Protocol and Statistical Analysis Plan

Inter-Atrial Shunt Treatment for Heart Failure: The randomized RELIEVE-HF trial

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RELIEVE-HF TRIAL:
REducing Lung congestIon symptoms using the v-wavE shunt in adVancEd Heart Failure

Protocol Number: CL7018

National Clinical Trial (NCT) Identifier Number: TBD Executive

Committee Investigators:

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IDE Sponsor: V-Wave, Ltd.

EU Representative: genae Belgium nv Version Number: v.1.0

March 20, 2018

Sponsor	V-Wave, Ltd. POB 3076, 5 Tarshish Street, Caesarea Industrial Park (North), 3088900, Israel
Medical Monitoring Oversight	Details will be provided upon request
European Legal Representative	genae Belgium nv Justitiestraat 6B 2018 Antwerp, Belgium
Site Monitoring/Safety/Regulatory	Details will be provided upon request
Echocardiography Core Laboratory	Details will be provided upon request
Clinical Investigation Plan Version and Date	Version 1.0, March 20, 2018

This Clinical Investigation Plan has been written in accordance with Annex A of EN ISO 14155 (2011): Clinical investigations of medical devices for human subjects -Good Clinical Practice and ICH E6 Guidelines. In accordance with EN ISO 14155, where information is held within other trial documentation, e.g. in the Investigator Brochure, this is referenced where appropriate.

Compliance Statement

The trial will be conducted in accordance with the design and specific provisions of this clinical investigation plan, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP), EN ISO 14155, ICH EG, and the applicable regulatory requirements.

PREPARED BY:

NAME	TITLE	DATE	SIGNATURE
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APPROVED BY:

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Summary of Changes from Previous Version:

Version	Release Date	Description of Changes
0.0	February 13, 2018	Initial Release
1.0	March 20, 2018	1) Replaced Executive Committee signature page with Sponsor's signature page. 2) Added language to require removal of delivery sheath immediately post implantation. 3) Included description of medication to be provided to US and international sites. 4) Expanded number of clinical sites to 75. 5) Minor typographical corrections.

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

REducing Lung congestIon symptoms using the v-wavE shunt in adVancEd Heart Failure

CIP No: CL-7018

I have read this clinical investigation plan and appendices and agree to adhere to the requirements. I will provide copies of this clinical investigation plan and all pertinent information to the trial personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the device and the conduct of the trial.

I will conduct the trial in accordance with the clinical investigation plan, Good Clinical Practice guidelines, EN ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice), as well as local regulations. I also accept respective revisions to the clinical investigation plan approved by authorized personnel of the Sponsor and by regulatory authorities.

Principal Investigator Name	Signature and Date
Institution Name	Location
Co-Investigator Name	Signature and Date

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator(s) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational Device Exemption (IDE) sponsor and FDA/Competent Authority review, and documented approval from the Institutional Review Board (IRB) or Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the trial participants. All site personnel will complete Human Subjects Protection and ICH GCP Training prior to be involved in the conduct of this study.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB/EC for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB and FDA/Competent Authority review before the changes are implemented to the study. All changes to the consent form will be IRB/EC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:

RELIEVE-HF TRIAL: REducing **L**ung congest**I**on symptoms using the v-wav**E** shunt in ad**V**anc**E**d **H**eart **F**ailure

Study Description:

The Study Device, the V-Wave Interatrial Shunt System, includes a permanent implant—the Shunt, placed during a minimally invasive cardiac catheterization procedure using its dedicated Delivery Catheter. By transferring blood from the left to the right atrium, the Shunt is intended to reduce excessive left-sided cardiac filling pressures in patients with advanced heart failure (HF). The anticipated outcomes are a reduction in symptoms related to pulmonary congestion including breathlessness, improved exercise capacity, and reduced need for hospitalization or emergency treatment for acute decompensated heart failure (ADHF).

The study is a prospective, multi-center, 1:1 randomized, patient and observer blinded trial, with a Shunt Treatment arm and a non-implant Control arm. A total of approximately 400 patients will be randomized, with a possible increase up to a total of approximately 600 patients based on the results of a planned interim analysis. Each site may implant up to 3 Roll-in patients before randomizing to become familiar with the device and

procedures. The primary analysis will be performed when the last enrolled patient has been followed for a minimum of 12 months from randomization. The duration of follow-up evaluated by the primary effectiveness endpoint will range from a minimum of 12 to a maximum of 24 months. All implanted patients (Roll-Ins, Randomized to Treatment and Control patients that cross-over and receive the shunt) will be followed for a total of 5 years from the time of the Study Device implantation.

Objective:

The objective of this study is to provide reasonable assurance of safety and effectiveness of the V-Wave Interatrial Shunt System to improve clinical outcomes in a certain high-risk subset of symptomatic patients suffering from HF.

Endpoints:

Primary Safety Endpoint

The percentage of Treatment Group patients experiencing device-related Major Adverse Cardiovascular and Neurological Events (MACNE) during the first 30-days after randomization, compared to a pre-specified Performance Goal.

Primary Effectiveness Endpoint

Comparison between Treatment and Control groups of the hierarchical composite ranking of all-cause death, cardiac transplantation or left ventricular assist device (LVAD) implantation, recurrent HF hospitalizations (including Emergency Room HF Visits with duration >6 hours), and change in 6-minute walk test (6MWT) distance. The analysis is based on the method of Finkelstein and Schoenfeld.

Hierarchically Tested Secondary Effectiveness Endpoints

- 6MWT changes from Baseline to 12 months
- KCCQ changes from Baseline to 12 months
- All-cause mortality and heart failure hospitalizations
- Time to all-cause death, LVAD/Transplant or heart failure hospitalization
- Time to all-cause death or first heart failure hospitalization
- Cumulative heart failure hospitalizations
- Time to first heart failure hospitalization
- Modified Primary Effectiveness Endpoint including all-cause death, LVAD/Transplant and HF Hospitalizations but without 6MWT

