inadvertent loss or damage. Database and web servers will be secured by a firewall and through controlled physical access. Database back-up will be performed daily using standard procedures in place at the DCC. All disk drives that provide network services, and all user computers, will be protected using virus-scanning software.

16. STUDY ADMINISTRATION

16.1 Data and Safety Monitoring Board
A Data and Safety Monitoring Board (DSMB) has been appointed by the NHLBI for the HF Network, and will function as the DSMB for this trial. This committee consists of a group of highly experienced individuals with extensive pertinent expertise in heart failure and clinical trials. The DSMB will advise the HFN Steering Committee regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial.

As noted in section 14.2, interim data analysis for the primary efficacy endpoint will not be conducted due to the relatively small size and short duration of this phase II clinical study. However, safety data will be frequently assessed by the DSMB based on reporting of AE/SAEs.   Also, as part of ensuring the safety of the patients in the trial, the DSMB will perform interim reviews of all-cause mortality. As a guide for interpreting mortality differences between the treatment arms, the Haybittle-Peto boundary, which requires p<0.001 to cross the boundary, will be provided to the DSMB.

16.2 Data Coordinating Center
The Duke Clinical Research Institute will function as the DCC for this trial as specified by the NIH/NHLBI Heart Failure Clinical Research Network grant.

16.3 Core Laboratories

16.3.1 Biomarker Core Laboratory
The University of Vermont will serve as the core laboratory for measurement of HFN biomarkers. Plasma specimens will be collected at baseline and 12 and 24 weeks, processed at the RCC/satellite site according to the procedures provided by the core laboratory, and shipped to the core laboratory on dry ice. Planned analyses include:
- HFN biomarker panel: BNP, NT pro-BNP, ET-1, TnT, hs-CRP, PIIINP, CITP, cystatin C, creatinine and uric acid
- Markers of oxidative stress: malondialdehyde (MDA), myeloperoxidase (MPO), nitrotyrosine, allantoin, ST2, and IL33 levels*
- Markers of insulin resistance: plasma insulin, glucose and free fatty acid (FFA) levels*

*These additional markers may require outsourcing to other clinical laboratories or specialized research laboratories (e.g., Dr. Richard T. Lee Laboratory, Harvard Medical School).

16.3.2 Echocardiography Core Laboratory
Mayo Clinic will serve as the core laboratory for measurement of echocardiographic parameters obtained at screening and 24 weeks (see section 11.3.1).

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18. APPENDICES
18.1 Appendix A. Study Flow Chart

	Screening	Baseline	Treatment and Follow-up						
Visit No.	-1	Visit 0	Telephone Contact Visit 1	Clinic Visit Visit 2	Telephone Contact Visit 3	Clinic Visit Visit 4	Telephone Contact Visit 5	Clinic Visit Visit 6	Telephone Contact Visit 7
Day/Week No.	-1-2 Weeks	Day 0	7-10 Days	4 Weeks	8 Weeks	12 Weeks	18 Weeks	24 Weeks	26 Weeks
Informed consent	X								
Medical history[1]	X								
Physical exam	X								
NYHA class	X			X		X		X	
Medication review	X	X		X		X		X	
Interim history		X		X		X		X	X
CV exam		X		X		X		X	
12-lead ECG		X				X		X	
Chemistry and hematology[2]	X			X		X		X	
Serum pregnancy test[3]	X								
Compliance check			X		X		X		
Up-titrate			X						
Echocardiogram[4]	X							X	
HFN Biomarkers[5]		X				X		X	
Metabolic cart and markers[6]		X						X	
6-minute walk test		X				X		X	
Patient Global Assessment					X	X		X	
KCCQ		X				X		X	
Randomize		X							
Dispense study medication		X		X		X			
Adverse events			X	X	X	X	X	X	X

[1]Include etiology and duration of HF and document history of HF hospitalization or ER visit within 12 months.
[2]Includes complete chemistry panel (sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, total protein, albumin, ALT, AST, alkaline phosphatase and total bilirubin) and complete blood count. Screening uric acid level will be used for "qualifying".
[3]Serum pregnancy test performed on all women of childbearing potential.
[4]Qualifying echocardiogram to be obtained at or within 4 weeks of screening in all patients.
[5] Includes BNP, NT pro-BNP, ET-1, TnT, hs-CRP, PIIINP, CITP, cystatin C, creatinine and uric acid
[6]Includes markers of oxidative stress (malondialdehyde (MDA), myeloperoxidase (MPO), nitrotyrosine, allantoin, ST2 and IL33) and insulin resistance (plasma insulin, glucose and FFA levels). Will be performed along with markers of insulin resistance in patients enrolled in the Ancillary Study.

