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A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation in Patients With Moderately Reduced Left Ventricular Ejection Fraction and a Narrow QRS Duration: Study Rationale and Design

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Abstract

Cardiac contractility modulation (CCM) signals are nonexcitatory electrical signals delivered during the cardiac absolute refractory period that enhance the strength of cardiac muscular contraction. The FIX-HF-5 study was a prospective randomized study comparing CCM plus optimal medical therapy (OMT) to OMT alone that included 428 New York Heart Association (NYHA) functional class III or IV heart failure patients with ejection fraction (EF) $\geq$ 45% according to core laboratory assessment. The study met its primary safety end point, but did not reach its primary efficacy end point: a responders analysis of changes in ventilatory anaerobic threshold (VAT). However, in a prespecified subgroup analysis, significant improvements in primary and secondary end points, including the responder VAT end point, were observed in patients with EFs ranging from 25% to 45%, who constituted about one-half of the study subjects. We therefore designed a new study to prospectively confirm the efficacy of CCM in this

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population. A hierarchic bayesian statistical analysis plan was developed to take advantage of the data already available from the first study. In addition, based on technical difficulties encountered in reliably quantifying VAT and the relatively large amount of nonquantifiable studies, the primary efficacy end point was changed to peak VO_2 , with significant measures incorporated to minimize the influence of placebo effect. In this paper, we provide the details and rationale of the FIX-HF-5C study design to study CCM plus OMT compared with OMT alone in subjects with normal QRS duration, NYHA functional class III or IV, and EF 25%–45%. This study is registered on www.clinicaltrials.gov with identifier no. NCT01381172.

Keywords

Heart failure; cardiac resynchronization therapy; cardiopulmonary stress testing; quality of life

Cardiac contractility modulation (CCM) is an electrical device–based approach developed for the treatment of chronic heart failure with reduced ejection fraction.^{1,2} CCM signals are nonexcitatory electrical signals applied during the cardiac absolute refractory period that enhance the strength of cardiac muscular contraction.³ Studies suggest that this improvement is due in part to electrical signal–mediated post-translational protein modification and expression of genes coding for proteins involved in regulation of calcium cycling and contraction.^{1,4,5} These studies, in both animals and humans, further suggest that the improvements in contractile strength are not associated with increases in myocardial oxygen consumption.^{4,6}

After completion of a successful double-blind double-crossover study in Europe (the FIX-HF-4 study)⁷ and a pilot study in the United States,⁸ the FIX-HF-5 study was designed to prospectively study the safety and efficacy of CCM in patients with New York Heart Association (NYHA) functional class III or IV symptoms and ejection fraction (EF) <35%.^{9,10} Four hundred twenty-eight (428) patients were enrolled. The study met its primary safety end point (a noninferiority assessment of the composite of all-cause mortality and all-cause hospitalizations). However, the primary efficacy end point, a responders analysis of changes in ventilatory anaerobic threshold (VAT) on cardiopulmonary stress testing, was not met.¹⁰ It is noteworthy that although enrollment was based on site evaluation of baseline echocardiographic EF, all echocardiographic analyses were based on an analysis performed by a core laboratory. Not surprisingly, patients with core laboratory–determined EFs up to 45% were actually included.¹¹ Discrepancy between site and core laboratory assessment of EF is not uncommon in heart failure clinical trials.¹² Although the efficacy end point of the FIX-HF-5 study was not met, a hypothesis-generating subgroup analysis showed significant treatment effects on primary and secondary end points (including peak VO_2 and Minnesota Living With Heart Failure Questionnaire [MLWHFQ]) in patients with EFs ranging from 25% to 45%.¹¹ This subgroup included about one-half of all the study subjects.

We therefore designed the FIX-HF-5 confirmatory study (the FIX-HF-5C study) to prospectively confirm the efficacy of CCM originally identified in patients with EF 25%–45%. A hierarchic bayesian statistical analysis plan was developed to take advantage of the

data already available from the original FIX-HF-5 study. In addition, based on difficulties encountered in reliably quantifying VAT, the relatively large number of studies in which VAT could not be quantified,¹³ and the statistical inefficiency and arbitrary nature of thresholds employed in a “responders” analysis of a continuous variable,¹⁴ the primary efficacy end point was switched to a comparison of changes in peak VO₂ between the treatment and control groups. Provisions have been incorporated to exclude the influence of placebo effect on peak VO₂. The details of this FIX-HF-5C study design are provided herein. This study is registered on www.clinicaltrials.gov with identifier no. NCT01381172.