Additional Effectiveness Outcome Measurements

- NYHA Class
- Patient Global Assessment
- Combined all-cause death and all-cause hospitalizations
- All-cause death
- Time to all-cause death (KM analysis)
- Time to cardiovascular death (KM analysis)
- Time to all-cause death, transplant or LVAD (KM analysis)
- Time to cardiovascular death, transplant or LVAD (KM analysis)
- Days alive free from heart failure hospitalization
- Outpatient intensification of heart failure therapy
- Emergency room HF visits
- HF Clinical Composite Assessment (improved, unchanged, or worsened) as described by Packer comprised of all-cause mortality, HF hospitalization, and changes in NYHA functional class ranking and Patient Global Assessment
- Comparison of transthoracic echocardiographic parameters as listed in Echocardiography Core Laboratory Manual
- Incidence of loss of shunt flow as measured on TTE and/or TEE
- Changes in 6MWT
- Changes in KCCQ
- Death: All-cause; Cardiovascular cause (with breakdown by cause, e.g. sudden death, myocardial infarction, pump failure, stroke); Non-Cardiovascular cause; Undetermined cause; and relationship to device, study intervention or other cardiovascular procedure
- Hospitalization: All-cause; HF hospitalization, Non-HF hospitalization (with breakdown for cause including if associated with secondary worsening of HF)
- Change in renal function
- Medication utilization including type, dose, frequency and changes
- Cost and cost-effectiveness data
- Technical success defined as successful delivery and deployment of the shunt and removal of the delivery catheter
- Technical success
- Device success
- Procedural success
- For Roll-in patients, transesophageal or intracardiac echocardiography at 6 and 12 months to assess shunt patency and

other parameters as listed in the Echocardiography Core Laboratory Manual

Additional Safety Data Collection

- Major Adverse Cardiovascular and Neurological Events (MACNE) and Bleeding Academic Research Consortium (BARC) types 3 and 5 bleeding at 30 days
- Percentage of Treatment Group patients with device-related MACNE at 12 months
- Incidence of all Serious Adverse Events by type at study duration
- Incidence of cerebrovascular events at study duration with sub-classification of CNS infarction, CNS hemorrhage, and TIA and their relationship to device or study procedures (per NeuroARC)
- Incidence of MI events at study duration after implantation
- Incidence of systemic embolization events at study duration after implantation
- Incidence of pulmonary embolism events at study duration after implantation
- Incidence of shunt implant embolization at study duration
- Device-related MACNE annually through 5 years

Study Population:

NYHA functional class III or ambulatory class IV HF irrespective of left ventricular ejection fraction, who have a history of hospitalization for worsening HF or BMI corrected elevated levels of BNP/NT-proBNP, in the setting of guideline-directed HF medical (including drug and device) therapy (GDMT).

Inclusion Criteria:

1. Ischemic or non-ischemic cardiomyopathy with either reduced or preserved LV ejection fraction and documented heart failure for at least 6 months.
2. NYHA Class III or ambulatory Class IV HF documented at Baseline Visit.
3. Receiving guideline directed medical therapy (GDMT) for heart failure which refers to those HF drugs carrying a Class I indication including the following for patients with reduced LVEF (≤40%):
   a) An inhibitor of the renin-angiotensin system (RAS inhibitor), including an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI) and a beta-blocker (BB), for at least 3 months prior to the Baseline Visit.

b) Other medications recommended for selected populations, e.g., mineralocorticoid receptor antagonist (MRA) or nitrates/hydralazine should be used in appropriate patients, according to the published guidelines.
c) Patient has been on stable medications optimized to the patient's tolerance of ACE or ARB or ARNI and MRA, if indicated, as determined by the investigator, for at least 1 month and BB for at least 3 months. Stable is defined as no more than a 100% increase or 50% decrease in dose within these periods.
d) Drug intolerance, contraindications, or lack of indications must be attested to by the investigator. Patients should be on appropriate doses of diuretics as required for volume control.

4. Receiving Class I recommended cardiac rhythm management device therapy. Specifically: if indicated by class I guidelines, cardiac resynchronization therapy (CRT), implanted cardioverter-defibrillator (ICD) or a pacemaker should be implanted at least 3 months prior to enrollment. These criteria may be waived if a patient is clinically contraindicated for these therapies or refuses them and must be attested to by the investigator.
5. Has a minimum of:
   a) One (1) prior Heart Failure Hospitalization with duration >24 hours or Emergency Room Heart Failure Visit with duration >6 hours, within the last 12 months.
   b) If a CRT device was previously implanted, the heart failure hospitalization must be ≥ 1 month after CRT implantation.
   c) Alternatively, if patients have not had a HF hospitalization or ER HF Visit within the prior 12 months, they must have a corrected elevated Brain Natriuretic Peptide (BNP) level of at least 300 pg/ml or an N-terminal pro-BNP (NT-proBNP) level of at least 1,500 pg/ml, according to local measurement, within 3 months of the Baseline Visit. (Note: "corrected" refers to a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m^2 in BMI above a reference BMI of 20 kg/m^2). If patient is on ARNI, NT-proBNP should be used exclusively.
6. Able to perform the 6-minute walk test with a distance ≥100 meters and ≤450 meters. The test will be performed twice separated by a minimum of 60 minutes between tests. The second test may be performed up to 7 days after the first test, if needed. The higher reading shall be used as the baseline value.

7. Provide written informed consent for study participation and be willing and able to comply with the required tests, treatment instructions and follow-up visits.

Exclusion Criteria:

Preliminary Exclusion Criteria at Baseline

1. Age <18 years old.
2. BMI >40 or <18 kg/m^2.
3. Females of childbearing age who are not on contraceptives or surgically sterile, pregnant or lactating mothers.
4. Resting systolic blood pressure <90 or >160 mmHg after repeated measurements.
5. Baseline echocardiographic evidence of unresolved, non-organized or mobile intracardiac thrombus.
6. Severe pulmonary hypertension defined as PA systolic pressure >70 mmHg by echo/Doppler (or PVR >4.0 Wood Units by PA catheter measurement that cannot be reduced to ≤4 Wood Units by vasodilator therapy).
7. RV dysfunction defined as TAPSE <12mm or RVFAC ≤30%.
8. Left Ventricular End-Diastolic Diameter (LVEDD) >8cm.
9. Atrial septal defect (congenital or iatrogenic), patent foramen ovale, or anomalous pulmonary venous return, with more than trace shunting on color Doppler or intravenous saline contrast (bubble study) or prior surgical or interventional correction of congenital heart disease involving the atrial septum (excluding closure by suture only but including placement of a PFO or ASD closure device).
10. Untreated moderate to severe aortic or mitral stenosis.
11. Untreated severe (3+ to 4+) regurgitant valve lesions, which are anticipated to require surgical or percutaneous intervention within 12 months.
12. Untreated coronary stenosis which requires surgical or percutaneous intervention.
13. Acute MI, acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), rhythm management system revision, lead extraction, or cardiac or other major surgery within 3 months.
14. Active valvular vegetations, atrial myxoma, hypertrophic cardiomyopathy with significant resting or provoked subaortic gradient, acute myocarditis, tamponade, or large pericardial effusion, constrictive pericarditis, infiltrative cardiomyopathy (including cardiac sarcoidosis, amyloidosis, and hemochromatosis), or congenital heart disease, as cause of HF.
15. Stroke, transient ischemic attack (TIA), systemic or pulmonary thromboembolism, or deep vein thrombosis (DVT) within the last 6 months. Any prior stroke with permanent neurologic deficit. Existing IVC filter.

