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Hope is Here

May 12, 2022

Centers for Medicare & Medicaid Services
Tamara Syrek-Jensen
Director, Coverage and Analysis Group
7500 Security Blvd
Baltimore, MD 21244

Re: Formal Request for a National Coverage Determination for Cardiac Contractility Modulation Therapy

Dear Ms. Syrek-Jensen:

Impulse Dynamics respectfully and formally requests to initiate a National Coverage Determination for Cardiac Contractility Modulation therapy, also known as CCM. CCM provides symptom relief and improves health outcomes for a vulnerable group of patients with a debilitating chronic condition and without other treatment options, a significant portion of whom are Medicare-eligible.

We believe this request to be full and complete based on the stipulations in CMS-3284-N.[1] There is strong support from the appropriate clinical communities for this request. Additionally, there is a substantial need for CCM therapy for Medicare beneficiaries. Patients indicated for CCM therapy have been diagnosed with chronic heart failure (HF), are on guideline-directed medical therapy, experience HF symptoms with less than ordinary activity levels, and are not indicated for any other HF treatment. CCM therapy is the subject of more than 20 years of clinical research. It has been shown to alleviate symptoms and improve health outcomes for more than 7,000 indicated patients globally.

CCM therapy helps Medicare and providers achieve one of their core missions – allowing patients to live their fullest lives possible. CCM therapy fills a gap in the treatment guidelines for heart failure, a chronic condition that creates great clinical and economic challenges for a very sizeable population of Medicare-eligible patients. For these reasons and based on the quality of evidence underlying CCM therapy's efficacy, we look forward to interactions with the agency and with public stakeholders on this NCD request.

Thank you for your consideration of this NCD request. If you or any of your Agency peers have additional questions regarding its content, please contact me at your earliest convenience.

Submitted with best regards,

Simos Kedikoglou, M.D.
CEO, Impulse Dynamics

[1] Federal Register, Vol 78, No 152, 48164-9, August 7, 2013

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U.S. Heart Failure Incidence and Prevalence and the Fit for CCM Therapy

HF is a progressive disease, although early diagnosis and treatment can improve both the quality and length of life. Initial treatments typically involve prescription medications along with physician recommendations to reduce sodium intake and increase daily physical activity levels. The 2022 update of AHA, ACC, HFSA guidelines for patients with reduced LVEF recommends all patients be on diuretics as necessary and an ACE inhibitor or an ARB, beta-blockers, and an aldosterone antagonist[2]. A combination ARB-neprilysin inhibitor (ARNI) is recommended to replace the ACE inhibitor or ARB when possible. Unfortunately, many patients with HF are refractory to medical therapy. This was evidenced in the PARADIGM trial evaluating the ARNI Sacubitril-Valsartan for treating HFrEF where even in the treatment arm, 22% of patients experienced a cardiovascular (CV) death or HF hospitalization event. Treatment failure is indicated by a continued deterioration in NYHA class.

ICDs are approved for use in most patients with heart failure with reduced ejection fraction (HFrEF). These devices detect potentially fatal arrhythmias and deliver high-energy electric shocks intended to reestablish a normal heart rhythm. Although ICDs can save lives, they do not treat the symptoms of heart failure, and patients may continue to experience progressively worsening symptoms.

CRT devices are intended for HF patients who have a QRS duration > 150ms and have HFrEF. In these patients, CRT can effectively resynchronize the mechanical contraction of the left ventricle and offers a device option that can meaningfully improve patients' functional capacity, quality of life, and exercise tolerance while decreasing hospitalizations and mortality. However, for patients with a QRS duration <130ms, the EchoCRT study found that CRT is not beneficial and may actually cause harm.[3] Additional data suggests patients with right bundle branch block (RBBB) experience minimal to no benefit from CRT.[4]

Until FDA approved the Optimizer® System, no device alternative was available for HF patients with NYHA Class III symptoms in the U.S. deemed ineligible for CRT. However, for patients with NYHA Class III, LVEF between 25% and 45%, and not indicated CRT, CCM therapy is now available to address this treatment gap. The Optimizer System has been proven to provide statistically significant and clinically meaningful improvements in functional status, exercise tolerance, and

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[2] Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145: e•••–e•••. doi: 10.1161/CIR.0000000000001063

[3] Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Gorcsan J 3rd, Gras D, Krum H, Sogaard P, Holzmeister J; EchoCRT Study Group. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med. 2013 Oct 10;369(15):1395-405.

[4] Wojciech Zareba, Helmut Klein, Iwona Cygankiewicz, W Jackson Hall, Scott McNitt, Mary Brown, David Cannom, James P Daubert, Michael Eldar, Michael R Gold, Jeffrey J Goldberger, Ilan Goldenberg, Edgar Lichstein, Heinz Pitschner, Mayer Rashtian, Scott Solomon, Sami Viskin, Paul Wang, Arthur J Moss, MADIT-CRT Investigators. Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation. 2011 Mar 15;123(10):1061-72.

quality of life in these patients.[5] Specifically, in comparison to randomized control groups, patients treated with CCM have experienced:

- Improved exercise tolerance, as measured by peak VO_2
- Improved quality of life, as measured by the MLWHF Questionnaire
- Improved functional assessment, as measured by 6 Minute Walk
- Improved functional status, as measured by NYHA class

Benefit Category Determination

CCM therapy falls under the following benefit categories, as it may be implanted or followed-up by physicians in the hospital (inpatient and outpatient) and Ambulatory Surgery Center (ASC) settings:

- Physician services (SSA Section 1861(q), (r), and (s)(1))
- Inpatient hospital services (SSA Section 1861(b))
- Outpatient hospital services (SSA Section 1861(s)(2)(B); Medicare Benefit Policy Manual, ch. 6, § 20)

Regulatory Approval Information

On December 4, 2018, the FDA Circulatory System Devices Panel voted 12 – 1 that there is reasonable assurance that CCM therapy is safe. The Panel voted 11 – 2 that there is reasonable assurance that CCM therapy is effective. The Panel voted 12 – 0 (one member abstained) that CCM therapy's benefits outweigh the risks for patients who meet the indication of:

- NYHA III despite being on guideline-directed medical therapy,
- Not a candidate for Cardiac Resynchronization Therapy (CRT) and
- Left ventricular ejection fraction (LVEF) 25 – 45%
- Are in normal sinus rhythm (this requirement was subsequently removed)

FDA agreed with the Panel's recommendations. CCM devices obtained PMA approval from the FDA on March 21, 2019. PMA number is P180036, and the SSED can be accessed at: https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180036b.pdf.

Subsequent FDA approvals for CCM eliminated the requirement of a right atrial lead (October 2019) and removed the requirement for normal sinus rhythm (October 2021). The therapy delivery mechanism and the mechanism of action for CCM therapy remain the same across these three separate FDA approvals. Three corresponding FDA approval letters have been appended to this NCD request.

Additionally, the FDA has mandated a post-approval study (PAS), which is currently enrolling patients. More information about the PAS may be found at: https://clinicaltrials.gov/ct2/show/NCT03970343?term=impulse+dynamics&draw=2&rank=7.

[5] Abraham WT, Kuck KH, Goldsmith RL, Lindenfeld J, Reddy VY, Carson PE, Mann DL, Saville B, Parise H, Chan R, Wiegn P, Hastings JL, Kaplan AJ, Edelmann F, Luthje L, Kahwash R, Tomassoni GF, Gutterman DD, Stagg A, Burkhoff D, Hasenfuß G. A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation. JACC Heart Fail. 2018 Oct;6(10):874-883. Epub 2018 May 10.

The PAS is a prospective, non-randomized, multi-center, single-arm open-label study designed to provide long-term safety and effectiveness data. The PAS also seeks to measure performance improvement and biomarker evidence data from the FDA-indicated population. Safety endpoints include procedure-related complications occurring up to 30 days and device-related complications occurring up to one year. Effectiveness endpoints include observed mortality as compared to the Seattle Heart Failure Model (SHFM) at one and three years, change in New York Heart Association (NYHA) classification, quality of life (QOL), left ventricular ejection fraction (LVEF), N-terminal pro b-type natriuretic peptide (NT-proBNP) and QRS duration. Each of these will be measured at one, two, and three years from the implant procedure. At full enrollment, the PAS will include 620 subjects.

