Design of a Phase 2b Trial of Intracoronary Administration of AAV1/SERCA2a in Patients With Advanced Heart Failure

The CUPID 2 Trial (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b)

Barry Greenberg, MD,* Alex Yaroshinsky, PhD,† Krisztina M. Zsebo, PhD,‡ Javed Butler, MD, MPH,§ G. Michael Felker, MD,¶ Adriaan A. Voors, MD,¶¶ Jeffrey J. Rudy, BS,¶ Kim Wagner, MA,¶ Roger J. Hajjar, MD#
San Diego and San Andreas, California; Atlanta, Georgia; Durham, North Carolina; Groningen, the Netherlands; and New York, New York

Objectives
Impaired cardiac isoform of sarco(endo)plasmic reticulum Ca^{2+} ATPase (SERCA2a) activity is a key abnormality in heart failure patients with reduced ejection fraction. The CUPID 2 (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b) trial is designed to evaluate whether increasing SERCA2a activity via gene therapy improves clinical outcome in these patients.

Background
Intracoronary delivery of recombinant adeno-associated virus serotype 1 (AAV1)/SERCA2a improves intracellular Ca^{2+} handling by increasing SERCA2a protein levels and, as a consequence, restores systolic and diastolic function. In a previous phase 2a trial, this therapy improved symptoms, functional status, biomarkers, and left ventricular function, and reduced cardiovascular events in advanced heart failure patients.

Methods
CUPID 2 is a phase 2b, double-blind, placebo-controlled, multinational, multicenter, randomized event-driven study in up to 250 patients with moderate-to-severe heart failure with reduced ejection fraction and New York Heart Association functional class II to IV symptoms despite optimal therapy. Enrolled patients will be at high risk for recurrent heart-failure hospitalizations by virtue of having elevated N-terminal pro-B-type natriuretic peptide/BNP (>1,200 pg/ml, or >1,600 pg/ml if atrial fibrillation is present) and/or recent heart failure hospitalization. The primary endpoint of time-to-recurrent event (heart failure–related hospitalizations in the presence of terminal events [all-cause death, heart transplant, left ventricular assist device implantation or ambulatory worsening heart failure]) will be assessed using the joint frailty model. This ongoing trial is expected to complete recruitment in 2014, with the required number of 186 recurrent events estimated to occur by mid 2015.

Results
Available data indicate that calcium up-regulation by AAV1/SERCA2a gene therapy is safe and of potential benefit in advanced heart failure patients.

Conclusions
The CUPID 2 trial is designed to study the effects of this therapy on clinical outcome in these patients. (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b [CUPID-2b]; NCT01643330) (J Am Coll Cardiol HF 2014;2:84–92) © 2014 by the American College of Cardiology Foundation

Heart failure (HF) prevalence has reached epidemic proportions with an estimated 23 million people worldwide currently living with this condition (1–4). Despite optimal guideline-directed therapy employing a wide range of pharmacological, device, and surgical options, many patients deteriorate over time and develop refractory advanced HF symptoms. A consequence of this is that there were more than 1 million primary HF hospitalizations and more than...
3 million secondary HF hospitalizations in the United States in 2009 (5,6). These numbers are likely to increase in the future as the population ages. Although strategies for treating HF and reducing readmissions have been developed, implementation remains variable (7–9). While the primary HF hospitalization rate has declined modestly for older patients, a similar reduction has not been seen in younger patients or in secondary HF hospitalizations (5,10). Thus, HF patients experience frequent hospitalizations and a high mortality rate, and the risk of both events is increased with each recurrent HF-related hospitalization (11,12). In 2010, the estimated direct and indirect cost of HF was $39 billion in the United States, one-half of which was related to repeated hospitalizations (2). By 2030, the total cost of HF is projected to increase to $70 billion (13). The 1- and 6-month readmission rate after HF hospitalization is close to 25% and 50%, respectively (14). The 3-month readmission rate after HF hospitalization is close in 2009 (5,6). These numbers are likely to increase in the future (5,6). These numbers are likely to increase in the future.