The Optimizer System and Implant Procedure

This study uses the Optimizer IVs System, which is smaller than but otherwise delivers the same CCM signals according to the same algorithms as the Optimizer III system used in the original study. The system consists of an implantable pulse generator (IPG) with a rechargeable battery, 1 atrial and 2 ventricular pacing screw-in leads, IPG programmer (similar to a standard pacer/implantable cardioverter-defibrillator [ICD] programmer), and a battery charger (Fig. 1). The implantation procedure has been detailed previously.^{2,8,9} In brief, an atrial lead is used for sensing and is placed in the same manner as for other standard pacemakers and defibrillators. Two ventricular leads, used for both sensing local electrical activity and CCM signal delivery, are placed on the right ventricular septum. The goal is to ensure that electrodes are placed such that an impact on left ventricular function can be detected when signals are applied. In practice, CCM signals are applied and changes in dP/dt_{max} are measured with an intra-ventricular high-fidelity pressure sensor. An acute increase of dP/dt_{max} 5% within ~10 minutes of signal application is considered to be adequate. If such a response is not elicited, the leads can be repositioned.

The battery of the IPG is a rechargeable lithium-ion battery. Each patient receives a charging unit, and is instructed to charge the device once per week. When performed at this frequency, a charging session lasts ~90 minutes. CCM signals used in this study consist of 2 biphasic square-wave pulses with peak-to-peak amplitude of ± 7.7 V that are applied 20–40 ms after the detection of electrical activation at the first ventricular lead.² CCM signal delivery is suspended on detection of suspected ectopic beats and during atrial fibrillation and is reinitiated once the device senses 3 consecutive normal sinus beats. The device is programmed to deliver CCM signals for 5 1-hour periods spaced equally through the 24 hours of a day.

FIX-HF-5C Study Overview and Objectives

The FIX-HF-5C study is designed to confirm findings of the FIX-HF-5 study, in which a subgroup analysis showed significant improvements in exercise tolerance measured by peak VO₂ in patients with EF ranging from 25% to 45%. The study is a prospective, randomized, parallel-controlled trial of optimal medical therapy (OMT) alone (control group) versus OMT plus CCM (CCM treatment group) in patients with medically refractory heart failure (NYHA functional class III or IV) with EF 25%–45%.

Study Population

The inclusion and exclusion criteria are summarized in Table 1. In brief, patients with NYHA functional class III or ambulatory class IV heart failure despite OMT, an EF of 25%–45%, and normal sinus rhythm with a narrow QRS duration (≤ 130 ms) are eligible for the study. Unless there are extenuating circumstances, patients with EF $\geq 35\%$ are required to have an ICD according to published guidelines.¹⁵ Patients will be recruited from up to 25 sites in the United States and 15 in Europe (total of up to 40 sites worldwide). At least 50% of patients will be recruited from the United States, and no single site will be allowed to enroll more than 15% of the subjects.

The overall study flow is summarized in Figure 1. After informed consent, baseline testing consists of a standard array of clinical and physiologic testing as detailed in Table 2. Of note, 2 cardiopulmonary exercise (CPX) tests are performed at baseline and at each follow-up time point. This is intended to reduce effects of habituation, to reduce variability in test results, and to provide evidence that patients have achieved their maximum exercise capacity. Details of how data from these will be analyzed are summarized below.

After passing baseline testing, a device implantation date is scheduled in the electrophysiology laboratory; this scheduled implantation date defines the study start date from which the timing of all future follow-up visits is determined for subjects in both groups. Subjects are then randomized 1:1 to either the control group or to the CCM treatment group. Subjects randomized to the treatment group undergo device implantation. For subjects not already having an ICD but for whom it is indicated based on current guidelines, one will be implanted at the same time as the Optimizer system. Subjects randomized to the control group not having an ICD but who meet criteria will undergo device implantation on the scheduled implantation date. However, for subjects randomized to the control group already having an ICD, the time in the laboratory will be canceled, but the putative implantation date will still serve as a study start date. Subjects in both groups will be followed identically (except for interrogation of the investigational device) for 24 weeks as detailed in Table 2. The first follow-up visit will be at 2 weeks after the start of the study, at which time the Optimizer system will be interrogated in those patients randomized to the treatment group.