Scope of the NCD Request

Impulse Dynamics requests CAG limits the scope of this NCD request to current FDA-labelled indications for CCM therapy, which include:

- NYHA III despite being on guideline-directed medical therapy,
- Not a candidate for Cardiac Resynchronization Therapy (CRT), and
- Left-Ventricular Ejection Fraction (LVEF) between 25 – 45%, inclusive

And

- Devices that deliver CCM with or without other FDA approved therapies (e.g., ICD backup)

CCM System Components, Implant Procedure, Physician Qualifications, and Infrastructure Requirements

A CCM system consists of an implantable pulse generator, an external device charger, and a device programmer. Two transvenous, active fixation pacing leads are also required to complete a CCM system implantation. The implant procedure for a CCM system closely mirrors that of two other standard-of-care cardiac devices, pacemakers and implantable cardioverter-defibrillators (ICDs). Both of those device categories are addressed by separate NCDs[6].

The operative steps to implant a CCM system are nearly identical to those two procedures, with the primary exception that a CCM implant requires the positioning of two leads in the right-ventricular septum. Implanting physicians first obtain vascular access, place two leads in the right-ventricular septum under fluoroscopic guidance, and fashion a device pocket in a CCM implant just as they would for either a pacemaker or ICD. Adverse events related to CCM implantation are rare. While they occasionally require surgical remedy, they are typically observed and resolved at the same, or even slightly lower, rate than with pacemakers or ICDs.

In general, physicians that are qualified to implant cardiac pacemakers should be considered qualified to implant CCM devices. No additional special training or credentialing is required.

[6] NCD 20.8, Cardiac Pacemakers, NCD 204, Implantable Automatic Defibrillators

Physicians should be comfortable assessing anatomical cardiac lead placement, specifically identifying the right-ventricular mid-septum under fluoroscopic guidance.

Aside from a physician qualified to place a cardiac implantable electrical device, trained non-physician personnel should be present to support the implant. These personnel may include scrub technicians, circulating nurses, monitoring personnel, and/or anesthesiologists (the procedure is performed under conscious sedation in nearly all instances). Hospital infrastructure should be similar to that in rooms equipped to implant pacemakers or ICDs. Operating room airflow and sterilization standards should be maintained. Fluoroscopy equipment should have the ability to store images and rotate to an LAO position of 40 – 50 degrees. Staff to operate the CCM device programmer should be available. If the patient has a concomitant pacemaker or ICD, staff to operate the respective programmer for that device should be available, as well. These conditions are most typically, but not exclusively, found in cardiac electrophysiology labs or hybrid cardiac catheterization labs.

Purpose for CCM Therapy

While the procedure to implant a CCM device closely mirrors that of a pacemaker or ICD, the characteristics of the CCM electrical signals differ dramatically from those of pacemakers and ICDs. Both pacemakers and ICDs monitor and treat heart rhythm disturbances using electrical energy. Primarily, pacemakers treat bradyarrhythmias, typically some form of sinus node dysfunction or some form of heart block. ICDs treat tachyarrhythmias, typically those originating in the ventricles.

Unlike pacemakers or ICDs, CCM therapy does not target heart rhythm issues. Rather, CCM devices deliver periodic, programmed electrical stimulation designed to alleviate symptoms associated with heart failure, improve quality of life, restore functional capacity and improve exercise tolerance. CCM therapy is delivered during the absolute refractory period. As such, CCM therapy is non-excitatory, meaning it does not trigger a cardiac depolarization. The intent of CCM is not to cause the heart to contract, but rather to increase the strength of the heart's contraction.

CCM Clinical Evidence Review

Over 15 clinical trials conducted in the US, Europe, and Asia have been published evaluating multiple aspects of CCM therapy. The following sections outline clinical trial designs and results. CCM publications span nearly a 20-year period. These publications both precede and follow FDA market authorization.

Several articles in this set of publications reflect research work undertaken early in the development of the technology to examine the feasibility and efficacy for patient populations that fall wholly or partially outside of the patient population currently indicated for CCM therapy in the United States. For example, several early publications examine patients with different LVEF range, QRS duration, and functional status. Others show the durability of the therapy for a shortened interval due to study design, either as early proof of concept or due to the unavailability of a suitable rechargeable battery at the time these studies were conducted.

Impulse Dynamics will note the publications that address patient cohorts or duration of CCM delivery unrelated to the current FDA-labelled indication. While earlier publications provide directional evidence supporting the use of CCM therapy, it is imperative to consider the results of these studies in light of the populations specifically studied that may differ from the current US FDA label.

In sum, for purposes of the NCD request, Abraham et al 2011 is the first US publication specifically addressing the patient population that corresponds to initial FDA labeling and Abraham 2018 is the main trial publication. Subsequent publications addressed eliminating the requirement of the right atrial lead and removing the normal sinus rhythm requirement from the FDA labeled indications. As noted, these publications included patients with the QRS duration and LVEF range of the current FDA labeling.

Additionally, CMS has approved an IDE trial[7] that seeks to expand indications for CCM therapy to include patients with, among other clinical characteristics, LVEFs as high as 60%. This trial also measures the morbidity and mortality effects of CCM therapy in the included patient population. The trial has begun to enroll and will continue to do so for several years. As such, the patient group included in that IDE trial will not be analyzed in this NCD request.

In terms of applicability to the Medicare population, the average age of patients enrolled in previous CCM trials is 63 years old. This average age indicates a significant number of patients who are CCM candidates to be Medicare-eligible. Real-world usage of CCM confirms applicability in the Medicare population, in which the incidence and prevalence of heart failure are both well-defined in clinical literature.

CCM Clinical Evidence Review – Efficacy Assessments for US Regulatory Approval

FDA approval of the Optimizer System was primarily supported by the FIX-HF-5C confirmatory trial; a prospective, randomized, multicenter study of subjects with left ventricular ejection fraction (LVEF) 25%-45% and NYHA Class III or IV HF symptoms.[8] At the FDA's direction, a prespecified Bayesian statistical approach was used to leverage primary endpoint (peak VO_2) data available from the prior pivotal randomized study (FIX-HF-5). The following capsule summaries address critical trials that have helped to establish efficacy for CCM therapy.

FIX-CHF-4 EU Trial[9]

FIX-CHF-4 was the first RCT of CCM therapy. It was a double-blind, double-crossover study performed in 164 subjects with LVEF ≤ 35% and NYHA Class II (24%) or III (76%). Subjects were randomly assigned to Group 1 (n = 80, CCM ON 3 months, CCM OFF second 3 months) or Group 2 (n

[7] https://www.cms.gov/medicarecoverageideapproved-ide-studies/g200042-nct05064709
[8] Abraham WT, Kuck KH, Goldsmith RL, Lindenfeld J, Reddy VY, Carson PE, Mann DL, Saville B, Parise H, Chan R, Wiegn P, Hastings JL, Kaplan AJ, Edelmann F, Luthje L, Kahwash R, Tomassoni GF, Gutterman DD, Stagg A, Burkhoff D, Hasenfuß G. A Randomized Controlled Trial to Evaluate the Safety and Efficacy of Cardiac Contractility Modulation. JACC Heart Fail. 2018 Oct;6(10):874-883. Epub 2018 May 10.
[9] Borggrefe MM, Lawo T, Butter C, Schmidinger H, Lunati M, Pieske B, Misier AR, Curnis A, Böcker D, Remppis A, Kautzner J, Stühlinger M, Leclerq C, Táborsky M, Frigerio M, Parides M, Burkhoff D, Hindricks G. Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. Eur Heart J. 2008;29(8):1019-28.

= 84, reversed treatment sequence). The co-primary endpoints were changes in peak VO_2 and MLWHFQ; both of which are standard endpoints in HF studies.

Baseline LVEF, peak VO_2, and MLWHFQ were similar between groups. Peak VO_2 increased similarly in both groups during the first 3 months (0.40±3.0 vs. 0.37±3.3 mL/kg/min, placebo effect). During the next 3 months, peak VO_2 decreased in Group 1 when CCM was switched OFF (-0.86±3.06 mL/kg/min) and increased in Group 2 when CCM was switched ON (0.16±2.50 mL/kg/min). Differences between treatments were statistically significant (p=0.03). MLWHFQ trended better when CCM was ON (-12.06±15.33 vs. -9.70±16.17) during the first 3 months and worsened during the second 3 months when CCM was switched OFF (+4.70±16.57) and improved further in patients when CCM was switched ON (-0.70±15.13).