**Molecular target: SERCA2a.** HF with reduced ejection fraction (HFREF) is characterized by reduced contractility as well as diastolic dysfunction. Calcium (Ca^{2+}) plays a critical role in cardiac contraction and relaxation. Contraction of the myocyte depends on the amount of Ca^{2+} released by the sarcoplasmic reticulum (SR), which then activates the contractile proteins in the cytoplasm to produce force. Relaxation is governed by the rate of the reuptake of Ca^{2+} by the SR during diastole. Abnormalities in calcium release have been related to “leakiness” of the Ca^{2+} release channel, ryanodine receptor 2 (RyR2) (18), while down-regulation of the SR/endoplasmic reticulum Ca^{2+} ATPase 2a (SERCA2a) impairs reuptake of Ca^{2+} from the cytoplasm and the myofilaments into the SR during diastole. Both contribute to the decrease in SR Ca^{2+} content that occurs in experimental and human HF (Fig. 1).

Gene transfer of SERCA2a improves both systolic and diastolic function in experimental HF models. Unlike currently available inotropic agents that increase ventricular arrhythmias, worsen energy depletion in the heart, and increase mortality, replacement of the deficient SERCA2a enzyme in HF improves contractility without increasing the oxygen demands on the heart (19,20) and reduces ventricular arrhythmias (21–23), resulting in improved survival (24). In a previous phase 2a trial, a single intracoronary infusion of AAV1/SERCA2a improved symptoms, functional status, biomarker profile, and left ventricular function, and reduced cardiovascular events in advanced HFREF patients without raising any safety concerns (25). The encouraging results of this phase 2a study informed the design and conduct of the current trial.

**Methods**

AAV1/SERCA2a intracoronary enzyme replacement therapy. AAV1/SERCA2a is a recombinant adeno-associated viral vector (AAV), which consists of an AAV serotype 1 capsid and the human SERCA2a cDNA flank by inverted terminal repeats derived from AAV serotype 2 (Fig. 2). AAV1/SERCA2a is intended for intracoronary administration. Extensive nonclinical pharmacology and safety studies have shown AAV1/SERCA2a to be a safe, well-tolerated, and effective treatment in normal and HF animals (26). Previous human studies (25,27) demonstrated initial safety and improvement in symptomatic, functional, biomarker, and left ventricular function parameters. In the phase 2a CUPID 1 (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease) study, advanced HF patients who received AAV1/SERCA2a at high doses up to 1 × 10^{13} DNase resistant particles (DRP) demonstrated improved clinical outcomes, including reduced frequency/delay of HF hospitalizations, cardiovascular deaths, left ventricular assist device (LVAD) placements, and heart transplants (25) with no untoward safety findings.

**The CUPID 2 study aims.** The primary objective of the CUPID 2 (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b) study is to determine the efficacy of a single intracoronary infuion of 1 × 10^{13} DRP AAV1/SERCA2a compared with placebo added to optimal treatment in reducing the frequency and/or delaying HF-related hospitalizations and episodes of ambulatory worsening HF (recurrent events) in symptomatic patients with HFREF (EF ≤ 35%) who are at increased risk of terminal events on the basis of elevated levels of N-terminal pro-B-type natriuretic peptide or a recent HF hospitalization. The secondary objectives include assessment of the safety of AAV1/SERCA2a by determining the incidence and severity of adverse events and changes in laboratory parameters.

**Study design and population.** The target population is adult patients, 18 to 80 years of age, with New York Heart Association (NYHA) functional class II to IV chronic HFREF that is due to ischemic or non ischemic etiology. The basic study inclusion and exclusion criteria are provided in Table 1 (the complete list of criteria are included as Online Tables 1 and 2 in Online Appendix 1). A total of up to 250 patients (n = 125 per treatment arm) will be enrolled to obtain at least 186 adjudicated recurrent events. Repeat events by the same patient will count towards the 186 recurrent events. Enrolled patients will be at increased risk...
for future events based on the presence of at least 1 of the following risk factors:

1. Hospitalization for HF within 6 months of screening, or in lieu of hospitalization, at least 2 outpatient interventions for the intended treatment of signs and symptoms of worsening HF (e.g., intravenous diuretics, peripheral ultrafiltration) (12);

2. N-terminal pro-B-type natriuretic peptide >1,200 pg/ml (BNP >225 pg/ml) within 30 days of screening; if the subject is in atrial fibrillation, N-terminal pro-B-type natriuretic peptide >1,600 pg/ml (BNP >275 pg/ml) within 30 days of screening (28,29).