Major follow-up visits are at weeks 12 and 24, at which time CPX, MLWHFQ, 6-minute walk test (6MWT), and NYHA functional class tests are performed. As noted above, 2 CPX tests are performed at each of these follow-up time points.

At the conclusion of the 24-week follow-up period, patients in the control group will have completed participation in the formal portion of the study; however, these patients will continue to be followed for vital status at 3-month intervals for an additional 18 months (2-year total follow-up for mortality). Patients in the CCM treatment group will continue to be followed at 3-month intervals for device-related serious adverse events, device interrogations, and vital status.

Approach to Reducing Placebo Effect and Bias

While a double-blind trial design employing an implanted control as used in some implantable device trials (including the prior feasibility study of the Optimizer⁸) was initially considered, this was deemed unfeasible as detailed in the description of the original FIX-HF-5 study.⁹ In brief, the need for weekly charging of the device with a wand the patient positions over the device would have likely led to significant (if not total) unblinding. Accordingly, given the unblinded nature of the study, several measures are being taken to minimize placebo effect and investigator bias. First, the primary efficacy end point, peak VO_2 , will be analyzed in a blinded core lab. Second, patients are required to perform 2 tests on separate days at baseline and at each follow up time point; this is intended to eliminate effects of habituation and test unfamiliarity and optimize conditions for patients to achieve maximal effort. The respiratory exchange ratio (RER) will be evaluated on each test and will be taken into account in secondary efficacy analyses of the peak VO_2 data, as detailed further below. Regarding safety evaluation, an independent Events Adjudication Committee (EAC) will evaluate original records of every adverse event, hospitalization and death. Third, clinical assessments of NYHA will be done by a clinician blinded to treatment assignment.

Efforts to Ensure Cardiopulmonary Stress Test (CPX) Quality

Several measures will be taken to optimize the quality of all CPX tests and obtain maximal effort from each patient. These measures include: 1) on-site training on standardized procedures for conducting CPX testing; 2) normal subject validation testing and revalidation every 6 months; 3) providing the patient with instructions and how to prepare for the CPX test; and 4) rapid feedback on test quality from the core laboratory. Once obtained, metabolic data are uploaded to the blinded CPX core lab for analysis. Peak VO_2 , RER and VE/VCO_2 slope are determined from averaged 20 second gas exchange data from the start of exercise to the end of exercise.

Events Adjudication Committee and Data Safety Monitoring Board

An event adjudication committee (EAC) has been established to review records of adverse events, hospitalizations and deaths. This committee is composed of 3 independent cardiologists experienced in the adjudication process. The committee provides definitions for protocol-specified hospitalizations which include an admission that results in a calendar date change or is related to an adverse event that causes a prolongation of the index hospitalization for device implantation. The committee also adjudicates the cardiac and heart failure relatedness of deaths and hospitalizations.

An independent Data and Safety Monitoring Board (DSMB) has also been established to review aggregate safety data and monitor for the emergence of any significant safety concerns. The DSMB is composed of 5 members with clinical trial experience in heart failure, electrophysiology, and statistics not otherwise participating in the study. The DSMB is unblinded to study group assignment.

Statistical Considerations and Analysis Plan

The major efficacy and safety end points are summarized in Table 3, and detailed further below.

Primary Efficacy Analysis—The trial's primary measure of efficacy is the change in peak VO_2 as evaluated by the blinded core laboratory. As mentioned previously, subjects undergo 2 tests at each time point (baseline, 12 weeks, and 24 weeks). Each test will be evaluated by the core lab to determine if the test is adequate. Tests may be deemed to be inadequate if:

- The subject has an erratic or oscillatory breathing pattern.
- The data are nonphysiologic.
- Testing equipment issues occur.
- The test is submaximal, meaning it was terminated by either the subject or the supervising clinician/technician prior to the subject reaching volitional exhaustion. Reasons for early termination include non-heart failure symptoms (eg, angina, heart rhythm disturbance, or leg, foot, or back pain) or the subject is technically challenged by performing the test.