The authors concluded that the study results contributed to a growing body of literature showing that CCM is safe and exercise tolerance and quality of life were significantly better when patients were receiving CCM therapy applied over a 3-month period. The study was positive and contributed to the early development of the CCM technology; however, from subsequent studies, we know that the 3-month period is not adequate for the full beneficial effect of CCM to develop.

FIX-HF-5 US Pivotal Trial[10,11]

The FIX-HF-5 study was a prospective, randomized, parallel-group, controlled trial of 428 patients comparing optimal medical therapy (OMT group) versus OMT plus CCM (CCM group). The study was conducted at 50 centers in the United States and included subjects at least 18 years old with LVEF ≤ 35% as determined by the site Investigator[12], with NYHA class III or IV symptoms despite treatment with stable doses of guideline-directed OMT. Additionally, subjects had baseline peak VO_2 measurements ≥9 mL/kg/min, were in normal sinus rhythm, and were not indicated for a CRT device.

The FIX-HF-5 study met its primary safety endpoint but did not meet the unique primary efficacy endpoint mandated by the FDA. The FDA-mandated endpoint required an intention-to-treat (ITT) responder analysis of VO_2 at anerobic threshold (VAT). FDA required the use of this primary endpoint due to its objectivity. Although theoretically appealing for an unblinded trial, VAT together with a responder analysis had never been validated for use in heart failure trials and has since been abandoned for subsequent trials[7]. Another significant issue with this endpoint was that VAT by its very nature, is indeterminate in a large proportion of patients with HF, especially in those with reduced exercise tolerance. This led to 30% of patients missing or having indeterminate data where the primary endpoint could not be specified and due to the large missing data, the primary endpoint was not met.

However, a significant difference was identified between treatment groups in peak VO_2, which is a commonly used primary endpoint for studies evaluating exercise tolerance in HF and had been used in prior trials for the widely used CRT technology. For this endpoint, a between-group difference of

[10] Kadish A, Nademanee K, Volosin K, Krueger S, Neelagaru S, Raval N, Obel O, Weiner S, Wish M, Carson P, Ellenbogen K, Bourge R, Parides M, Chiacchierini RP, Goldsmith R, Goldstein S, Mika Y, Burkhoff D, Abraham WT. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. *Am Heart J.* 2011;161:329-337.

[11] Abraham WT, Nademanee K, Volosin K, Krueger S, Neelagaru S, Raval N, Obel O, Weiner S, Wish M, Carson P, Ellenbogen K, Bourge R, Parides M, Chiacchierini RP, Goldsmith R, Goldstein S, Mika Y, Burkhoff D, Kadish A; FIX-HF-5 Investigators and Coordinators. 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(9):710-7.

[12] Upon core lab review, 38 of the baseline tests were subsequently determined to have an LVEF 35-45%.

1.31 ml/kg/min favoring CCM compared to OMT was observed and the quality-of-life score improved by nearly 10-points with CCM compared to OMT. This magnitude of effect compares favorably to improvements seen with established heart failure drug therapies or CRT.

Subsequent analyses identified that patients with LVEF $\geq$ 25% had an even better response in VAT, QOL, 6MW, and NYHA compared with those patients with ejection fraction less than 25% and that the magnitude of the change was positively associated with the baseline LVEF. These findings informed subsequent steps agreed upon between Impulse Dynamics and the FDA, resulting in a new, randomized trial (the FIX-HF-5C study) designed to prospectively confirm the findings from these subgroup analyses.

FIX-HF-5C US Confirmatory Trial

FIX-HF-5C was a prospective, randomized, multicenter study of subjects with LVEF between 25% and 45% and NYHA Class III or IV HF symptoms. Subjects (n=160) were randomly assigned to one of two treatment groups (CCM Treatment or Control) with an allocation ratio of 1:1 (Abraham et. al. 2018). The quantitative and categorical baseline characteristics between the treatment groups for all randomized subjects were well balanced.

A prespecified Bayesian statistical approach was used to leverage the peak VO_2 data available from the FIX-HF-5 subgroup mentioned above. The Bayesian model incorporated the 160 subjects from FIX-HF-5C as well as a prior distribution of the treatment effect from the FIX-HF-5 subgroup. The Bayesian approach was used at the advice of the FDA with the purpose to decrease the number of patients required for the confirmatory study. The FIX-HF-5 subgroup could contribute up to 30% weight to the overall assessment, thereby ensuring that the prospective FIX-HF-5C data would not be dominated by the prior subgroup data. Although the study could borrow up to 30% from the Abraham et al 2011 cohort, only 11% borrowing was required, showing the confirmatory study exceeded design expectations.

The primary endpoint was met as the model-based estimated mean difference in peak VO_2 at 24 weeks between CCM Treatment and Control groups was 0.84 ml/kg/min. Figure 1 below shows the results of the Bayesian analysis along with the 95% confidence interval showing that the lower bound exceeds 0. The posterior probability that CCM treatment was superior to Control was 0.989, which exceeded the 0.975 threshold required by FDA to attain statistical significance in the primary endpoint.[13] This result was supported by numerous Bayesian and non-Bayesian sensitivity analyses.[14]

[13] *Note that traditional frequentist methods for statistical analyses use p-values to measure how likely an observed outcome is, due to chance alone, assuming there is no effect. Using a one-sided test, this is commonly reported as a p-value of 0.025 or less. In contrast, Bayesian analyses assess the posterior probability of benefit which represents the likelihood that the therapy meets the study objective. Therefore, values close to 1.0 are indicative of study success.*

[14] Summary of Safety and Effectiveness (https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180036B.pdf)

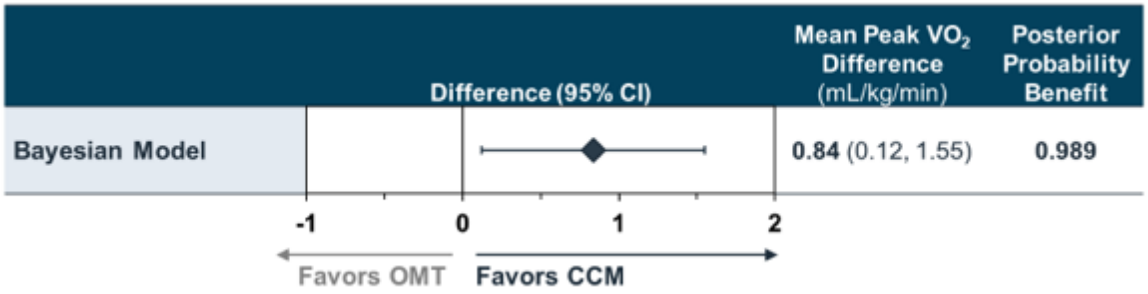

Figure 1: Primary Effectiveness Assessment of Peak VO_2

Given that the primary effectiveness endpoint was met, the FIX-HF-5C analysis proceeded to the testing of the secondary and additional endpoints using non-Bayesian methods as specified in the statistical analysis plan. All other secondary endpoints on quality of life and functional capacity were statistically significant in the standalone 160-patient FiX-HF-5C study (using frequentist, not Bayesian, analysis).