Patients will be randomized in parallel to either $1 \times 10^{13}$ DRP AAV1/SERCA2a or placebo in a 1:1 ratio. The study protocol was approved by the institutional review boards and institutional biosafety committees at each site, and written informed consent and release of medical information is obtained from all patients before screening. The study will be conducted at approximately 60 sites in the United States and Western Europe with randomization stratified by country.

As outlined in Figure 3, potential candidates will be prescreened for the presence of neutralizing antibodies against AAV serotype 1. Those with a negative titer (up to 50% of all patients screened) will undergo further screening tests and procedures to determine eligibility before randomization and enrollment into the study. On day 0, eligible patients who consent to participate will undergo cardiac catheterization and angiography, followed by infusion of the investigational medicinal product. At study months 1, 3, 6, 9, and 12 (the 12-month active observation period), patients will undergo safety, efficacy, and economic assessments, followed by quarterly visits (months 15, 18, 21, 24, and so on) in the long-term follow-up period for collection of information on clinical events and resource utilization. The primary data analyses will be performed when all patients have completed the full 12-month active observation period and at least 186
adjudicated recurrent events have occurred (repeat events by the same patient will be included in the total count of 186).

Each patient will be followed for a minimum cumulative total of 24 months, including time in the 12-month active observation period and the long-term follow-up period. In addition, the study will continue until a total of at least 186 adjudicated recurrent events have occurred, even if all patients have completed the active observation period and the long-term follow-up period. The end of study will occur when both conditions have been met.

### Table 1: Study Basic Inclusion/Exclusion Criteria

Subjects must meet the following criteria to be eligible for the study:

1. Negative NAb (titers < 1:2 or equivocal) within 90 days of screening.
2. 18 to 80 years of age, inclusive, at the time of signing the informed consent.
3. Chronic systolic HF due to ischemic or nonischemic cardiomyopathy.
4. LVEF < 35% any time during the 60-day window before administration of investigational medicinal product.
5. Diagnosis of NYHA functional class II, III, or IV HF for a minimum of 90 days before screening.
6. Individualized, maximal, optimized HF therapy consistent with American College of Cardiology/American Heart Association and European Society of Cardiology practice guidelines for the treatment of chronic HF and as updated from time to time.
7. All women of childbearing potential must have a negative urine pregnancy test before administration of investigational medicinal product and agree to use adequate contraception.
8. Presence of at least 1 of the following risk factors:
   a. Hospitalization for HF within 6 months of screening, or in lieu of hospitalization, at least 2 outpatient interventions for the intended treatment of signs and symptoms of worsening HF (e.g., intravenous diuretics, peripheral ultrafiltration);
   b. N-terminal pro-B-type natriuretic peptide > 1,200 pg/ml (BNP > 225 pg/ml) within 30 days of screening; if subject is in atrial fibrillation, N-terminal pro-B-type natriuretic peptide > 1,600 pg/ml (BNP > 275 pg/ml) within 30 days of screening.