If both tests are deemed to be adequate, the average of the 2 tests will be used. If only 1 test is deemed to be adequate, then only that 1 value will be used for the analysis. The primary analysis is an intent-to-treat analysis based on a generalized linear mixed-effects regression model.¹⁶ Unlike end point analyses using propensity score matching for imputation of missing data, the proposed analyses use all available longitudinal data (baseline, 12 weeks, and 24 weeks from each subject). This statistical approach does not require imputation but still provides the same level of robustness to missing values and drop-outs enjoyed by the multiple imputation procedure used in the original FIX-HF-5 study.¹⁷ Specifically, we will include log-transformed time in a mixed-effects linear model for the outcome. The primary effect of interest is the treatment by time interaction. The model contains a random intercept and random slope to absorb the correlation between the repeated assessments. Using a bayesian approach to borrow strength between the 2 studies (to be described subsequently), superiority of the treatment arm will be declared if the posterior probability that the mean change from base-line to 24 weeks in peak VO_2 in the prospective trial is $\geq 97.5\%$ in the treatment group (ie, $\beta_{\text{int}} > 0$), conditioned on the prospective data and the original FIX-HF-5 data.

As noted previously, although the original FIX-HF-5 study did not meet the primary effectiveness end point, in the subgroup of subjects with EF $\geq 25\%$ (which are the focus of the present study), a statistically significant increase in peak VO_2 was observed in treatment versus control groups. We will use hierarchical bayesian design for borrowing strength from the original study for the primary efficacy analysis. The Food and Drug Administration released the document "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials."¹⁸ This document lays out important guidelines that must be satisfied to avoid putting strong priors on favorable outcomes, because this will inflate type I error above acceptable levels. Specifically, the statistical model must be able to borrow in a

flexible manner so that more borrowing is done when results for the prospective study are consistent with the favorable prior information but relatively little borrowing is done when the prospective results are consistent with the null hypothesis. Hierarchic models are a natural approach to achieving this flexible borrowing strategy. The model used to achieve this is a hierarchic model consistent with one presented by Pennello and Thompson.¹⁹ In brief, inference for this model centers around the difference in mean changes in peak VO_2 between the treatment arm and control arm in the prospective data set conditional on all of the data for both the prior study (both subgroups) and the prospective study (focused only on the single subgroup), and it will be required that the posterior probability of superiority be 97.5%. The design simultaneously gives incremental power above and beyond that of a stand-alone analysis while preserving the low (5%) type I error of a stand-alone analysis. Operating characteristics for the bayesian design are determined by simulating a large number of possible data sets for a variety of true values of the model parameters and then determining the associated posterior inference with the use of Markov chain Monte Carlo methods.²⁰ The type I error of the design is ~5%. More than adequate power (86%) is ensured if the true interaction term (ie, difference in mean change from baseline to 24 weeks for treatment vs control arms) is 75% of that observed in the subgroup in the original study.

Secondary Efficacy Analyses—Secondary efficacy parameters include change in quality of life as assessed by the MLWHFQ, comparison of mean changes in peak VO_2 between groups with change in respiratory exchange ratio (RER) included as a covariate, change in NYHA functional classification assigned by a blinded site clinician, and comparison of mean change in peak VO_2 between groups that only includes tests on which RER is ≤ 1.05 .

These analyses will be conducted on both the prospective data alone and the prospective data pooled with the data from the original FIX-HF-5 study of the subgroup of interest (EF $\geq 25\%$). Pooled models will include a study indicator to adjust for differences in overall success rate between studies. Analysis from the pooled data will constitute the analysis upon which success will be determined. Since there are multiple efficacy hypotheses to be tested, the method of alpha control is the closed-form hierarchic method, with statistical testing in the order in which the secondary end points are listed above.

Additional Efficacy Analyses—Additional efficacy analyses will be performed that are descriptive in nature, and will include comparisons between groups of changes from baseline in 6MHW distance and mean changes in VE/VCO_2 .

Primary Safety Analysis—The safety of the Optimizer system will be assessed by evaluating the incidence of Optimizer device- or procedure-related complications. The primary safety end point is the proportion of subjects who do not experience either an Optimizer device-related complication or a procedure-related complication by 24 weeks. The criterion for satisfying the safety analysis is that the proportion of complication-free subjects is significantly larger than 70% (1-sided significance level of 0.025); equivalently, the safety end point will be met if the lower bound for the 95% confidence interval of the percentage of subjects surviving without experiencing a primary safety event is not $<70\%$. This lower limit of 70% was chosen to be the same criterion used in several earlier studies of

cardiac resynchronization therapy (CRT). Satisfying the primary safety end point will require rejecting the null hypothesis at a 1-sided significance level of 0.025 with the use of an exact binomial test. It is noteworthy that point estimate of freedom from this composite end point at 24 weeks among subjects in the subgroup of EF $\geq$ 25% in the original FIX-HF-5 study was 88%.