The key results were as follows:

- CCM subjects improved 11.7 points more in the MLWHFQ score compared to the OMT group ($p<0.001$)
- CCM subjects improved their NYHA heart failure status by ≥1 class 81% of the time compared to 42% in the OMT group ($p<0.001$)
- CCM subjects walked on average 33.7 meters further than the OMT group during the 6MW test ($p=0.0093$)

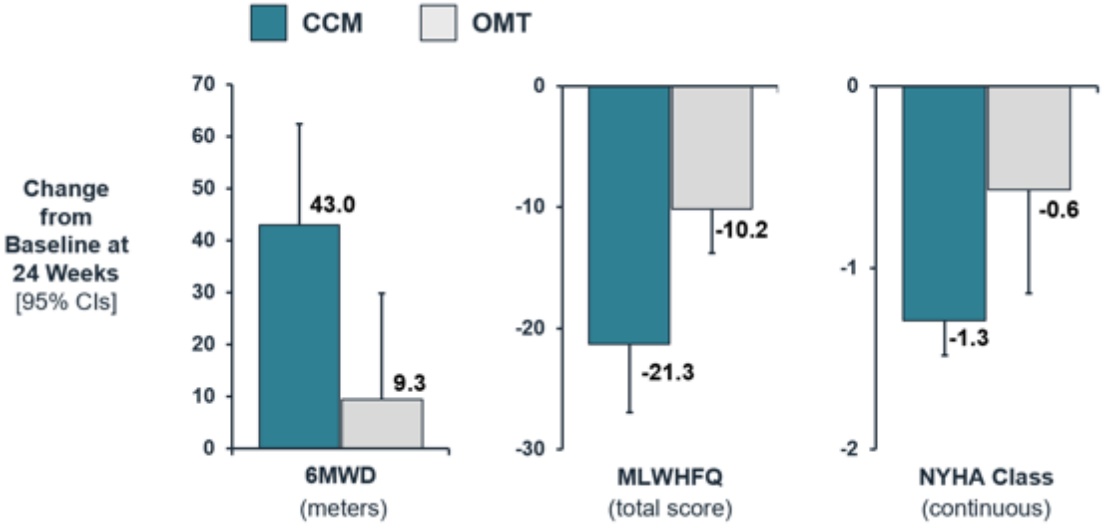

Figure 2: Secondary Endpoint Results from the FIX-HF-5C Study

Unrelated to CCM, a large, NIH funded study (HF-ACTION, with 1,620 patients contributing peak VO_2 measurements) showed that a 6% improvement in peak VO_2 among HF patients was associated with an 8% lower risk for CV mortality or HF hospitalization.[15] Very importantly, the combined patient group of ~400 patients showed, in a pre-specified analysis, a statistically significant

[15] Swank A, 10.1161/CIRCHEARTFAILURE.111.965186

reduction in CV mortality and HF hospitalization (97% event-free survival for CM therapy vs. 89% for control with a p-value of 0.036 (Abraham et al 2018); this 8% reduction is consistent with the prediction of the HF-Action trial for a 6% increase in peak VO_2.

FIX-HF-5C2 Study[16]

All of the aforementioned studies were performed with an Optimizer device that employed three leads placed in the heart: one in the right atrium and two in the right ventricular (RV) septum. While the RV septal leads are used for both sensing and CCM signal delivery, the atrial lead was used only for sensing the timing of atrial depolarization. This requirement imposed a technical limitation for the use of CCM in patients with atrial fibrillation or flutter. In contrast, the algorithms of the two-lead configuration Optimizer device operate with just the two RV leads for signal delivery and sensing, with no requirement for an atrial sensing lead, instead utilizing a proprietary wavefront conduction velocity algorithm. The CCM therapy delivered by the 2- and 3-lead Optimizer systems are identical.

In order to confirm that the signal delivery algorithm in the two-lead configuration, FDA authorized a parallel confirmatory extension study (FIX-HF-5C2) of 60 subjects in the same patient population as studied in the FIX-HF-5C study. Consistent with the goal of implementing the two-lead system in subjects with atrial fibrillation, 15% of FIX-HF-5C2 subjects had permanent atrial fibrillation compared to 0% in the prior study ($p<0.0005$).

The same Bayesian statistical approach used for the primary analysis in the FIX-HF-5C study was incorporated for the FIX-HF-5C2 extension study, as well as incorporating the data from the FIX-HF-5C study. The Bayesian model-based mean change in peak VO_2 from baseline to 24 weeks in the FIX-HF-5C2 study increased by 0.80 (95% BCI: 0.18,1.40) ml/kg/min, whereas the model-based mean change in peak VO_2 from baseline to 24 weeks in the FIX-HF-5C control group decreased by 0.93 (95% BCI: -1.46, -0.39, Figure 3A). The primary endpoint of peak VO_2 increased by 1.72 (95% BCI:1.02, 2.42) ml/kg/min great than the Control group by 24 weeks, which was highly statistically significant (Figure 3B)[17]. This was supported by a frequentist analysis (*i.e.*, no borrowing) which showed an even higher 2.21 ml/kg/min CCM treatment effect. 83.1% of 2-lead subjects compared to 42.7% of controls experienced ≥1 class NYHA improvement ($p<0.001$, Figure 4).

[16] Wiegn P, Chan R, Jost C, Saville B, Parise H, Prutchi D, Carson P, Stagg A, Goldsmith R, and Burkhoff D. Safety, Performance and Efficacy of Cardiac Contractility Modulation Delivered by the 2-Lead Optimizer Smart System: The FIX-HF-5C2 Study. Circulation-HF Epub April 2020

[17] Bayesian posterior probability of superiority equals 1.00, exceeding the threshold of 0.975 required to demonstrate superiority

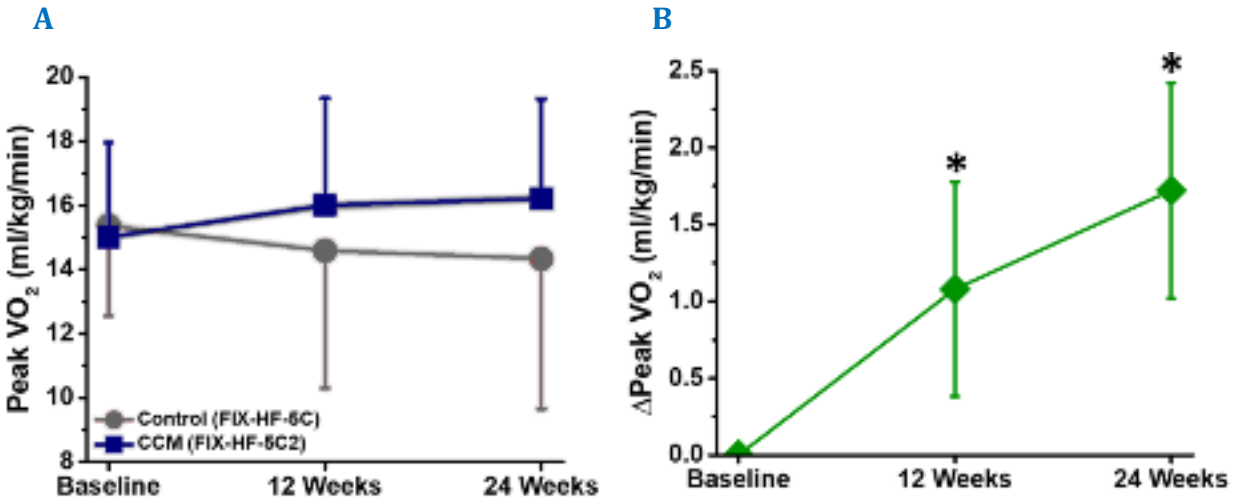

Figure 3: Comparison of Peak VO_2 over time. **(A)** Comparing the FIX-HF-5C Control group and the FIX-HF-5C2 CCM treatment group. Values represent mean ±SD frequentist values at each time point. **(B)** Between-group treatment effects with 95% confidence intervals over time as estimated by the primary Bayesian analysis. *Indicate statistically significant treatment effect.

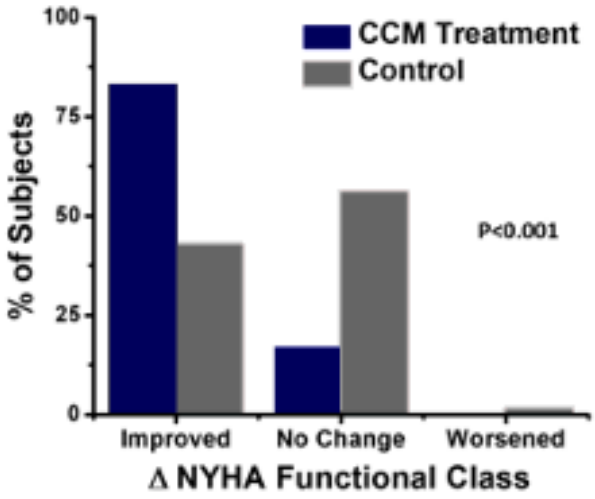

Figure 4: Distributions of changes of NYHA at 24 weeks in FIX-HF-5C Control and the FIX-HF-5C2 CCM Treatment groups

CCM-HF[18]

CCM-HF was a multi-site registry enrolling 143 patients, 106 of whom completed 24-month follow-up across 24 sites in Europe. Subjects in this trial were followed for NYHA classification,

[18] D. Muller, A. Remppis, P. Schauerte, S. Schmidt-Schweda, D. Burkhoff, B. Rousso, D. Gutterman, J. Senges, G. Hindricks, K.-H. Kuck. Clinical effects of long-term cardiac contractility modulation (CCM) in subjects with heart failure caused by left ventricular systolic dysfunction. Clin Res Cardiol DOI 10.1007/s00392-017-1135-9.