Subjects meeting any of the following criteria will be excluded from the study:

1. Any IV therapy with positive isotropes, vasodilators or diuretics, within 30 days before screening.
2. Restrictive cardiomyopathy, obstructive cardiomyopathy, acute myocarditis, pericardial disease, amyloidosis, infiltrative cardiomyopathy, uncorrected thyroid disease, or discrete LV aneurysm.
3. Cardiac surgery, percutaneous coronary intervention, or valvuloplasty within 30 days before screening.
4. Myocardial infarction (e.g., STEMI or large non-STEMI) within 90 days before screening. Large non-STEMI shall be defined as > 3 × ULN for CK-MB or > 5 × ULN for troponin.
5. Prior heart transplant, LVRS, cardiomyoplasty, passive restraint device (e.g., CorCap Cardiac Support Device, Acom Cardiovascular Inc., St. Paul, Minnesota), surgically implanted LVAD or cardiac shunt.
6. Likely need for an immediate heart transplant or LVAD implant because of hemodynamic instability.
7. Prior CABG is not considered ideal for inclusion in the study; however, potential candidates can be reviewed on a case-by-case basis.
8. Liver function tests (ALT, AST, alkaline phosphatase) > 3 × ULN within 30 days before investigational medicinal product administration or known intrinsic liver disease (e.g., cirrhosis, chronic hepatitis B, or hepatitis C virus infection).
9. Current or likely need for hemodialysis within 12 months following enrollment or current GFR < 20 ml/min/1.73 m² estimated by MDRD calculation.
10. Bleeding diathesis or thrombocytopenia defined as platelet count < 50,000 platelets/µl.
11. Anemia defined as hemoglobin < 9 g/dl, provided that there is no evidence of bleeding.
12. Diagnosis of, or treatment for, any cancer other than basal cell carcinoma within the last 5 years. (Past medical history of cancer is not exclusionary as long as subject has been disease-free for at least 5 years since the time of diagnosis and treatment.)
Percutaneous intracoronary administration of AAV1/SERCA2a. Intravenous nitroglycerin infusion will be initiated 15 to 25 min before infusion of the investigational medicinal product and continued throughout administration as tolerated. AAV1/SERCA2a or matching placebo is diluted with normal saline before administration, and 50 ml of the diluted solution will be infused over 10 min into the left and/or right coronary artery via antegrade epicardial coronary artery infusion using the B. Braun Perfusor Space Syringe Pump (B. Braun Melsungen AG, Melsungen, Germany).

Coronary anatomy and administration strategy will be defined before administration to accomplish homogenous delivery to the myocardium, with the overall goal to deliver two-thirds of the dose to the anterolateral and one-third to the posterolateral myocardium, if the coronary anatomy and viability of the myocardium allow it (26). However, multiple infusion scenarios exist based on collateralization patterns, occlusive disease, and anatomic variation, with the expectation that at most 3 infusions will be performed to subserve the largest portion of left ventricular blood flow. Patients are required to have at least 1 major coronary vessel with Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 for infusion of the investigational medicinal product. In the event that significant left main or ostial right coronary artery disease is present, the treating physician is given the option to perform percutaneous coronary intervention or other intervention or surgical procedure according to standard of care. If the intervention restores TIMI flow grade 3, a second attempt to infuse the investigational medicinal product can then be made after 30 days.

Study assessments and endpoints. With new treatments on the market, cardiovascular event rates have been declining, and sizes of confirmatory classical morbidity and mortality trials have had to increase considerably in order to have adequate power to detect an effect of therapy. The classic time-to-first event analysis of a composite endpoint of mortality and disease-related morbidity has limitations, and does not efficiently capture disease burden in a HF population that often has multiple recurrent events as well as terminal events. Thus, in the CUPID 2 trial, the primary endpoint was chosen to capture disease burden more fully and to gain efficiency by including all primary endpoint events (e.g., recurrent hospitalization and episodes of ambulatory worsening HF, transplants, LVAD implantation, and death) in the primary analysis. There have been many statistical methods proposed for the analysis of recurrent events (30,31). However, the joint frailty model addresses the limitations of other approaches, because it accounts for the correlation between the recurrent event process and the terminal event process (informative censoring) (32).