Sample Size Calculations—Power calculations for a longitudinal design are normally quite complex, and the addition of the Bayesian hierarchic framework increases the complexity. We adopted the following approach. We assumed that the longitudinal data in the prospective study will be generated with the same random-intercept random-slope model that we used to analyze the original data. We assume that all variance components (the residual error variance, the random intercept variance, the random slope variance, and the correlation of the random intercept and slope) for the prospective study will be the same as their estimated values in the subgroup of interest analysis from the original data. We also assume that the control group intercept and slope is the same as it was in the subgroup of interest for the original trial. We then simulate a large number of prospective data sets under these assumptions for a variety of possible true treatment effects (differences between control and treatment arm slopes) and calculate the proportion of these data sets that would satisfy the bayesian superiority criterion of the previous section. Assuming a true treatment effect of 0 (ie, the slopes in the 2 arms are identical) yields the type I error. Based on these assumptions, a total sample size of 230 subjects split evenly between treatment and control groups will give more than adequate (86%) power to conclude superiority of treatment if the true treatment effect is $\sim$ 75% of that observed in the FIX-HF5 subgroup. The hierarchic modeling approach used keeps type I error rate (ie, the chance of concluding superiority if in fact there is no treatment effect) well controlled at 5%; this is notable, because the stand-alone *P* value for the FIX-HF5 subgroup was statistically significant ($P < .01$).

For the safety end point, assuming 115 patients in the treatment group, the minimum allowable observed rate for complication-free survival is 79% (91 complication-free patients). The design has 82% power for an 82% true rate and 89% power for an 83% true rate. The type I error at the lower boundary (70%) is $<2\%$.

Therefore, a sample size of 115 subjects per treatment group ensures adequate power while maintaining appropriate type I error for both the primary efficacy and the safety study end points.

Secondary Safety Analysis—Secondary safety analyses include all-cause mortality, cardiac mortality, heart failure mortality, all-cause hospitalizations, cardiac-related hospitalizations, heart failure-related hospitalizations, and overall incidence and seriousness of adverse events.

Discussion

Currently, in the United States, CRT is the only approved electrical therapy for patients with heart failure, specifically for those with EF $\geq$ 35% and a wide QRS duration.^{21–23} Fewer than 30% of heart failure patients meet QRS duration criteria for CRT. Approximately 30% of

patients receiving CRT are considered to be nonresponders because their symptoms do not improve,²¹ and CRT does not improve clinical status or outcomes in patients with a narrow QRS duration.^{24,25} In fact, CRT may harm patients with QRS <130 ms.²³ Moreover, despite major advances in drug and device therapies, heart failure remains a cause of substantial disability, hospitalizations, and mortality. Thus, there is a crucial need for additional safe and effective heart failure therapies.

The original FIX-HF-5 study was designed to provide evidence of safety and efficacy of CCM treatment delivered by the Optimizer system. The cohort enrolled in the study was composed of patients with moderately advanced heart failure despite appropriate medical therapy who did not have indications for CRT. Two unique aspects of that study were the choice of ventilatory anaerobic threshold as the primary measure of efficacy and the use of a responders analysis (with an arbitrarily chosen threshold value to define responders) as the statistical means of assessing that end point. Given the pitfalls of these study design elements,^{13,14} both have been dropped for the current study in favor of the more traditional use of peak VO₂ analyzed as a continuous variable as a primary end point. In this regard, it is noteworthy that the difference in peak VO₂ between groups in the FIX-HF-5 study was significant (according to an analysis performed on the completers population), with patients in the CCM treatment group demonstrating significant improvement compared with control subjects (Fig. 2).¹⁰ A similar treatment effect on peak VO₂ was identified in the original FIX-HF-4 study.⁷

In addition, a detailed subgroup analysis revealed significantly greater treatment effects in the group of patients with baseline EF $\geq$ 25%, the median baseline EF among FIX-HF-5 study subjects.¹¹ This group constituted almost one-half of the entire study cohort. This was true for all efficacy parameters, including peak VO₂ and VAT. Additional analysis of a smaller subgroup of patients having EFs 35%–45% showed an even greater effect on peak VO₂ and VAT (Fig. 2).²⁶ These observations form the basis for the inclusion criteria of the current study. In addition, the use of a Bayesian statistical approach allows use of these original data to enhance the current study and reduce sample size. As such, the current FIX-HF-5C study is positioned to confirm findings of the FIX-HF-5 subgroup analysis.