MLWHFQ score, 6-minute walk distance, LVEF, and peak VO_2 at baseline and 6-month intervals, as clinically indicated. Adverse events, as well as all-cause mortality, were tracked. Data were presented with results for all subjects, those with LVEF < 35% and those with LVEF ≥ 35%. Baseline parameters were similar among all three patient subgroups.

Of the 106 patients who completed 24-month follow-up, NYHA, MLWHFQ, and LVEF improved in each of the three subgroups at each measurement. LVEF increased 2.5% at 6 months, 2.9% at 12 months, 5% at 18 months and 4.9% at 24 months. This trial is a registry, in which follow-up tests were performed based on the clinical need to do so. While clinicians were reliably able to measure NYHA classification and MLWHFQ scores during the follow-up period, too few patients completed follow-up tests for 6-minute walk or peak VO_2 for comparative assessment to have been possible on those metrics.

Figure 5 below shows the effect of CCM on NYHA classification and MLWHFQ score. Results are shown for the entire trial population, as well as the patient subgroups noted previously.

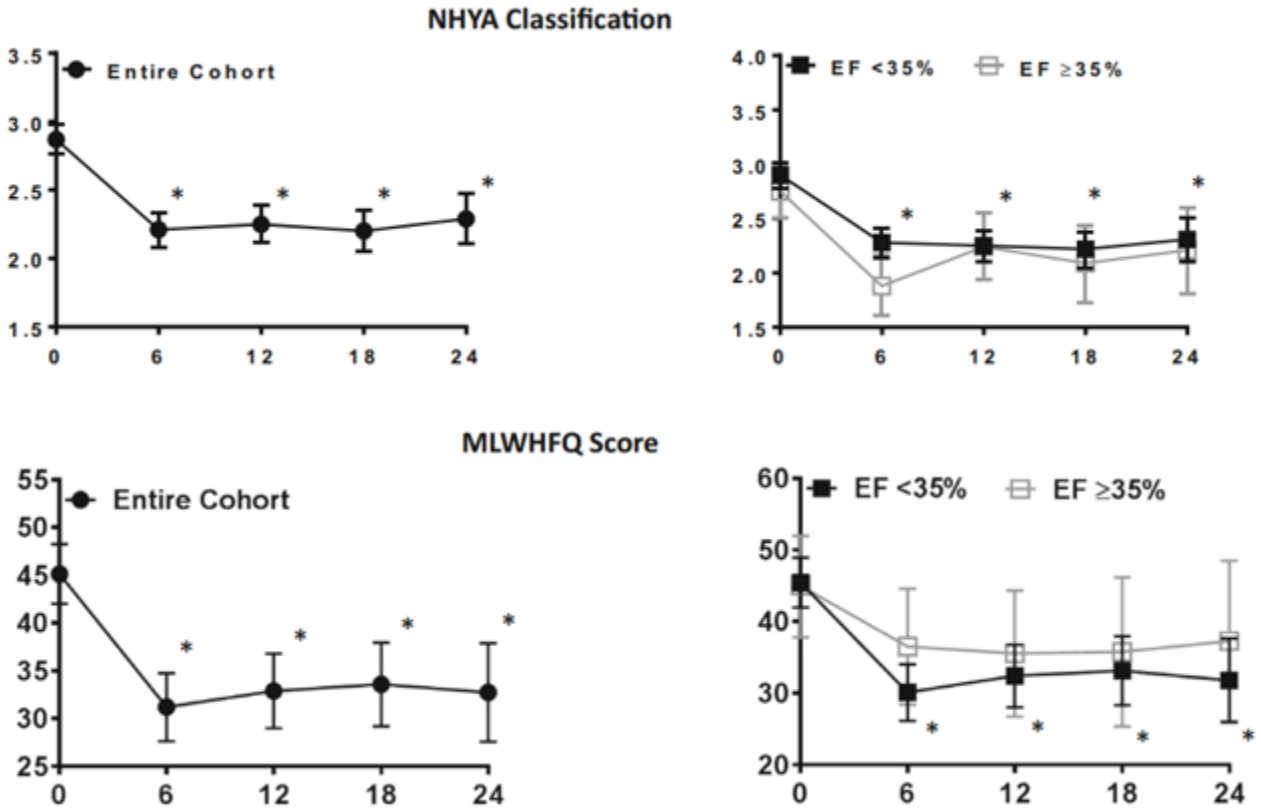

Figure 5: Effect of CCM on NYHA and MLWHFQ. NYHA classification and MLWHFQ both showed sustained improvements over the course of the study. No difference in improvement was seen between LVEF subgroups. * $p < 0.05$ vs. corresponding baseline. Changes from baseline to specific time points are tested with allowance for multiple comparisons using Sidaks method mixed-effects models.

CCM Registry

CCM-REG was a larger prospective registry conducted across 51 centers in Europe that has resulted in two publications. The entire cohort numbers 503 patients. The first publication examined 140 patients with indications matching FDA labeling[19]. These 140 patients were assessed for cardiovascular and HF hospitalizations, Minnesota Living with Heart Failure Questionnaire (MLHFQ), and NYHA class over 2 years. Mortality was tracked for 3 years and compared with predictions by the Seattle Heart Failure Model (SHFM).

In the 140-patient cohort, hospitalizations decreased by 75% (from 1.2/patient-year the year before, to 0.35/patient-year during the 2 years following CCM in the cohort with LVEF 25 – 45% (P<0.0001). MLWHFQ and NYHA class improved at all measured intervals, showing progressive and statistically-significant improvements over time in this group, as well. Finally, three-year survival in the group with LVEF 25-45% was 82.8%, as compared to predicted survival using the SHFM of 76.7% (P=0.16).

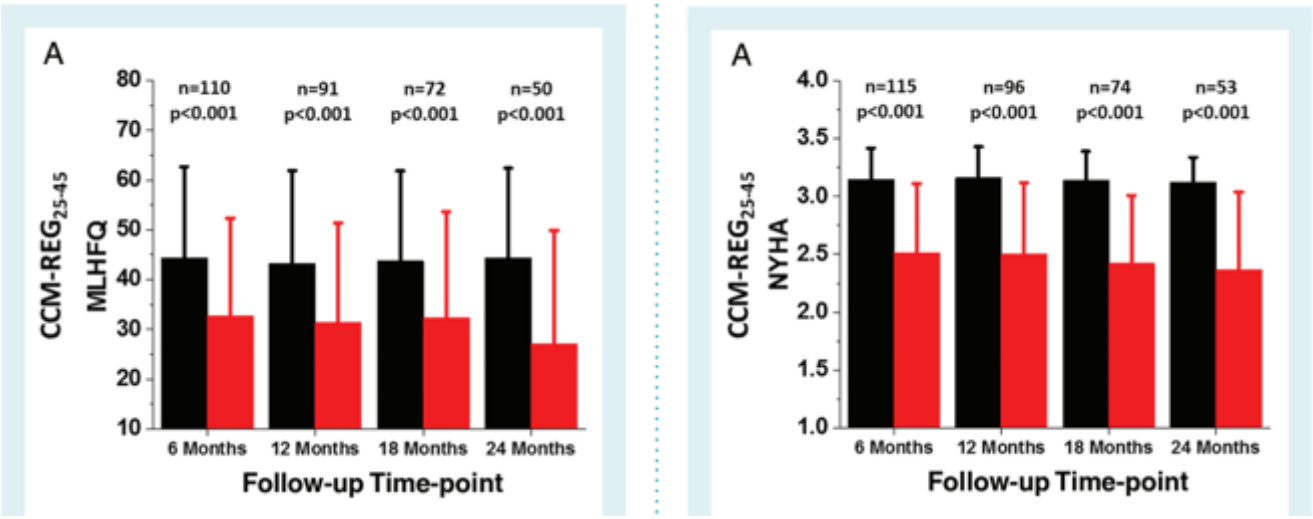

Figure 6: Changes in MLWHFQ and NYHA classification over time in the subgroup from CCM-REG that corresponds to FDA labeling

A separate analysis was performed on patients with LVEFs for the entire cohort of 503 patients, including those with LVEFs outside of the range included in the FDA labeling.[20] Results for both the cohort matching FDA indications and the overall cohort were very favorable on all outcomes, as shown in the following figures, 7 and 8.