16. Transseptal procedure for another indication (e.g. AF ablation, left atrial appendage occlusion, mitral valve repair/replacement) anticipated within 6 months.
17. Bradycardia with heart rate <45 bpm (unless treated with a permanent pacemaker) or uncontrolled tachyarrhythmias. This includes defibrillation shocks reported by the patient within the last 30 days.
18. Intractable HF with:
    a) Resting symptoms despite maximal medical therapy (ACC/AHA HF Stage D).
    b) Treatment with IV vasoactive medications (e.g., IV inotropes, IV vasodilators) within the last 30 days.
    c) Cardiac Index <1.5 L/min/m^2.
    d) Treated with a ventricular assist device (VAD).
    e) Listed for cardiac transplantation.
19. Prior cardiac transplantation.
20. Patients with HFrEF (LVEF ≤40%) who are intolerant to a RAS inhibitor including all of ACEI, ARB or ARNI, and intolerant to beta-blocker medical therapy.
21. Not eligible for emergency cardiothoracic or vascular surgery in the event of cardiac perforation or other serious complication during study intervention procedure.
22. Life expectancy <1 year due to non-cardiovascular illness.
23. Coagulopathy or is taking anticoagulation therapy which cannot be interrupted for the study intervention procedure, or has contraindications for heparin or for all of the study-mandated post implantation anticoagulation / antiplatelet regimens.
24. Estimated glomerular filtration rate (eGFR) <25 ml/min/1.73 m^2 by the MDRD method, or not responsive to diuretics, or is receiving dialysis.
25. Hepatic impairment with at least one liver function test (transaminases, total bilirubin, or alkaline phosphatase) ≥ 3 times upper limit of normal.
26. Severe chronic pulmonary disease requiring daytime home oxygen or chronic oral steroid therapy (Note: nighttime oxygen therapy and inhaled steroid therapy are acceptable).
27. Active infection requiring parenteral or oral antibiotics.
28. Known or suspected allergy to nickel.
29. Any condition that may interfere with compliance of all protocol procedures, such as history of active drug addiction, active alcohol abuse, or psychiatric hospital admission for psychosis within the prior year.
30. Currently participating in a clinical trial of any investigational drug or device that has not reached its primary endpoint, or any study that may interfere with the procedures or endpoints of this trial. Participation in an observational study or registry with market approved drugs or devices would not exclude a patient from participation in this trial.

31. Patient is otherwise not appropriate for the study as determined by the investigator or the Eligibility Committee, for which the reasons must be documented.
32. Patient belongs to a vulnerable population per investigator's judgment or patient has any kind of disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures.

Final Exclusion Criteria (FEC): Assessed during cardiac catheterization, at Study Intervention Visit, just prior to Randomization

1. Change in clinical status between baseline screening and Study Intervention visit that would no longer meet all of the inclusion/exclusion criteria.
2. Females with a positive pregnancy test on laboratory testing for FEC.
3. Unable to undergo TEE or ICE.
4. Unable to tolerate or cooperate with general anesthesia or conscious sedation.
5. Anatomical anomaly on TEE or ICE that precludes implantation of Shunt across fossa ovalis (FO) of the interatrial septum including:
   a) Minimal FO Thickness >3mm.
   b) Minimal FO Length <10mm.
   c) ASD or PFO with more than a trace amount of shunting.
   d) Intracardiac thrombus felt to be acute and not present on prior exams.
   e) Atrial Septal Aneurysm defined as ≥ 10 mm of phasic septal excursion into either atrium or a sum total excursion of ≥ 15 mm during the cardiorespiratory cycle, with a base of ≥ 15 mm.
6. Inadequate vascular access for implantation of Shunt. Femoral venous or inferior vena cava (IVC) access for transseptal catheterization are not patent as demonstrated by failure to pass Swan-Ganz or ICE catheter from the right or left femoral vein to the right atrium.
7. Hemodynamic, heart rhythm, or respiratory instability at time of cardiac catheterization including:
   a) Mean PCWP <7 mmHg, not correctable by IV volume infusion (maximum 1,000 ml normal saline or equivalent).
   b) Mean PCWP >35 mmHg, not correctable by medical therapy (e.g. IV Furosemide, IV or sublingual nitroglycerin).
   c) Right Atrial Pressure (RAP) ≥ Left Atrial Pressure (LAP or PCWP) when LAP (PCWP) ≥7 mmHg.
   d) Cardiac Index (CI) <1.5 liters/min/m^2 after correction of volume depletion with IV fluids (maximum 1,000 ml normal saline or equivalent).
   e) Severe pulmonary hypertension defined as PASP >70 mmHg.
   f) PVR >4.0 Wood Units that cannot be reduced to ≤4 Wood Units by vasodilator therapy.
   g) Resting systolic Blood Pressure <90 or >160 mmHg, not corrected with IV fluid administration or vasodilators, respectively.

h) Need for IV vasopressor or inotropic medication.
i) Malignant arrhythmias such as ventricular fibrillation, ventricular tachycardia, atrial fibrillation/flutter with rapid ventricular response associated with hypotension and requiring cardioversion.
j) Acute respiratory distress or hypoxemia.

8. Patient is otherwise not appropriate for study as determined by the Investigator.

Study Duration:

The study duration from first patent enrolled until completion of the last follow-up is expected to take approximately 9 years.

Participant Duration:

Primary analysis will occur when the last patient enrolled completes 12 months of follow-up. Patients will be followed for the primary data analysis a minimum of 12 months and a maximum of 24 months from the time of randomization at the Study Intervention Procedure. Patients with less than 24 months of follow-up will complete randomized blinded follow- up when the last randomized patient has completed the 12-month visit.
Patients reaching 24 months prior to the last enrolled patient reaching 12 months will be unblinded. Patients randomized to the Control group who still meet inclusion/exclusion criteria will have the opportunity to cross- over and receive a shunt implant when they are unblinded. All implanted patients (Roll-Ins, Randomized to Treatment and Control patients that cross-over and receive the shunt) will be followed for a total of 5 years from the time of the Study Device implantation. Control group patients who do not cross-over to receive a shunt implant, will cease to be followed once unblinding has occurred.