Intent-to-treat (ITT), modified ITT, and per protocol analyses will be performed. The primary efficacy endpoint is time-to-recurrent events (HF-related hospitalizations, ambulatory worsening HF) in the presence of terminal events (all-cause death, heart transplant, LVAD implantation) at the primary analysis data cutoff. Patients alive and LVAD/transplant free will be censored at the primary analysis data cutoff, and those lost to follow-up will be
Table 2 The CUPID 2 Study Endpoint Definitions

<table>
<thead>
<tr>
<th>Endpoint Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy endpoint</td>
<td>The primary endpoint analysis will examine the impact of AAV1/SERCA2a versus placebo on the frequency and timing of recurrent events in the presence of terminal events by determining the time to recurrent events (heart failure-related hospitalizations, ambulatory worsening heart failure) in the presence of terminal events (all-cause death, heart transplant, LVAD implantation) based on the joint frailty model.</td>
</tr>
<tr>
<td>Secondary efficacy endpoint</td>
<td>Time-to-first terminal event (defined as all-cause death, heart transplant and LVAD implantation), based on the joint frailty model and performed simultaneously with the primary endpoint analysis.</td>
</tr>
<tr>
<td>Heart failure hospitalization</td>
<td>Unplanned presentation to an acute care facility for an exacerbation of heart failure requiring an overnight stay (change in calendar day) which meets all the following criteria:</td>
</tr>
<tr>
<td></td>
<td><strong>I. New or Worsening Symptoms of Heart Failure</strong></td>
</tr>
<tr>
<td></td>
<td>At least 1 of the following:</td>
</tr>
<tr>
<td></td>
<td>1. Worsening dyspnea</td>
</tr>
<tr>
<td></td>
<td>2. Worsening orthopnea</td>
</tr>
<tr>
<td></td>
<td>3. Paroxysmal nocturnal dyspnea</td>
</tr>
<tr>
<td></td>
<td>4. Increasing fatigue/worsening exercise tolerance</td>
</tr>
<tr>
<td></td>
<td>5. Worsening swelling</td>
</tr>
<tr>
<td></td>
<td>6. GI distress related to congestion/low output</td>
</tr>
<tr>
<td></td>
<td><strong>II. New or Worsening Signs of Heart Failure</strong></td>
</tr>
<tr>
<td></td>
<td>At least 2 of the following physical exam or laboratory findings considered to be due to heart failure:</td>
</tr>
<tr>
<td></td>
<td>1. Peripheral edema</td>
</tr>
<tr>
<td></td>
<td>2. Increasing abdominal distension or ascites</td>
</tr>
<tr>
<td></td>
<td>3. Pulmonary edema or rales</td>
</tr>
<tr>
<td></td>
<td>4. Elevated jugular venous pressure or hepatojugular reflux</td>
</tr>
<tr>
<td></td>
<td>5. S3 gallop</td>
</tr>
<tr>
<td></td>
<td>6. Rapid weight gain (thought to be related to fluid retention)</td>
</tr>
<tr>
<td></td>
<td>7. Hepatomegaly (not related to a primary liver problem)</td>
</tr>
<tr>
<td></td>
<td>8. Increased BNP or N-terminal pro-B-type natriuretic peptide* consistent with heart failure decompensation</td>
</tr>
<tr>
<td></td>
<td>9. Radiologic signs of heart failure</td>
</tr>
<tr>
<td></td>
<td>10. Invasive or non-invasive tests showing elevated cardiac filling pressures or low cardiac output</td>
</tr>
<tr>
<td></td>
<td><strong>III. Intensification of Treatment for Heart Failure</strong></td>
</tr>
<tr>
<td></td>
<td>At least 1 of the following:</td>
</tr>
<tr>
<td></td>
<td>1. Treatment with intravenous diuretics, vasodilators, or inotropes.</td>
</tr>
<tr>
<td></td>
<td>2. Mechanical fluid removal (e.g., ultrafiltration or dialysis).</td>
</tr>
<tr>
<td></td>
<td>3. Insertion of an intra-aortic balloon pump for hemodynamic compromise.</td>
</tr>
<tr>
<td>Ambulatory worsening heart failure</td>
<td>Urgent, unscheduled office/practice or emergency department visit for heart failure management not meeting the criteria for hospitalization:</td>
</tr>
<tr>
<td></td>
<td>1. New or worsening signs and symptoms of heart failure, defined by the same criteria as for the heart failure hospitalization endpoint above and</td>
</tr>
<tr>
<td></td>
<td>2. Initiation or intensification of treatment for heart failure, as defined for heart failure hospitalization.</td>
</tr>
</tbody>
</table>

*In patients with chronically elevated natriuretic peptides a significant increase should be noted above baseline or a recent measurement.
NYHA functional class will be descriptively summarized by time point for each treatment group.