Study Limitations

The major limitation of the current study is that it is un-blinded. As discussed above, although blinding is preferable, it is not practical owing to the requirement for charging and the probability of a high degree of accidental unblinding. Assessment of the amount and impact of un-blinding would be difficult to assess. Accordingly, an un-blinded study was accepted. To address this issue, the most robust and objective primary efficacy end point, peak VO₂, was chosen and several secondary efficacy end points based on changes in RER are included to assess and account for potential placebo effects. In addition, although the number of protocol-specified visits have been matched between treatment and control groups, subjects in the treatment group will also have a device interrogation. It will be undetermined if there is any additional placebo effect of a device interrogation.

Conclusion

In summary, the FIX-HF-5C study will enroll 230 subjects with NYHA functional class III or ambulatory class IV symptoms despite OMT, having a QRS duration < 130 ms, and having left ventricular EF 25%–45%. The primary efficacy assessment is based on changes in peak VO₂ between groups at 6 months of follow-up. Bayesian statistics will be used to combine the prospectively collected FIX-HF-5C data with those of the original FIX-HF-5 study. The study is anticipated to require 1 year for recruitment and an additional 6 months until the last enrolled patient has reached the study end point.

Acknowledgments

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References

1. Burkhoff D, Ben Haim SA. Nonexcitatory electrical signals for enhancing ventricular contractility: rationale and initial investigations of an experimental treatment for heart failure. *Am J Physiol Heart Circ Physiol*. 2005; 288:H2550–6. [PubMed: 15897327]
2. Lawo T, Borggrefe M, Butter C, Hindricks G, Schmidinger H, Mika Y, et al. Electrical signals applied during the absolute refractory period: an investigational treatment for advanced heart failure in patients with normal QRS duration. *J Am Coll Cardiol*. 2005; 46:2229–36. [PubMed: 16360051]
3. Bruckhorst CB, Shemer I, Mika Y, Ben Haim SA, Burkhoff D. Cardiac contractility modulation by non-excitatory currents: studies in isolated cardiac muscle. *Eur J Heart Fail*. 2006; 8:7–15. [PubMed: 16202650]
4. Imai M, Rastogi S, Gupta RC, Mishra S, Sharov VG, Stanley WC, et al. Therapy with cardiac contractility modulation electrical signals improves left ventricular function and remodeling in dogs with chronic heart failure. *J Am Coll Cardiol*. 2007; 49:2120–8. [PubMed: 17531662]
5. Butter C, Rastogi S, Minden HH, Meyhofer J, Burkhoff D, Sabbah HN. Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. *J Am Coll Cardiol*. 2008; 51:1784–9. [PubMed: 18452785]
6. Butter C, Wellnhofer E, Schlegl M, Winbeck G, Fleck E, Sabbah HN. Enhanced inotropic state of the failing left ventricle by cardiac contractility modulation electrical signals is not associated with increased myocardial oxygen consumption. *J Card Fail*. 2007; 13:137–42. [PubMed: 17395055]
7. Borggrefe MM, Lawo T, Butter C, Schmidinger H, Lunati M, Pieske B, et al. Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. *Eur Heart J*. 2008; 29:1019–28. [PubMed: 18270213]
8. Neelagaru SB, Sanchez JE, Lau SK, Greenberg SM, Raval NY, Worley S, et al. Nonexcitatory, cardiac contractility modulation electrical impulses: feasibility study for advanced heart failure in patients with normal QRS duration. *Heart Rhythm*. 2006; 3:1140–7. [PubMed: 17018340]
9. Abraham WT, Burkhoff D, Nademanee K, Carson P, Bourge R, Ellenbogen KA, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation in patients with systolic heart failure: rationale, design, and baseline patient characteristics. *Am Heart J*. 2008; 156:641–8. [PubMed: 18926146]
10. Kadish A, Nademanee K, Volosin K, Krueger S, Neelagaru S, Raval N, et al. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. *Am Heart J*. 2011; 161:329–37. [PubMed: 21315216]
11. Abraham WT, Nademanee K, Volosin K, Krueger S, Neelagaru S, Raval N, et al. Subgroup analysis of a randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. *J Card Fail*. 2011; 17:710–7. [PubMed: 21872139]
12. Chung ES, Katra RP, Ghio S, Bax J, Gerritse B, Hilpisch K, et al. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. *Eur J Heart Fail*. 2010; 12:581–7. [PubMed: 20150328]