1.2 SCHEMA

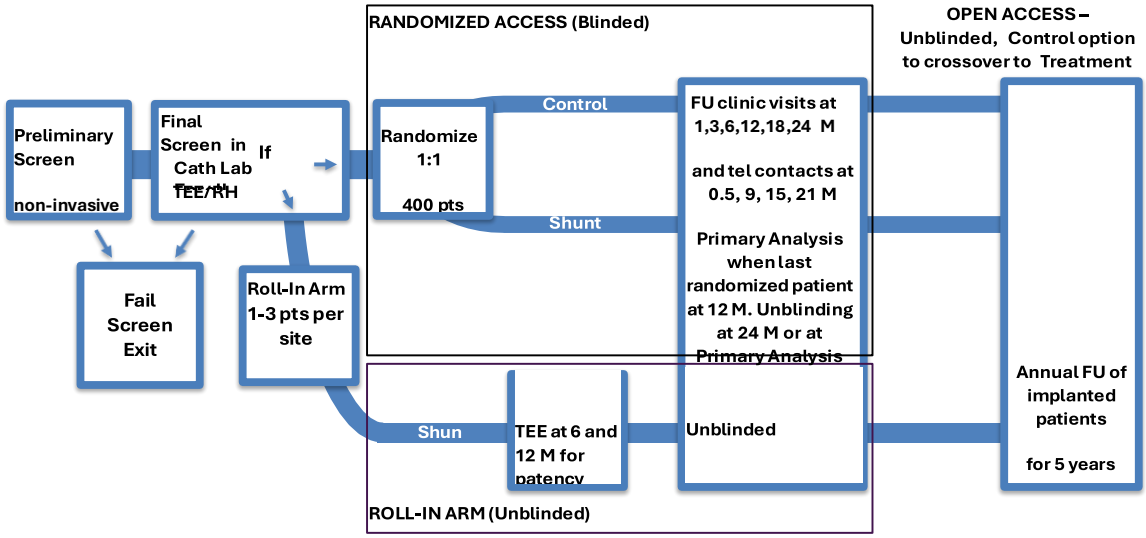


Figure 1. Patients are enrolled after successful two-phase screening. Up to 3 patients per site are enrolled into the open-label Roll-in arm where they are implanted with shunts, cases are proctored, and patients are followed as per the Randomized cohort with the addition of TEEs done at 6 and 12 months to evaluate shunt patency.
One to one patient randomization begins into the Shunt and Control arms. All patients receive GDMT. Control patients may receive the shunt device at the end of their 24-month follow-up or when the last patient reaches 12 months, if they consent and meet all study eligibility criteria again. Cross-over patients who receive the Shunt will be followed for 12 months according to the follow-up schedule described for the first 12 months post randomization. All patients implanted with shunts are followed annually for a total of 5 years from time of enrollment.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Visit Assessment	BASELINE SCREENING	FINAL SCREEN-STUDY INTERVENTION Implant or control	POST ENROLLMENT PRIOR TO DISCHARGE	2 WEEKS (telephone)	1, 24 MONTHS (in-clinic)	3, 18 MONTHS (in-clinic)	6, 12 MONTHS (in-clinic)	9, 15, 21 MONTHS (telephone)	ANNUAL years 3-5 (in-clinic)
Informed Consent	✓								
Demographics & Medical History	✓								
Vital signs, including weight and pulse oximetry	✓[1]	✓[1]	✓[1]		✓	✓	✓		
Physical Exam	✓		✓		✓	✓	✓		✓
Medications	✓	✓	✓	✓	✓	✓	✓	✓	✓
Na, K, Hgb, HCT, PLTS, WBC, Cr, BUN, AST, ALT, T Bili, Alk phos	✓		✓[2]		✓[2]		✓[2]		
Pregnancy, PT, PTT, INR, Hgb, HCT, Cr		✓							
BNP or NT-proBNP	✓								
12 Lead ECG	✓								
Chest X-Ray			✓						
Transthoracic echo (TTE)	✓				✓[3]		✓[3]		✓[3]
Transesophageal or intra cardiac echo (TEE/ICE)		ICE/TEE					TEE[4]		
Right Heart Catheterization (RHC), oximetry		✓							
NYHA Functional Class, Patient Self-Assessment	✓				✓	✓	✓		✓
KCCQ, EQ-5D	✓				✓	✓	✓		✓
Cost Effectiveness		✓	✓		✓	✓	✓		
6-min walk test (x2) / Borg scale	✓				✓	✓	✓		✓[5]
Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓
I/E Criteria Review	✓	✓							
Complete Case Report Forms (CRFs)	✓	✓	✓	✓	✓	✓	✓	✓	✓
Assure Blinding Procedures (Randomized pts)		✓	✓	✓	✓	✓	✓	✓	

1 Temperature and Pulse oximetry only required at Baseline, Study Intervention and Prior to Discharge
2 Limit to CR, Hgb and HCT
3 Once unblinded, shunted patients will have TEE if no shunt flow seen on prior TTE
4 Only Roll-in patients have routine follow-up TEE
5 A single 6-min walk test is required during extended follow-up on years 3-5

2 INTRODUCTION

2.1 RATIONALE

Heart failure (HF) is a syndrome characterized by high mortality, frequent hospitalization, reduced quality of life and a complex therapeutic regimen.[1] Over 6 million Americans and more than 26 million people worldwide have HF.[2,3,4] In the coming decades, HF is expected to become an increasingly larger healthcare problem as the population ages. HF is most often an incurable disorder. There are more than one million hospitalizations each year in the US where the primary diagnosis is Acute Decompensated Heart Failure (ADHF) with 80-90% of patients having a history of pre-existing chronic HF. About 90% of ADHF hospitalizations present with clinical manifestations of pulmonary congestion.[5,6,7] When ADHF develops, respiratory symptoms, such as tachypnea and dyspnea predominate. Ultimately, if this process is not reversed, pulmonary edema ensues and there is increased likelihood of death. A persistent rise in left atrial pressure (LAP) during the preceding days is the predominant pathophysiological factor driving the development of pulmonary congestion.[8] Having an implanted passive device that automatically decompresses the left atrium as heart failure acutely worsens, would constitute a real and important advance that could improve symptoms, quality of life, exercise tolerance, and potentially prolong life expectancy for a significant proportion of these patients who often have few or no alternative therapeutic options.