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[19] Stefan D. Anker, Martin Borggrefe, Hans Neuser, Marc-Alexander Ohlow, Susanne Röger, Andreas Goette, Bjoern A. Remppis, Karl-Heinz Kuck, Kevin B. Najarian, David D. Gutterman, Benny Rousso, Daniel Burkhoff, and Gerd Hasenfuss. Cardiac contractility modulation improves long-term survival and hospitalizations in heart failure with reduced ejection fraction. European Journal of Heart Failure (2019) doi:10.1002/ejhf.1374

[20] Jürgen Kuschyk, Peter Falk, Thomas Demming, Oliver Marx, Deborah Morley, Ishu Rao, and Daniel Burkhoff. Long-term clinical experience with cardiac contractility modulation therapy delivered by the Optimizer Smart system. European Journal of Heart Failure (2021) doi:10.1002/ejhf.2202

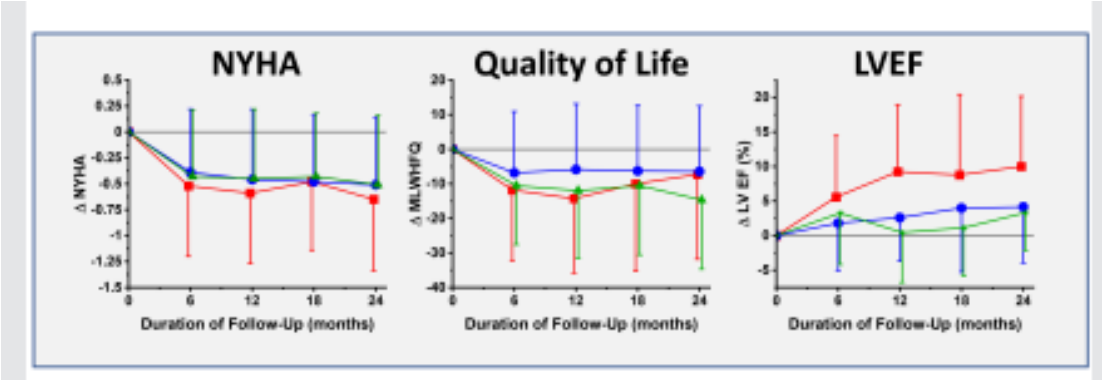

Figure 7: Changes in MLWHFQ, NYHA classification, and LVEF over time in the entire CCM-REG population

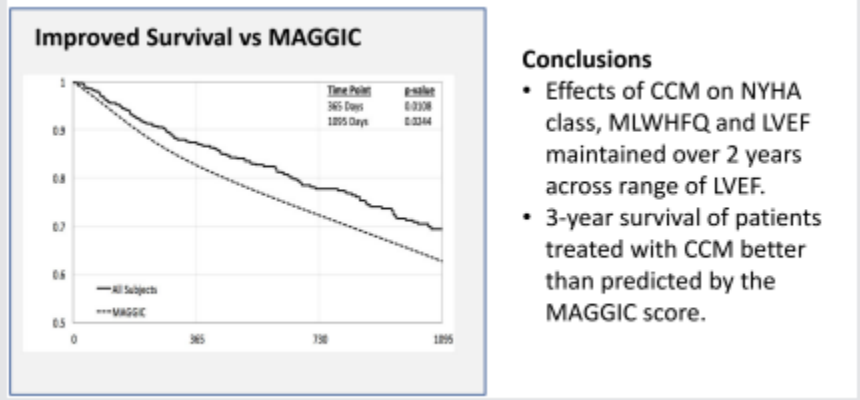

Figure 8: Comparison of survival rate compared to MAGGIC score for the entire CCM-REG population

These metrics directionally support durability of the effect of CCM therapy and its sustained efficacy in a real-world setting for patients with clinical characteristics matching FDA labeling. Duration of follow-up and outcomes metrics included in the Optimizer PAS are very similar to those measured in the CCM REG patient group.

CCM Clinical Evidence Review – Safety Assessments

The primary safety analyses in both the FIX-HF-5 study (all-cause mortality and all-cause hospitalization) and the FIX-HF-5C study (Optimizer device- or procedure-related complications) were met. All serious adverse events (SAEs) were collected and adjudicated during the studies and similar rates were seen in both the CCM and OMT groups. A decrease in Optimizer-related adverse events was reported in the FIX-HF-5C2 extension study (two-lead device) compared to the three-lead system (0% vs. 8%, p=0.03).

Safety outcomes were similar between treatment groups in the combined FIX-HF-5 subgroup and FIX-HF-5C trials, for all but one endpoint. There was a substantial difference in the composite clinical endpoint of CV death and HF hospitalizations from baseline through 24 weeks in favor of the CCM group (95.5% vs. 89.8%, p=0.042 by log-rank test, Figure 9). The magnitude of the effect is very similar to the one observed in the HF Action study for similar peak VO_2 differences. No claims

have been made about this endpoint; rather it is hypothesis-generating and supports the overall safety of CCM therapy.

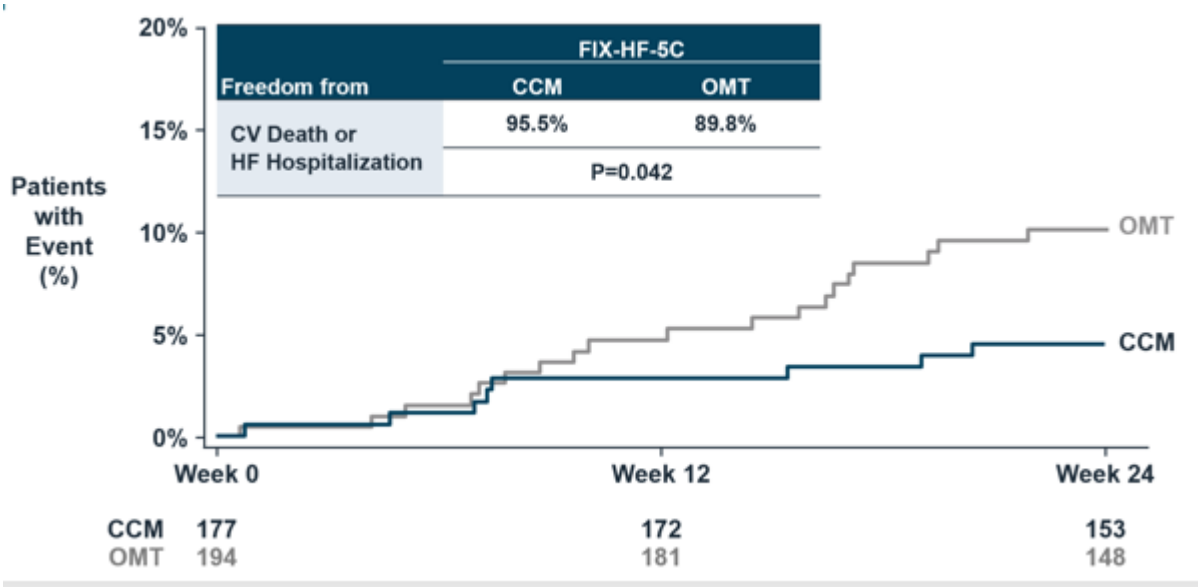

Figure 9. Freedom from Cardiovascular Death or Worsening Heart Failure Hospitalizations

Additionally, the total number of days alive out of hospital for heart failure ($DAOOH_{HF}$) was significantly greater in the CCM treatment group compared with Controls during the 24-week study period. Follow-up adjusted $DAOOH_{HF}$ in the CCM group was 167.7±2.2 days, versus 158.3±35.8 days in the Control group (p=0.011).

FIX-HF-5C Study

The rate of cardiac hospitalizations that occurred in the year prior to study enrollment was compared to the rate during the 24-weeks after study enrollment. The results expressed as events per patient-year are summarized in Figure 10 for both all cardiovascular ("CV") hospitalizations and HF hospitalizations alone. Although there were imbalances in the event rates between groups at baseline, both CV and HF event rates were significantly and substantially reduced during the study period compared to the event rates prior to the study in the CCM group but were unchanged in the Control group.