13. Myers J, Goldsmith RL, Keteyian SJ, Brawner CA, Brazil DA, Aldred H, et al. The ventilatory anaerobic threshold in heart failure: a multicenter evaluation of reliability. *J Card Fail.* 2010; 16:76–83. [PubMed: 20123322]
14. Burkhoff D, Parides M, Borggreffe M, Abraham WT, Kadish A. “Responder analysis” for assessing effectiveness of heart failure therapies based on measures of exercise tolerance. *J Card Fail.* 2009; 15:108–15. [PubMed: 19254669]
15. Russo AM, Stainback RF, Bailey SR, Epstein AE, Heidenreich PA, Jessup M, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *Heart Rhythm.* 2013; 10:e11–58. [PubMed: 23473952]
16. Hedeker, D.; Gibbons, RD. Longitudinal data analysis. New York: Wiley; 2006.
17. Rubin D. Inference and missing data. *Biometrika.* 1976; 63:581–92.
18. [Accessed November 16, 2014] Guidance for the use of bayesian statistics in medical device clinical trials. Available at: <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071072.htm>
19. Pennello G, Thompson L. Experience with reviewing bayesian medical device trials. *J Biopharm Stat.* 2008; 18:81–115. [PubMed: 18161543]
20. Lunn DJ, Best N, Thomas A, Wakefield J, Spiegelhalter D. Bayesian analysis of population PK/PD models: general concepts and software. *J Pharmacokinet Pharmacodyn.* 2002; 29:271–307. [PubMed: 12449499]
21. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med.* 2002; 346:1845–53. [PubMed: 12063368]
22. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004; 350:2140–50. [PubMed: 15152059]
23. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CARDiac RESynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J.* 2006; 27:1928–32. [PubMed: 16782715]
24. Beshai JF, Grimm RA, Nagueh SF, Baker JH 2nd, Beau SL, Greenberg SM, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med.* 2007; 357:2461–71. [PubMed: 17986493]
25. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, et al. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med.* 2013; 369:1395–405. [PubMed: 23998714]
26. Borggreffe M, Burkhoff D. Clinical effects of cardiac contractility modulation (CCM) as a treatment for chronic heart failure. *Eur J Heart Fail.* 2012; 14:703–12. [PubMed: 22696514]

Fig. 1. FIX-HF-5C study flow diagram. This is a prospective randomized (with 1:1 randomization) study in which one-half of the patients receive optimal medical treatment (OMT) alone (control) and one-half receive an Optimizer system implant and continued OMT (treatment). Patients in both groups are followed for 24 weeks.

Fig. 2.

Analysis of completers' population of the FIX-HF-5 study, showing the difference in changes in peak VO_2 between groups (positive value favors cardiac contractility modulation treatment over control) in the entire population, in the subgroup with EF $\geq$ 25% (n = 221) and in the subgroup with EF $\geq$ 35% (n = 38).²⁶

Table 1**Study Inclusion and Exclusion Criteria****Inclusion Criteria**

- 1 Age 18 years.
- 2 Baseline EF 25%–45% according to echocardiography and quantified by a core laboratory.
- 3 Subject has been treated for heart failure for 90 days (including treatment with a β -blocker for 90 days unless intolerant) and are in New York Heart Association functional class III and IV at the time of enrollment.
- 4 Subject has been receiving appropriate stable medical therapy during the 30 days before enrollment for treatment of heart failure according to region-specific guideline recommendations. For patients with EF $\geq 35\%$, this regimen shall consist of the appropriate doses of diuretics, angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker, and β -blocker. In Europe, ivabradine may also be considered in subjects with a heart rate ≥ 70 beats/min. Stable is defined as no more than a 100% increase or 50% decrease in dose.
- 5 Female subjects of childbearing potential must be using a medically approved method of birth control, must be surgically sterilized, and should agree to continue to use birth control throughout the study.
- 6 Willing and able to return for all follow-up visits.
- 7 Provides informed consent to participate in the study