2.2 BACKGROUND

HF is defined as the pathophysiologic state where the heart requires an elevated diastolic filling pressure to be able to pump blood adequately to meet the requirements of the metabolizing tissues or where the ability to eject blood is reduced.[9] The underlying etiologies of HF are most commonly ischemic heart disease, hypertension, diabetes mellitus, idiopathic cardiomyopathy, valvular heart disease, myocarditis, followed by a host of other less common causes. While traditionally associated with reduced left ventricular (LV) systolic function, it is now widely recognized that HF can occur with normal or mildly reduced LV ejection fraction. Left heart failure is often divided into two clinical syndromes: systolic heart failure or heart failure with reduced ejection fraction (HFrEF), and diastolic heart failure or heart failure with preserved ejection fraction (HFpEF), where the left ventricle fails to relax and fill normally (diastolic dysfunction).[10] Patients with HFpEF tend to be older, are more commonly female, hypertensive and diabetic. The prevalence of patients with HFpEF presenting to hospital with ADHF is growing and is now approximately equally split with or in some cases surpassing HFrEF.[11,12,13]

2.2.1 STANDARD OF CARE TREATMENT

The mainstay therapy for HFrEF patients are medications that regulate the neurohormonal milieu or heart rate. These drug classes include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors—*Entresto* (ARNI), beta blockers, mineralocorticoid receptor inhibitors (MRA), and a hyperpolarization-activated cyclic nucleotide channel

blocker—*Ivabradine* (HCN). These agents have been demonstrated in randomized trials to reduce mortality and morbidity (heart failure hospitalization) and in some cases to result in beneficial ventricular remodeling. All have received Class I guideline indications in patients with HFrEF, except for Ivabradine which is class IIa in both the US and European guideline recommendations.[14,15,16] Several devices also have evidence-based, Class I guideline indications for treating specific subsets of HFrEF patients including Cardiac Resynchronization Therapy (CRT), Implantable Cardioverter Defibrillator (ICD), and Left Ventricular Assist Devices (LVAD) for patients with end-stage disease. Nonetheless, symptoms, especially dyspnea on exertion and poor exercise tolerance require management of excess fluid volume with dietary sodium restriction in all, and chronic use of loop diuretics, in most patients. Fluid removal with intravenous loop diuretics is the most common approach to relieving the worsening symptoms of ADHF.

In the HFpEF patient population, no randomized controlled trials of drugs or devices have achieved their primary effectiveness endpoints, with the exception of implantable hemodynamic monitoring guidance of diuretic or venodilator dosing, which has been shown to significantly reduce HF-hospitalization.[17] Even so, due to a combination of lack of confirmatory trials in the literature, and need for constant monitoring and adjustment without reimbursement, this approach has seen slow adoption. Otherwise, guideline-based medical therapy is limited to treating underlying predisposing conditions such as controlling hypertension, ventricular rate control in atrial fibrillation, treating ischemic heart disease and using diuretics for relief of symptoms of volume overload.

Despite current recommendations for evaluation and management, HF morbidity and mortality remain high. HF is the most common reason for acutely hospitalizing patients 65 years or older.[18,19] In the US, HF is the primary cause of more than 308,000 deaths, over a million hospitalizations, at least 6 million office visits, and almost 700,000 emergency room visits, annually. Most patients (77%) presenting to hospital are severely symptomatic with New York Heart Association (NYHA) Functional Class III or IV symptoms.[20] The factors associated with decompensation and hospitalization are most commonly noncompliance with diet and medications followed by failure to seek care or patients being on inappropriate therapy. These factors result in either total body fluid retention, or fluid redistribution to the pulmonary venous vasculature, or both. Patients admitted with ADHF have an in-hospital mortality of 4%, a 90-day mortality of 10%, and per the OPTIMIZE-HF Registry and other studies, a one-year risk- adjusted mortality rate of 30%.[21,22,23] The mortality and hospitalization rates for patients with HFrEF and HFpEF are generally alike.[24]

A particular area of focus in recent years has been hospital readmission. This is not only important for controlling runaway costs but also because there is a supra-additive mortality risk associated with subsequent HF hospitalizations. Readmission rates following a hospitalization for ADHF average 25% at 30-days and are nearly 50% at 6 months, regardless of systolic function.[25,26,27,28] In a large Canadian database review, the median survival (50% mortality) after the first, second, third, and fourth HF-hospitalizations were 2.4, 1.4, 1.0, and 0.6 years, respectively. Most patients were alive 2 years after the first HF hospitalization, but approximately half were dead by 1 year after 3 hospitalizations.[29]

Irrespective of the state of LV systolic function, most patients tend to have a progressive course characterized by worsening HF stage, symptom class, periodic acute symptomatic worsening with the need for hospitalization, and ultimately death. There remain large unmet medical and societal needs to reduce the incidence of acutely worsening HF in ambulatory patients. The benefits of doing so would likely include reducing HF morbidity and improving patient reported outcomes such as quality-of-life for countless patients while controlling costs and utilization of resources.

2.2.2 INTERATRIAL SHUNTING AND ITS ANTICIPATED CLINICAL BENEFITS

The V-Wave Shunt is a permanent medical implant that creates a small fixed communication between the left and right atria at the location of the fossa ovalis. The aim of shunting is to reduce symptoms and the frequency of ADHF in patients with advanced chronic HF irrespective of LVEF. Interatrial shunting is expected to be a complementary treatment to other established therapies in HF patients that remain moderately to severely symptomatic.

The background observations supporting interatrial shunting as HF treatment are:

- Sustained elevation of left atrial pressure (LAP) is the direct cause of pulmonary congestion with symptoms responsible for 90% of HF hospital admissions. Studies with implantable hemodynamic monitoring have demonstrated that persistent elevation of LAP is the immediate cause of pulmonary congestive symptoms in ADHF irrespective of the underlying etiology of the patient's heart disease, left ventricular systolic function, or precipitant of clinical worsening.[30] This is because LAP is transmitted to the pulmonary veins where it is the predominate force causing transudation of blood plasma fluid into the pulmonary interstitial and alveolar spaces resulting in worsening dyspnea, orthopnea, and finally in acute pulmonary edema requiring hospitalization. When left-sided filling pressures were used to guide diuretic or venodilator therapy in blinded randomized trials, heart failure hospitalization was significantly reduced, and symptoms and quality of life was improved over a mean follow-up of 18 months.[31,32] Similar benefits were seen in HFrEF and HFpEF patients irrespective of lower boundary cutoff EF levels for HFpEF (40% vs 50%). Moreover, control patients that cross-over to device-guided therapy show the same benefits.[33,34]