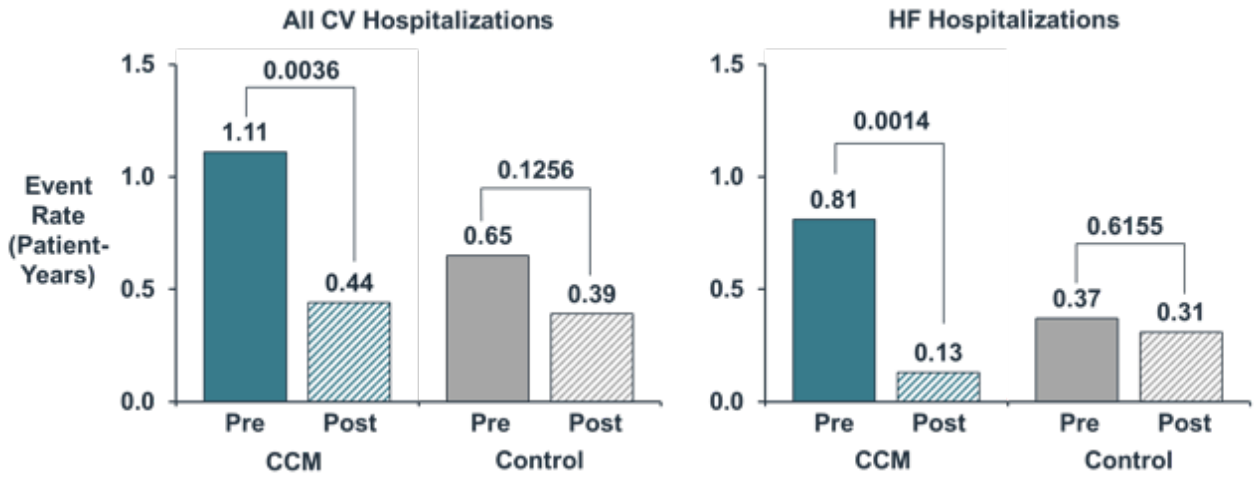

Figure 10: Pre and Post Study Cardiac Hospitalization Rates by Treatment Group[21]

FIX-HF-5C2 Study

The primary safety endpoint in the FIX-HF-5C2 study was the composite of the percentage of subjects in the 2-lead Optimizer group who experienced an Optimizer device- or procedure-related complication through the 24-week follow-up period as determined by an events adjudication committee (EAC). There was only one complication observed (hematoma, procedure-related); there were no Optimizer device-related complications reported. Thus, the complication rate was 1.7% (1/60; CI 0.0%,8.9%). This compares favorably with the 10.3% (CI 4.2%,20.1%) complication rate seen in three-lead Optimizer subjects in the FIX-HF-5C study (p=0.07). The majority of the Optimizer device-related events with the three-lead system study were due to lead dislodgements and lead fractures; none were reported with the two-lead device.

Registry Studies

The safety results in the pivotal studies are supported by findings from the two registries as detailed below.

CCM-HF Registry

In the CCM-HF 24-month registry, serious adverse events (n = 193) were observed in 91 subjects (Müller et. al. 2017). A total of 32 SAEs in 25 subjects were adjudicated by the investigator as either definitely or possibly related to the device. Eighteen deaths (7 CV-related, 8 non-CV-related, 3 unknown) occurred over 2 years. Overall survival at 2 years was 86.4% (95% confidence intervals: 79.3, 91.2%).

CCM-REG Registry

The primary endpoint in this registry was defined as death from any cause compared to the Seattle Heart Failure Model (SHFM) (Anker et. al. 2019). Survival was numerically higher than predicted by SHFM, but this difference was not statistically significant.

[21] Impulse Dynamics, Inc. Optimizer System Executive Summary Circulatory System Device Panel. Meeting Date: December 4, 2018.

A subgroup safety analysis was performed on the cohort of patients that correspond precisely to the US FDA label[22]. In this group, there were 168 cardiac hospitalizations in 98 of the 140 patients during the year prior to CCM activation yielding a yearly rate of 1.2 hospitalizations per patient-year. During the two years following CCM activation there was a 75% decrease to 0.35 cardiac hospitalizations per patient-year (P<0.001) for heart failure or cardiovascular causes. The reduction in events with CCM was also observed when considering heart failure hospitalizations and other cardiac-related hospitalizations separately.

The reduction in rates of heart failure hospitalizations observed in the CCM-REG cohort was significant and consistent with the reduction reported in the U.S. FIX-HF-5C study. Reducing heart failure-related hospitalizations in this population where this is a major source of morbidity is extremely important.

These results are detailed below in Table 1:

	Pre-CCM	Post-CCM		
	Event Rate	Event Rate	% reduction	P-value
CCM-REG	0.96	0.26	73%	<0.0001
FIX-HF-5C	0.81	0.13	84%	0.0014

Table 1: Consistent Reduction in HF Hospitalizations Pre and Post CCM Implant compared to the US pivotal trial.

The results of this study provide the largest, longest-term prospective analysis of survival and hospitalizations in patients with heart failure treated with CCM. Furthermore, the results provide important insights into the sustainability of the clinical effects of CCM when applied in addition to guideline-directed medical therapy in patients deemed ineligible for CRT, with LVEF 25%-45% and persistent NYHA III or IV symptoms. Over the 2-year study period, CCM showed similar positive effects in reducing HF hospitalizations to those observed in the shorter randomized studies.

CCM provides symptom relief to the segment of HF patients that have exhausted pharmaceutical treatments and are not eligible for CRT therapy. CCM provides statistically significant and clinically meaningful improvements in key HF outcomes across multiple randomized controlled trials as well as sustained benefit in long-term registry studies.

CCM Clinical Study Summary Table

Table 2: Summary of CCM therapy trials and applicability to the FDA approved US label.

STUDY TITLE	LOCATION	DEVICE	N	DESIGN	ENDPOINTS	RESULTS	INCLUSION CRITERIA MATCH FDA LABELLING
Pilot study (FIX-HF-1) 2001	EU	External, line-powered	24	Treatment only, acute Single Center	Cardiac Function	Cardiac function is enhanced when 2 electrodes delivering CCM signal to the RV septum applied.	No

[22] Subgroup of patients classified as NYHA III-IV, Ejection Fraction 25%-45%, and with no CRT implant

STUDY TITLE	LOCATION	DEVICE	N	DESIGN	ENDPOINTS	RESULTS	INCLUSION CRITERIA MATCH FDA LABELLING
						Pappone, Am J Cardiol (2002)	
Chronic feasibility study (FIX-HF-2) 2001	EU	Implantable Optimizer® I, Primary Battery (non-rechargeable)	6	Treatment only, 8 weeks feasibility study Single Center	Echo, CPX, 6 MW, Holter	Improvement with CCM vs sham therapy in all measures. No clinically significant adverse events.	No
Chronic safety and performance study (FIX-HF-3) 2002	EU	Optimizer® II, Primary Battery (non-rechargeable)	22	Treatment only, 8 weeks, safety and functionality Multicenter	NYHA Class, Quality of Life (QoL), LVEF	All endpoints showed improvement with CCM therapy. CCM therapy did not increase the incidence of arrhythmias. Adverse event profile was acceptable for the patient population.	No
Randomized double-blind study of CCM (FIX-CHF-4) 2002	EU	Optimizer® II (non-rechargeable) and Optimizer® III (rechargeable), Optimizer® III Charger	164	Prospective, randomized to CCM ON or OFF, double-blind study. Effectiveness evaluation, double-crossover, 6 months Multicenter	LVEF, pVO_2, MLWHFQ, Holter Monitoring for changes in nature of arrhythmias	The device improved quality of life, and exercise tolerance and appeared safe when used over a period of 3 months. *Borggrefe, Eur HJ (2008)*	No
Feasibility IDE Trial (FIX-HF-5 Phase I) 2004	US	Optimizer® II	49	Prospective, randomized to Optimizer with CCM ON or CCM OFF, double-blind, 6 months Multicenter	Primary: 6MWD, NYHA, pVO_2, and MLWHFQ. Secondary: LVEF, LVEDD, VO_2 at AT	Even though the CCM ON group was sicker at baseline, event-free survival, adverse event profiles, and measures of effectiveness trended to be better in the treatment group. *Neelagaru, Heart Rhythm (2006)*	No
Pivotal IDE Trial (FIX-HF-5 Phase II) 2005	US	Optimizer® III, Optimizer® III Charger	428	Randomized, unblinded, 12 months Multicenter	Efficacy: VO_2 at Anaerobic threshold (primary endpoint), pVO_2, and MLWHFQ score at 6 months. Primary safety: 12-month composite all-cause mortality and hospitalizations	The primary endpoint was not met as there was no improvement in VAT. However, there was improvement in pVO_2 and quality of life questionnaire. *Abraham Am Heart J (2008), Kadish, Am Heart J (2011)*	No
Impact of Optimization of lead position on CCM clinical effects (FIX-HF-9) 2005	Hong Kong	Optimizer® III, Optimizer® III Charger	40	Randomized to dP/dt testing or not, double-blind, 6 months Single Center	Changes in dP/dt_{max}, MLWHFQ, exercise tolerance, safety, and LV reverse remodeling.	No added benefit to using invasive pressure measurements for CCM lead placement. Reduce implant time and safety risks. CCM induced reverse remodeling and increased ejection fraction.	No
Report of Long Term (1 year) Safety Evaluation of the Optimizer® III System in Subjects with Heart Failure	EU	Optimizer® III, Optimizer® III Charger	110	Un-blinded, non-randomized, treatment only, safety evaluation, 1 year. Subjects	NYHA and MLWHFQ score.	Improvement in quality of life was noted. The severity and rate of adverse events were consistent with prior studies and no new safety concerns were identified. Improvement in long-term,	No