18.2 Appendix B. Kansas City Cardiomyopathy Questionnaire and Patient Global Assessment

18.2.1 Kansas City Cardiomyopathy Questionnaire

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a self-administered, 23-item questionnaire developed to provide a better description of health-related quality of life (QOL) in patients with heart failure.[12] It quantifies physical limitation, symptoms, QOL, social interference and self-efficacy. The survey requires 4-6 minutes to complete, and is scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning and summing items within each domain. Scale scores are transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. A clinical summary score will be calculated by combining the functional status with the quality of life and social limitation domains.

18.2.2 Patient Global Assessment

A seven category global assessment of clinical status that is completed by the patient will be utilized in the assessment of the composite score. This Patient Global Assessment (PGA) tool consists of the categories of: markedly improved, moderately improved, mildly improved, no change, slightly worse, moderately worse and markedly worse.

Patients will be asked to define their status using this tool at specified times during the protocol by marking their current status, relative to the baseline condition. The Patient Global Assessment tool will be prepared in a manner which is simple to read (large print) and fully identified by patient initials, randomization number and visit, and will be retained as a source document in the CRF binder.

18.3 Appendix C. 6-Minute Walk Test

Because usual daily activities generally require much less than maximal exertion, the measurement of submaximal exercise capacity may provide information that is complementary to that provided by maximal exercise testing.[18] The 6-minute walk test (6-MWT) is the most common of the fixed-time tests; it measures the distance walked on level ground in 6 minutes. In this test, the patient is asked to walk along a level corridor as far as he or she can in 6 minutes. The patient can slow down or even stop, may be given a carefully controlled level of encouragement, and is told when 3 and 5 minutes have elapsed. The 6-minute walk test is moderately predictive of maximal oxygen consumption, and independently predicts morbidity and mortality in heart failure.[19,20] For a complete description of the indications, contraindications, technical aspects, safety issues, and interpretation of the 6-MWT, the investigator is referred to the 2002 guidelines published by the American Thoracic Society.

18.4 Appendix D. New York Heart Association Functional Classification

Class	NYHA Classification
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

18.5 Appendix E. Ancillary Study of the Effect of Xanthine Oxidase Inhibition on Insulin Resistance in Hyperuricemic Heart Failure Patients

Investigators: Todd S. Perlstein, Michael M. Givertz, Joshua A. Beckman, Brigham and Women's Hospital

Primary Objective: To determine whether chronic inhibition of xanthine oxidase improves insulin resistance in hyperuricemic heart failure patients with left ventricular systolic dysfunction.

Hypothesis: In patients with symptomatic heart failure, reduced ejection fraction and hyperuricemia, treatment with allopurinol for 24 weeks will improve insulin resistance and energy substrate utilization compared to placebo.

Secondary Objectives:
- To evaluate if allopurinol therapy improves energy substrate utilization in hyperuricemic HF patients compared with placebo therapy
- To explore whether changes in insulin sensitivity attributable to allopurinol therapy correlate with changes in left ventricular function in hyperuricemic HF patients
- To examine potential mechanisms underlying an observed change in insulin sensitivity and substrate utilization due to allopurinol therapy in hyperuricemic HF patients

Background:

Heart failure. Heart failure (HF) is a common and disabling condition that causes substantial morbidity and mortality.[1] Many aspects of HF pathophysiology are incompletely understood, and novel therapies to improve outcomes in HF are needed.