- There is a resting interatrial pressure gradient, where LAP exceeds right atrial pressure (RAP) in ~98% of HF patients, nearly all of the time throughout the day.[35]

- HF patients with coexisting congenital atrial septal defects (ASD) or patent foremen ovale (PFO) have better than expected outcomes, and closure of ASD and PFO may unmask subclinical left ventricular dysfunction, provoking pulmonary edema.[36,37,38]

- Atrial septostomy (creation of an interatrial communication) has been used to reduce intracardiac pressures and improve forward flow in patients with congenital heart disease and for HF.[39]

In brief, the theory of operation for the Study Device is that the greater the left-sided cardiac filling pressure is elevated relative to right-sided pressure, the more blood will be "shunted" from left-to-right, attenuating further elevation in left-sided pressure. Specifically, due to the presence of an interatrial pressure gradient, a small portion of the blood normally flowing from the left atrium to the left ventricle is diverted to the right atrium instead. This in turn modestly reduces LV end-diastolic filling volume. When the LAP is elevated, the LV is operating on the steeper portion of its diastolic compliance curve.[40] Even a modest reduction in LV end-diastolic volume leads to a substantial fall in LV end-diastolic pressure. There will be a commensurate fall in upstream filling pressures including LAP, pulmonary venous pressure, and pulmonary artery pressure. The anticipated clinical result will be relief or even prevention of pulmonary congestive symptoms. At smaller interatrial gradients with less shunting, the effect on LV volume and filling pressures becomes progressively smaller until it is negligible. As interatrial shunting primarily affects LV filling and not afterload, the beneficial effects on lowering end- diastolic pressure would be anticipated regardless of LV systolic function. That is, interatrial shunting would be expected to be effective in patients with either HFrEF or HFpEF.

The location, the amount of flow, and the hemodynamic consequences, are similar to what occurs with a hemodynamically insignificant congenital ostium secundum atrial septal defect (ASD). Namely, the shunt is located in the fossa ovalis portion of the atrial septum, the orifice is 5 mm in diameter and the pulmonary to systemic blood flow ratio (Qp:Qs) is less than 1.5. In the absence of severe right ventricular dysfunction, the right heart can tolerate small left-to-right atrial shunts because the additional blood volume causes only a minimal rise in RV end-diastolic pressure. This is due to the right heart having a relatively high compliance (ability to enlarge without a significant pressure increase).

A previous version of the V-Wave Shunt was validated in a pre-clinical ovine model of ischemic dilated cardiomyopathy.[41] The Shunt differed from the current Study Device primarily in that it had a tissue valve disposed on its right atrial side to prevent right-to-left shunting but was otherwise dimensionally similar. Heart failure induction with selective left circumflex coronary artery microembolization resulted in the rapid development of left ventricular dysfunction with LVEF falling to 36% with elevation in LAP and echocardiographic evidence of pathological myocardial remodeling within 2 weeks.

Animals were then either treated with Shunts (n=14) or were Sham Controls (n=7). Control group animals continued to progressively deteriorate so that after another 12 weeks, LVEF was markedly reduced to 18%, the septum further thinned, and LAP monotonically elevated to 25 mmHg. Control animals developed severe secondary pulmonary hypertension (PAP_{mean} 37 mmHg), and worsening right atrial pressure averaging 15 mmHg, consistent with right ventricular volume overload. Control animals had a 43% mortality, which was associated with rapidly worsening hemodynamics, particularly pulmonary hypertension and tachycardia.

Despite comparable left ventricular function at baseline in the Shunt group, there were marked contrasts in the evolution of objective heart failure indices between the control and shunted animals consistent with a device treatment effect. Shunting abolished the course of rapidly deteriorating left and right ventricular function and induced stability that was associated with global improvement of left ventricular systolic function. Specifically, after shunt placement, instead of LAP rising to levels resulting

in pulmonary congestion, LAP fell significantly, approaching normal and remained steady for the study duration. Instead of developing severe pulmonary hypertension and RV volume overload, pulmonary artery and right atrial pressure remained minimally elevated. Instead of progressive worsening of LVEF, shunting improved systolic function with the ejection fraction increasing to 46% and was still trending upward at study conclusion. The interventricular septum ceased to thin, consistent with interruption of the ventricular remodeling seen in controls. At study termination, high fidelity measurements of left ventricular pressure showed that Control group sheep had diminished indices of contractility and reduced diastolic function, while in shunted animals these indices were nearly normal. Although these measurements are load-dependent, the magnitude and breadth of these data suggest that shunting prevented deterioration of left ventricular inotropic and lusitropic states. Finally, shunting was also associated with a statistically significant survival benefit. These marked salutary effects were accomplished with a 5-mm diameter orifice shunt device with an observed shunt ratio Qp:Qs that averaged ~1.2. This equated to a shunt flow of approximately 700 ml/min.

In summary, these data demonstrate mechanistically how a small interatrial shunt device can selectively unload the heart, resulting in sustained reductions of left-atrial pressure and improved left ventricular function while right-sided cardiac pressures and function remained preserved. Shunt-induced reductions in wall stress due to decreased loading and attenuated remodeling may be important mechanisms behind these beneficial effects. These establish a preclinical proof-of-principle that left-to-right interatrial shunting is a promising therapeutic approach for patients with heart failure with reduced systolic function.

2.2.3 CLINICAL FEASIBILITY STUDY

Methods

V-Wave conducted two concurrent open-label human feasibility studies with a prior version of the V-Wave Interatrial Shunt System, which included a tissue valve located on the right atrial side designed to prevent early reversed (right-to-left) shunting, but was otherwise constructed of the same materials and was dimensionally identical to this study device.

A Canadian Special Access Program (CSAP) at a single site and a First-in-Man (FIM) trial (NCT01965015) at 5 sites in Israel and Spain were performed. The two trials had similar major inclusion/exclusion criteria, follow-up study testing and schedules, trial conduct, monitoring and oversight procedures. The patient's baseline demographics and clinical characteristics were substantially similar, allowing the data to be pooled into a single experience of 38 patients.