All randomized patients will be included in the ITT analysis. All patients who were randomized and infused will be included in the modified ITT analysis. Missing data for exploratory endpoints (KCCQ and 6-min walk test) will be imputed for ITT analyses. Missing data will not be imputed for the per-protocol analyses, and no imputations will be made in the safety data. Statistical significance will be evaluated at the 2-sided 0.05 level.

**Study hypothesis, power, and sample size.** The study hypothesis is that the risk of recurrent events adjusted for correlated terminal events is reduced for AAV1/SERCA2a compared with placebo (i.e., the estimated recurrent event hazard ratio obtained using the joint frailty model is <1).

The sample size for this phase 2b study, based on Monte Carlo simulation, is 250 patients with an estimated total of 186 recurrent events, which will provide 83% power at the 0.05 2-sided significance level to detect at least a 45% risk reduction (hazard ratio: 0.55) in recurrent events in the presence of the terminal events. The sample size calculation assumptions included background event rates based on published studies in HF patients (35–38) and a conservative estimate of the anticipated magnitude of effect of AAV1/SERCA2a based on 12-month results from the CUPID 1 study that showed an 88% risk reduction in recurrent clinical events adjusted for correlated terminal events with high-dose AAV1/SERCA2a compared with placebo (25).

**Study oversight.** An independent data monitoring committee is responsible for monitoring safety of the study and, per written charter, the study may only be terminated based on safety findings. Because the CUPID 2 trial is an event-driven study, all clinical events will be reviewed by both the unblinded data monitoring committee and by an independent blinded clinical endpoint committee. The clinical endpoint committee reviews and adjudicates clinical events in a consistent and unbiased manner according to standardized definitions to ensure that all clinical events that are reported by the site are adjudicated uniformly, using the same criteria throughout the study. To ensure that no clinical events or endpoints are missed, any hospitalization or use of intravenous diuretics, vasodilators, inotropes, or mechanical fluid removal serves as an automatic trigger for adjudication by the clinical endpoint committee. Lastly, a blinded study executive steering committee oversees the conduct of this clinical trial and provides medical and scientific advice on all aspects of the study and the clinical development of AAV1/SERCA2a. See Online Appendix 1 for a list of the members and affiliations of each of these committees.

**Discussion**

Recent advances in understanding of the molecular basis of myocardial dysfunction, together with the evolution of increasingly efficient gene transfer technology, have placed HF within reach of gene-based therapy. A decrease in SERCA2a activity that results in a reduced calcium uptake during relaxation has been identified as a key abnormality in both human and experimental HF. Pharmacological targeting of SERCA2a, however, has been difficult, and this led to efforts to enhance its activity by gene transfer. Recombinant AAV vectors with their safety profile and long-term expression characteristics, especially in nondividing cells such as the cardiomyocyte, provide an ideal vehicle to carry SERCA2a into the failing myocardium.

Based on the results of the earlier CUPID 1 phase 2 study, which showed that $1 \times 10^{13}$ DRP AAV1/SERCA2a improved numerous clinically relevant domains in advanced HF patients (25), CUPID 2 was designed to test the hypothesis that the risk of recurrent events adjusted for correlated terminal events is reduced for AAV1/SERCA2a compared with placebo (i.e., the recurrent event hazard ratio estimated by the joint frailty model is <1). Although the CUPID 2 trial will recruit a similar population as the CUPID 1 study, entry criteria have been modified to enhance the likelihood of hospitalizations by requiring either previous hospitalization for decompensated HF within 6 months or an elevated natriuretic peptide level. Cardiopulmonary exercise testing, which had been required in the CUPID 1 study was dropped from the entry criteria because of difficulties in performing the test in a standardized manner in an international study. As in the earlier study, however, patients with evidence of antibodies against AAV will be excluded because there is evidence that SERCA2a activity is diminished by their presence, and in experimental models, the presence of even very low levels of antibodies prevents successful transduction (39).