The contribution of insulin resistance to heart failure. Insulin resistance (IR) is most commonly appreciated as impaired insulin-stimulated glucose disposal.[2] Insulin resistance is common in HF and directly correlates with HF severity.[3,4] Accumulating evidence suggests that IR contributes to impaired myocardial function in heart failure by causing inefficient energy generation and/or utilization.[5] Heart failure is characterized by a high rest respiratory exchange ratio (the ratio of carbon dioxide production to oxygen consumption), consistent with inefficient energy substrate utilization.[6] Heart failure itself aggravates insulin resistance, thus producing a self-amplifying loop.[5] In addition to contributing to impaired heart function, IR leads to impaired skeletal muscle energy utilization, further exacerbating the heart failure syndrome.[7] Finally, IR portends a worse prognosis in heart failure independently of other variables including peak oxygen consumption and left ventricular ejection fraction, implying that IR is indeed pathogenic and not merely a marker of worsened HF.[8] In fact, insulin sensitive NYHA class II and III HF patients are 1/3 as likely to die as their insulin resistant counterparts.[9]

Xanthine oxidase as a potential source of insulin resistance in heart failure. The etiology of IR is complex, but increased oxidative stress is an important contributor.[10]

Xanthine oxidase (XO) is a major source of reactive oxygen species (ROS) in heart failure, and XO inhibition reduces oxidative stress in HF.[11] Independent of HF, IR itself is characterized by increased XO activity.[12] In addition, uric acid, the end-product of XO activity, may also contribute to insulin resistance by direct pro-inflammatory effects on adipocytes, vascular smooth muscle cells and endothelial cells.[13-15] Finally, experimental data suggests that XO inhibition may improve insulin sensitivity,[16] though we are not aware of intervention data addressing IR associated with HF. That XO inhibition may improve IR in HF is suggested by the benefit of XO inhibition on endothelial function in HF, as endothelial function and insulin sensitivity are reciprocally linked.[17]

Xanthine oxidase inhibition as a strategy to improve outcomes in heart failure. The OPT-CHF trial randomized chronic HF patients to oxypurinol (an XO inhibitor) or placebo for 24 weeks, with a primary outcome of clinical benefit.[18] While the overall study result was negative, a benefit of oxypurinol was observed in the hyperuricemic subgroup. This may have been due to the fact that serum uric acid level serves as a surrogate for XO activity or that uric acid itself is pathogenic and the relevant therapeutic target. In an analogous fashion, acute XO inhibition improved endothelial function in hyperuricemic but not normouricemic HF patients.[19] If the present study demonstrates a clinical benefit of allopurinol therapy in hyperuricemic HF, an improvement in IR due to XO inhibition would be a strong candidate mechanism for this benefit for the reasons discussed above. At the present time, however, there is no data regarding the effect of XO inhibition on IR in HF.

The present study presents a unique opportunity to examine whether long-term XO inhibition results in improved insulin sensitivity and energy substrate utilization in HF. In addition, this study will be the first to address whether changes in insulin sensitivity over time predict clinical outcomes in HF. Finally, if allopurinol therapy benefits hyperuricemic HF, this study will afford the opportunity to explore whether an improvement in insulin resistance and energy substrate utilization in part explains this benefit.

Study Design:
The overall study is a randomized, double-blinded, placebo-controlled, 24-week trial of allopurinol in patients with HF due to systolic dysfunction and hyperuricemia. We propose an ancillary study of insulin sensitivity and energy substrate utilization. The homeostasis model assessment of insulin resistance (HOMA-IR), derived from fasting plasma insulin and glucose levels, will be used to measure insulin sensitivity.[20] Efficiency of energy substrate utilization will be assessed by a metabolic cart.[21] Assessment of insulin sensitivity and energy substrate utilization will be performed at baseline and at 24 weeks.

Primary Endpoint. The primary endpoint will be insulin sensitivity. Fasting plasma insulin and glucose levels will be measured, and the HOMA-IR will be derived.

Secondary Endpoints. The main secondary endpoint will be efficiency of energy

substrate utilization. A metabolic cart will be used to measure carbon dioxide production and oxygen consumption, and the ratio of these, the respiratory exchange ratio, will be derived.