STUDY TITLE	LOCATION	DEVICE	N	DESIGN	ENDPOINTS	RESULTS	INCLUSION CRITERIA MATCH FDA LABELLING
Resulting from Systolic Dysfunction (FIX-HF-10) 2004				served as their own control group. Multicenter		all-cause mortality when compared to matched cohort up to 7 years. *Liu, Int J of Cardiology (2016)*	
CCM in CRT non-responders (FIX-CHF-12) 2008	EU	Optimizer® III, Optimizer® III Charger	17	Open-label trial of CRT non-responders, treatment only, feasibility study, 6 months Multicenter	MLWHFQ, pVO_2, exercise tolerance, and ejection fraction	CCM therapy improved the quality of life, heart failure symptoms, and exercise tolerance in CRT non-responders. The rate and type of adverse events were low. *Nägele, Europace (2008)*	No
Comparison of 5 versus 12 CCM hours per day (FIX-CHF-13) 2008	EU	Optimizer® III Optimizer® III Charger	19	Double-blind, active control study, 6 months Single center	MLWHFQ and exercise tolerance	Both 5 CCM hours and 12 CCM hours benefited subjects suffering from heart failure with no undue risk. Adverse events were reported to be not related to the device or procedure. *Kloppe, Cardiol J (2016)*	No
CCM-HF (FIX-HF-16) 2010	EU	Optimizer® III, Optimizer® III Charger	143	24 months follow up period Multicenter	NYHA, MLWHFQ, LVEF, pVO_2 and rate of SAEs	The NYHA classification, MLWHFQ and LVEF showed significant improvement. The SAE rate was comparable to the rates observed in prior studies of CCM in patients with heart failure. *Muller, Clin Res Cardiol. 2017*	No
A Randomized Comparison: CCM Delivered from 1 versus 2 Leads (FIX-CHF-18) 2009	EU	Optimizer® III and Optimizer® IVs, Mini-Charger	50	All subjects received a 2-lead system and randomized to either 1 or 2 leads active, Blinded study, effectiveness evaluation, 6 months Single center	MLWHFQ and pVO_2	There were no significant differences between groups for any of the study endpoints. This suggests that CCM delivered through 1 lead is not inferior to CCM delivered through 2 leads after 6 months of therapy. *Röger J Cardiol (2017)*	No
CCM Registry (CCM-REG)	EU	Optimizer® IVs, Optimizer® Smart	140	36 months follow up period Multicenter	Mortality vs. SHFM, NYHA, MLWHFQ, LVEF	Mortality numerically lower vs. SHFM in the overall cohort and statistically significant in the 35-45% EF cohort. Sustainable benefits for MLWHF, LVEF, NYHA. *Anker, Eu J of HF (2019)*	Yes
Confirmatory IDE clinical trial (FIX-HF-5C)	US, EU	Optimizer® IVs	160	Randomized (CCM+OMT vs OMT alone), 6-months. Multicenter	pVO_2, MLWHFQ, NYHA, safety, hospitalizations	CCM significantly improved pVO_2, MLWHFQ, and NYHA. *Abraham JACC:HF (2018)*	Yes
Confirmatory Extension Study (FIX-HF-5C2)	US, EU	Optimizer® Smart (2-lead)	60	Prospective, single-arm, 6 months follow up period Multicenter	pVO2, NYHA, CCM delivery, complications	The 2-lead device is equally safe and effective as the 3-lead device and enables CCM in patients with atrial fibrillation. *Wiegn Circulation-HF (2019)*	Yes

A comprehensive individual patient data meta-analysis of the effects of cardiac contractility modulation on functional capacity and heart failure-related quality of life	US, EU	Optimizer® Smart (2-lead and 3-lead)	801	Single-patient Meta-analysis (please note this trial summarized data for existing CCM patients and did not include additional patients)	QOL, exercise tolerance, functional capacity	CCM provides statistically significant and clinically meaningful benefits in measures of functional capacity and HF-related quality of life. *Giallauria et al ESC Heart Failure (2020)*	Yes
Long-term clinical experience with cardiac contractility modulation therapy delivered by the Optimizer system (CCM-REG)	EU	Optimizer® Smart (3-lead)	503	Prospective registry, Multicenter	NYHA, LVEF, hospitalizations for 2 years, survival for 3 years	CCM improved functional status, QOL, LVEF, and, compared to patients' prior history, reduced HF hospitalization rates. Survival at 1 and 3 years was significantly better than predicted by the MAGGIC score. *Kuschyk Eur J Heart Failure (2021)*	No (Anker et al publication is a sub-study from this cohort that includes patients matching FDA-labelled indication for CCM therapy)

Finally, table 3 below categorizes the main conclusions from the significant work undertaken so far on CCM, in completed studies and registries (1,145 patients) and in ongoing ones (620 patients):

Table 3: Main conclusions from CCM Therapy trials by type and duration of effect.

	Effect <1 year	**Longer-term effect**
Exercise & QoL Improvement	▪ FIX-HF-5 SG (229 patients) ▪ FIX-HF-5C (160 patients) ▪ FIX-HF-C2 (60 patients)	▪ CCM-REG (503 patients) ▪ CCM-HF (193 patients) ▪ US PAS (620 patients - ongoing)
HF Hospitalization Reduction	▪ FIX-HF-5 (229 patients) ▪ FIX-HF-5C (160 patients)	▪ CCM REG (503 patients)

Conclusion

CCM therapy has demonstrated the ability to be implanted safely and durability of effect on objective health outcomes and patient-centered outcomes in more than 15 trials and during commercial use, which includes more than 7,000 implants worldwide. Additionally, patients living with heart failure who are indicated for CCM therapy are not indicated for any other therapeutic interventions, be they pharmacological or device-based. This patient cohort, plagued by fatigue, dyspnea, angina, or palpitations with less-than-normal levels of physical activity, is well-represented in the Medicare-eligible population. These patients remain at high-risk for heart failure hospitalization, an event associated with a cascade of negative consequences. On top of the drastic impairment these patients face from this debilitating chronic condition, the impacts of heart failure stretch to multiple comorbidities commonly observed in this patient cohort – atrial fibrillation, hypertension, and diabetes, among others – that present significant clinical challenges.

CCM therapy meets the statutory requirements for a National Coverage Determination. Such a coverage policy aids the Centers for Medicare & Medicaid Services' ongoing mission to secure timely access to appropriate emerging therapies for the Medicare-eligible patient population. Fittingly, to help them live their fullest lives possible, these patients deserve access to CCM therapy and the guarantees to it afforded by a National Coverage Determination.

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