The study objectives were to evaluate the early safety and performance of the V-Wave Shunt implanted in a population consisting of patients with chronic NYHA functional class III or ambulatory class IV heart failure (HF) patients with either reduced or preserved systolic function. The major eligibility criteria satisfied by all patients in both CSAP and FIM studies included that patients: be receiving guideline-directed medical therapy (GDMT) inclusive of recommended device therapies; have at least 1 hospitalization in the prior 12 months for worsening HF requiring intravenous therapy or a corrected

elevated BNP level of at least 300 pg/ml or an NT-proBNP level of at least 1,500 pg/ml. Patients with severe pulmonary hypertension ($PAP_{systolic}$ >70 mmHg) or severe RV dysfunction (TAPSE <12 mm, or RVFAC ≤30) were excluded. To maximize the likelihood that the CSAP and FIM patient data would be poolable, the baseline records of each screened patient being considered for V-Wave Shunt implantation were reviewed by a site-independent Eligibility Committee, consisting of at least two physicians skilled in the conduct of heart failure device trials, who were familiar with the inclusion/exclusion criteria. An independent Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB) comprising of three cardiologists with expertise in clinical trials and specializing in interventional procedures, echocardiography, and heart failure and with access to statistical resources met approximately quarterly to adjudicated adverse events and monitor trial safety. A peer-reviewed manuscript describing the first 10 patients with reduced ejection fraction and 3-month follow-up was published in The Lancet in March 2016.[42]

The primary safety outcome measure was the incidence of device, procedure or study-related (device-related) Major Adverse Cardiovascular and Neurological Events (MACNE) at 3-months. The definition of MACNE was pre-specified as the hierarchical composite rate of all death, stroke, MI, device embolization, tamponade, and device related re-intervention or surgery during the 3-months after implantation. Secondary safety measures further assessed the frequency of all-cause MACNE, and all- cause Serious Adverse Events (SAEs) and Serious Adverse Device Effects (SADEs). The primary device performance measure was procedural success defined as the ability to deliver and deploy the V-Wave Shunt across the fossa ovalis with a patent shunt at 3-months.

Secondary effectiveness outcome measures included the assessment of NYHA Functional Class, Quality of Life Changes (KCCQ or MLWHF Questionnaire, depending on site), 6-minute walk test (6MWT) and the rate of hospitalization for worsening HF. The eligibility criteria, follow-up schedule, and definitions for heart failure hospitalization were pre-specified to comport with those used in the CardioMEMS Champion Study, a prospective randomized control study of pulmonary artery pressure guided therapy for historical control purposes.**Error! Bookmark not defined.,Error! Bookmark not defined.** A heart failure hospitalization required a non-elective in-hospital stay for worsening heart failure that was present at the time of admission and considered as the primary cause of hospitalization and that included at least one calendar date change and required intravenous or mechanical heart failure therapies or the significant augmentation of oral heart failure medications. Serial transthoracic and transesophageal echocardiograms were systematically acquired at specified intervals and analyzed by an independent Echo Core Laboratory. Case report forms were captured in a computerized data management system and data entry was reviewed and locked.

Results

Patient Characteristics: Between October 10, 2013, and March 17, 2016 the CSAP Study enrolled 22 patients and the FIM Study enrolled 16 for a combined total of 38 patients. For purpose of providing clinical perspective, **Table 1** compares baseline patient characteristics for the combined CSAP/FIM study cohorts with the Champion Study.

The SAP/FIM cohorts were elderly, predominantly male, and moderately obese. Except for one class IV patient receiving regularly scheduled milrinone infusions, the 37 (97%) remaining patients were NYHA class III. A substantial majority (79%) had heart failure of ischemic etiology. The use of ACE inhibitors, ARB, beta blockers, and MRA medications and ICD and CRT devices were consistent with pre-specified management guidelines. Comorbidities including diabetes, renal dysfunction, and atrial fibrillation were frequent. At baseline, 26/38 (68%) patients were taking anticoagulants (20 vitamin K antagonists, 6 novel oral anticoagulants). The most common indication for anticoagulation was atrial fibrillation in 19 (53%) patients. Of the 38 patients enrolled, 30 had HFrEF defined as LVEF<40 and 8 had HFpEF with LVEF≥40. Natriuretic peptide levels and resting left and right atrial and pulmonary pressures were elevated, while exercise capacity and cardiac index were reduced. The combined CSAP/FIM cohort was well-matched with the Champion Study population with the exception that the shunted patients were significantly ($p<0.05$) older, more frequently male, more frequently had HF of ischemic origin, more had diabetes and renal function was on average reduced —all factors generally associated with a worse prognosis in HF patients.

Table 1. Baseline Patient Demographics

BASELINE CHARACTERISTICS	CSAP + FIM (N=38)	CHAMPION TREATMENT AND CONTROLS (N=550)
Age, y	66±9	62±13†
Male Sex, %	92	73†
Body Mass Index, kg/m^2	30±6	31±7
NYHA class, %	III (97), IV (3)	III (100)
Ischemic Cardiomyopathy, %	79	60†
DM / HTN / AFIB, %	68 / 84 / 53	49† / 78 / 46
ACEi-ARB / BB / MRA / DIUR, %	71 / 89 / 68 / 87	76 / 87 / 42 / 92
ICD / CRT, %	74 / 39	68 / 35
Frequency LVEF ≥ 0.40, %	21.1	21.6
LVEF HFrEF/HFpEF	26±7/50±9	23±7 / 51±9
NT-proBNP, pg/ml	2640±2301	-
eGFR, mL.min^{-1}.1.73 m^{-2}	54±20	61±23†
6-Minute Walk Distance, m	289±112	-
PCWP, mmHg	21±5	18±8
RAP, mmHg	8±4	-
PAP systolic, mmHg	44±12	45±15
Cardiac Index, L.min^{-1}.m^{-2}	2.2±0.4	2.3±0.7

NYHA, New York Heart Association; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; AFIB, atrial fibrillation; ACEi-ARB, angiotensin converting enzyme inhibitor-angiotensin receptor blocker; BB, beta blocker; MRA, mineralocorticoid receptor antagonist; Diur, diuretic; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate; PCWP, pulmonary capillary wedge pressure; RAP, right trial pressure; PAP, pulmonary artery pressure. Continuous measures shown as mean ± SD. † = $p<0.05$.

Implantation: All 38 subjects were implanted successfully with shunts placed across the fossa ovalis portion of the interatrial septum. There were no device maldeployments or the need for intraprocedural device repositioning or reintervention resulting in a Procedural Success Rate of 100%. The average procedure time was 72 $\pm$ 24 minutes, which included pre-shunt TEE, RHC, transseptal catheterization, shunt implantation, and post implant data collection. The median length of stay was 2 days.

Device Performance: The shunt patency was confirmed in all subjects by TEE at 3 months. By 12 months, 86% (31/36) of shunts had echo/Doppler evidence of left-to-right flow through their Shunts. In the 5 subjects with no observed flow there was no echocardiographic or clinical evidence of thrombus formation in or near the devices, migration of device from the site of deployment, or erosion of the device into adjacent cardiac structures.