Characteristics of the advanced HF population may complicate the determination of the treatment effect on disease-related events because these patients experience frequent HF-related hospitalizations, high mortality, and continued worsening of the disease, often leading to interventions such as LVAD implantation and/or heart transplant. The primary endpoint of the CUPID 2 study is time-to-recurrent events (HF-related hospitalizations or episodes of ambulatory worsening HF) and will be analyzed in the presence of terminal events (LVAD implant, heart transplant or death), and taking into account multiple recurrent events per patient as well as different follow-up times because of terminal events occurring for some patients on-study. This approach is different from the traditional time-to-first event analysis that may produce controversial and biased results that limit its applicability in an advanced HF population. For example, a patient with multiple consecutive HF hospitalizations who later dies and a patient with a single HF hospitalization who fully recovers would be equivalent in the traditional time-to-first event analysis. Moreover, each recurrent event a patient experiences may increase the risk of additional recurrent events, as well as terminal events. For instance, the risk of mortality after a fourth HF hospitalization is twice as high as that after a first HF hospitalization (12). The risks of recurrent and terminal events must therefore be jointly estimated to avoid any substantial bias.
The joint frailty model (33,34), a semiparametric analysis that accounts for recurrent clinical events, unequal follow-up times between treatment groups, and terminal events as a competing risk, will be used for the study primary analysis. This primary endpoint analysis will be accompanied by various sensitivity and secondary analyses to demonstrate that the benefit is not due to a specific endpoint definition or analysis method. The joint frailty model takes into account:

- Differences in follow-up times as a result of terminal events and their impact on recurrent event rates
- The impact of random between-subject differences on the risk of both terminal and recurrent clinical events
- The substantially increased risk of a terminal event due to recurrent events and quantifies this risk (as a hazard ratio)
- The possibility of a differential treatment effect for recurrent and terminal events; risks of recurrent and terminal events are jointly estimated preventing possible bias because of independent analyses of related processes.

Extensive simulation studies have demonstrated that when recurrent and terminal events are correlated, the joint frailty model provides unbiased risk estimates, strong control of false-positives, and high power to detect treatment effect. Simulations were done under a broad range of data assumptions, including varied strength of correlation between recurrent and terminal events (from mild to strong), and a range of event rates (from 0.5 to 2.2 recurrent events per subject per year, for combined annual terminal event rates of 20% to 30%). These simulations confirmed that the designed study has at least 80% power to detect a reduction in risk of recurrent events of 45% in the presence of terminal events. The joint frailty model accounts for correlation among recurrent events within a patient so that reduction by 2 events in the same patient contributes less to treatment effect than reduction by 1 event in each of 2 patients, thereby ensuring that few patients with recurrent events do not dominate the analysis. Given the advantages of the joint frailty model in reflecting real clinical experiences of advanced HF patients, the primary and secondary endpoints of the CUPID 2 trial were deemed appropriate by the Food and Drug Administration.

Acknowledgment
The authors would like to thank Janice Pogoda, PhD, for biostatistical and programming support.

Reprint requests and correspondence: Dr. Barry Greenberg, Cardiology Division, Department of Medicine, University of California, San Diego, 9444 Medical Center Drive, La Jolla, California 92037-7411. E-mail: bgreenberg@ucsd.edu.

REFERENCES

15. Zaya M, Phan A, Schwarz ER. The dilemma, causes and approaches to avoid recurrent hospital readmissions for patients with chronic heart failure. Heart Fail Rev 2012;17:345–53.


Key Words: clinical trial ■ heart failure ■ joint frailty model ■ recurrent events ■ SERCA2a.

APPENDIX

For supplemental tables, an abbreviated statistical plan, and detailed lists of the study oversight committees, please see the online version of this paper.