The following additional analyses will also be done:
- Plasma free fatty acid levels, characteristically elevated in insulin resistance and thought to directly contribute to impaired energy substrate utilization
- Plasma nitrotyrosine, allantoin, ST2, and IL33, malondialdehyde (MDA) and myeloperoxidase (MPO) levels, as measures of oxidative stress, and the latter additionally reflecting superoxide generation by xanthine oxidase

HOMA-IR methodology. After an overnight fast, venous blood will be drawn to measure plasma insulin and glucose levels. Patients taking long-acting insulin the evening prior or any insulin the morning of will be asked to withhold that dose. The HOMA-IR is calculated as insulin [(μU/ml) * glucose (mmol/l)] / 22.5. A value of < 1.0 is considered normal. Insulin sensitivity derived from the HOMA-IR correlates well with that from the gold-standard euglycemic clamp technique (r ~ 0.85).[20]

Metabolic cart. A standard metabolic cart will be used to measure oxygen consumption (VO2) and carbon dioxide production (VCO2) at rest. The respiratory quotient (RQ) will be calculated as the ratio of VCO2/VO2.   A higher RQ is indicative of a greater proportion of free fatty acid compared to carbohydrate metabolism and therefore inefficient energy substrate utilization.[21]

Statistical methods:
The change in insulin sensitivity and RQ observed during allopurinol vs. placebo therapy will be compared using a two-sample t-test or the Wilcoxon rank sum test, as appropriate.

- **Power calculation.** We anticipate a mean HOMA-IR of ~ 3.0.[3] Allowing for 30% within-subject variability, 250 analyzable subjects (the target enrollment) provides 95% power to detect a 10% improvement in insulin sensitivity.

Interpretation:
If insulin sensitivity improves in response to allopurinol compared to placebo therapy, we will conclude that chronic XO inhibition improves insulin sensitivity in hyperuricemic heart failure patients. If the respiratory exchange ratio improves in response to allopurinol compared to placebo therapy, we will conclude that chronic XO inhibition improves energy substrate utilization in hyperuricemic heart failure. If the overall study has a positive result, and insulin sensitivity and/or RQ improves due to allopurinol therapy, we will conclude that improvement in insulin sensitivity and/or energy substrate utilization may account for the observed clinical benefit of allopurinol therapy. If the overall study result is positive and there is no change in either insulin sensitivity or RQ, we will conclude that the benefit of chronic XO inhibition in hyperuricemic HF is not dependent upon these.

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18.6 Appendix F. Guidance on the Definition of an SAE

Life Threatening
"Life-threatening" means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (e.g. hepatitis that resolved without hepatic failure).

Hospitalization
Out-patient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (e.g. bronchospasm, laryngeal edema). Hospital admission and/or surgical operations planned before or during a study are not considered an AE if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event/Medical Intervention
Medical and scientific judgment should be exercised in deciding whether a case is serious in those situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity. These include events that may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. Such events should usually be considered as serious. Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by acetaminophen overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

18.7 Appendix G. List of Abbreviations

Abbreviation	Definition
6-MWT	6-minute walk test
ACE	angiotensin-converting enzyme
AE	adverse event
ARB	angiotensin receptor blocker
CABG	coronary artery bypass grafting
CCE	Composite Clinical Endpoint
CRF	case report form
DBP	diastolic blood pressure
DCC	Data Coordinating Center
DCF	computerized validation check
ECG	electrocardiogram
EE	Expedited Event
ER	emergency room
FFA	free fatty acid
GFR	glomerular filtration rate
HF	heart failure
HFN	Heart Failure Clinical Research Network
HR	heart rate
ITT	intention to treat
IV	intravenous
IVRS	Interactive Voice Recording System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	left ventricular ejection fraction
MDA	malonyldialdehyde
MPO	myeloperoxidase
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PGA	Patient Global Assessment
RCC	Regional Clinical Center
ROS	reactive oxygen species
RQ	respiratory quotient
SAE	serious adverse event
SBP	systolic blood pressure
UA	uric acid
XO	xanthine oxidase