Exclusion Criteria

- 1 Baseline peak VO_2 is <9 or $>20 \text{ mL O}_2 \text{ min}^{-1} \text{ kg}^{-1}$.
- 2 Subject has a potentially correctable cause of heart failure, such as valvular heart disease or congenital heart disease.
- 3 Subject has clinically significant angina pectoris, consisting of angina during daily life (ie, Canadian Cardiovascular Society Angina score II), an episode of unstable angina within 30 days of enrollment, or angina and/or electrocardiographic changes during exercise testing performed during baseline evaluation.
- 4 Subject has been hospitalized for heart failure that required the use of inotropic support within 30 days of enrollment.
- 5 Subject has a clinically significant amount of ambient ectopy, defined as $>8,900$ premature ventricular contractions (PVCs) per 24 hours on baseline Holter monitoring.
- 6 Subject has a PR interval >375 ms.
- 7 Subject has permanent or persistent atrial fibrillation or atrial flutter, or has been cardioverted within 30 days of enrollment.
- 8 Exercise tolerance is limited by a condition other than heart failure (eg, angina, chronic obstructive pulmonary disease, peripheral vascular disease, orthopedic or rheumatologic conditions) or is unable to perform baseline stress testing.
- 9 Subject is scheduled for a coronary artery bypass graft (CABG) or a percutaneous transluminal coronary angioplasty (PTCA) procedure, or has undergone a CABG procedure within 90 days or a PTCA procedure within 30 days of enrollment.
- 10 Subject has a biventricular pacing system, an accepted indication for such a device, or a QRS width of ≥ 130 ms.
- 11 Subject has had a myocardial infarction within 90 days of enrollment.
- 12 Subject has mechanical tricuspid or aortic valves.
- 13 Subject has had a heart transplant.
- 14 Subject is on dialysis.
- 15 Subject is participating in another experimental protocol.
- 16 Subject is unable to provide informed consent.

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17 Subject has been previously randomized in an Optimizer system study.

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1. It is desired to deliver cardiac contractility modulation (CCM) signals for 70% of the time.
 2. CCM signals are suppressed for 3 beats following a PVC. Therefore, if there is one PVC every 13 beats there will be 9 CCM signals delivered (no CCM on the PVC and no CCM for 3 additional normal sinus rhythm beats).
 3. If the average HR is 85, there are 115,200 beats/d.
 4. If 1/13 of these are PVCs, that equals an estimated 8,861 beats/24 h. The actual percent of CCM signal delivery will depend on whether PVCs occur as singlets, doublets, runs, etc.

Table 2

Schedule of Events

Test	Follow-Up Schedule (Relative to Study Start Date)					
	Screening	Baseline	Implant [*]	Week 2 ±2 d	+4 ± 1 wk	+12 ± 2 wk
Informed consent	X					
History	X			X	X	X
NYHA functional class (blinded site clinician assessment)	X				X	X
Medications	X				X	X
Physical examination	X				X	X
12-lead electrocardiography		X				
Echocardiogram		X				
MLWHFQ		X			X	X
Cardiopulmonary stress test		2X			2X	2X
6-minute walk test		X				X
24-hour Holter monitor		X				
Urine pregnancy test		X				X
Eligibility determination		X				
Randomization		X				
Optimizer system implantation [*]			X			
Chest X-ray [*]			X			
Optimizer device interrogation/programming [*]			X	X	X	X
Adverse events, hospitalizations, and procedures (as needed)/Optimizer device-related SAEs after 24 wk		X	X	X	X	X

NYHA, New York Heart Association; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; SAE, serious adverse event.

^{*} For subjects randomized to active treatment group. Subjects in both groups are followed every 3 months (±4 wk) after the 24-week visit.

Table 3

Summary of Study Safety and Efficacy End Points

Class	Hierarchy	Parameter
Efficacy	Primary	Peak VO ₂
	Secondary	MLWHFQ
		Peak VO ₂ with RER included as a covariate
		NYHA functional class
		Peak VO ₂ including on tests with
		RER 1.05
	Additional	6MWT
		VE/VCO ₂
Safety	Primary	Device- or procedure-related SAEs

RER, respiratory exchange ratio; 6MWT, 6-minute walk test; other abbreviations as in Table 2.