Safety: During the first 12-months, there were 30 SAEs (**Table 2**), not including hospitalization for worsening HF, which were assessed separately. Of these 30, three were adjudicated as Major Adverse Cardiovascular or Neurologic Events (MACNE). Two of the MACNE were deaths due to cardiovascular cause and were not device-related. The one device-related MACNE, cardiac tamponade was a complication of a transseptal catheterization procedure but not of the shunt *per se*. The patient was treated with pericardiocentesis, did not require surgical intervention, and was later discharged with no lasting sequelae. There were no strokes, TIAs, systemic or pulmonary thromboembolic events. There were no device infections. No shunt removals, surgical or percutaneous, were required. The Primary Safety Outcome Measure, Freedom from Device-Related MACNE at 3 months, was 97.4% (95% CI, 92.3% to 100%) and remained unchanged at one year. Six additional SAEs, were adjudicated as SADEs, which included one case of GI bleed due to gastric erosion while on study mandated anticoagulation, four cases of vascular access complications that resolved with local treatment and did not require surgery and one case of acute urinary retention requiring catheterization. All SADEs except 1 presented within 9 days of shunt implantation. The brachial plexopathy resulted from the right heart catheterization procedure performed at the 12-month follow-up visit.

Table 2. Serious Adverse Events at 12-Months

SAE Type	Number SAE	Number SADE
Acute Coronary Syndromes	5	0
Abdominal Pain	1	0
Arrhythmia (VT)	1	0
GI Bleed	2	1
Heart failure, other	1	0
Depression	1	0
Pulmonary (pneumonia, COPD, etc.)	9	0
Vascular access	4	4
Urinary	2	1
Tamponade	1*	1*
Trauma	1	0
Stroke or thromboembolism	0	0
Death	2*	0
total	30	7
MACNE*	**3**	**1**

* Counted as MACNE

Effectiveness Measures: All patients were NYHA Class III/IV at enrollment. At 3-months. 78% improved to Class to I or II; at 6 months 80% remained improved; and at 12 months 60% continued to be class I or II ($p<0.001$ for all comparisons). For Quality of Life, the proportions improved by ≥ 5 points 74%, 59% and 72% at 3, 6, and 12 months, respectively ($p<0.001$ for all comparisons). 6MWT increased by +41 m at 3 months ($p<0.001$), +41 m at 6 months ($p=0.01$), decreasing to +28 m vs. baseline at 12 months ($p=0.03$).

Table 3 summarizes blood, echo, and hemodynamic parameters in the 36 surviving patients at baseline, 3 and 12-months. Shunt flow was 17% of systemic output at 3 months but fell to 10% at one year. In general, NT-proBNP, renal function, LV and RV function and hemodynamics remained stable throughout the first year after shunting.

Table 3. Selected Blood, Echocardiographic and Hemodynamic Parameters in Surviving Patients

	Baseline	3M	12M
n	36	36	35
Blood			
Log_e NT-proBNP (pg/mL)	7.5 ± 0.9	7.4 ± 1.0	7.5 ± 0.9
eGFR (mL/min·1.73m$^{2)}$	54 ± 20	55 ± 23	53 ± 22
Echocardiographic variables			
LVEF (%), HFrEF / HFpEF	26 ± 7 / 50 ± 9	27 ± 9 / 52 ± 10	28 ± 8 / 54 ± 9
LAV (mL), HFrEF / HFpEF	90 ± 28 / 79 ± 25	84 ± 2 / 75 ± 22	84 ± 28 / 80 ± 24
TAPSE (mm)	16 ± 4	17 ± 4	16 ± 4
Qp:Qs	0.99 ± 0.11	1.17 ± 0.12	1.10 ± 0.13
Hemodynamic variables			
PCWP mean (mmHg)	21 ± 5	20 ± 7	19 ± 7
RAP mean (mmHg)	8 ± 4	9 ± 5	9 ± 4
PAP mean (mmHg)	30 ± 8	29 ± 8	30 ± 10
CI ((L/min·m^2), thermodilution	2.2 ± 0.4	2.4 ± 0.4	2.3 ± 0.5
PVR (WU)	2.8 ± 1.6	2.6 ± 1.1	2.8 ± 1.9

Log_e NT-proBNP (pg/mL), natural logarithm of amino terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LAV, left atrial volume; TAPSE, tricuspid annular plane systolic excursion; Qp:Qs, pulmonary to systemic flow ratio; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; PAP, pulmonary artery pressure; CI, Cardiac Index; PVR, pulmonary vascular resistance.

Medication Changes: Baseline drug therapy with standard heart failure medications is summarized in **Table 4**. In addition, 5 patients were receiving PDE-5 inhibitors (4 sildenafil, 1 tadalafil), 1 patient was taking an HCN channel blocker (Ivabradine), and 1 patient was receiving twice weekly infusions of milrinone.

For the 36 patients surviving 6 months, there were 86 changes in the daily dosage of heart failure medications for a frequency of 0.40 changes per patient per month. Medication dosages were increased in 55% of instances and decreased 45% of the time. The most frequently adjusted medication drug classes were loop/thiazide diuretics (38%), followed by ACE/ARBs (21%), beta blockers (17%), mineralocorticoid receptor antagonists (8%), and nitrates/hydralazine (8%). During follow-up, 1 patient was switched from an ACE inhibitor to a newly available combination ARNI (*Entresto*) and 1 additional patient began receiving twice weekly milrinone infusions.

Table 4 also shows that CSAP/FIM patients were on nearly identical doses of ACE/ARB and beta-blockers as Champion Study Control group patients at baseline and 6 months. CSAP/FIM patients were, however, taking almost 20-35% higher doses of loop diuretic and 65% lower doses of MRA agents throughout the study. This is likely due to the CSAP/FIM patients having significantly poorer renal function. **Figure 2** compares the frequency of medication changes by drug class during 6-month follow-up in shunt patients with the CHAMPION Control group. The frequency of adjusting dosages of neurohormonally active medications including ACE/ARBs, beta blockers and mineralocorticoid receptor antagonists were nearly

identical between the two studies. The observed frequency of adjusting diuretics was less than half in patients treated with interatrial shunts.

Table 4. Baseline and 6-Month Medication Dosing: Comparison Between CSAP/FIM and Champion Trials

CSAP and FIM				CHAMPION Control		
	Baseline	(n)	6 Months	Baseline	(n)	6 Months
ACE or ARB (enalapril equivalents, mg)	21±18	(24)	18±14	20±18	(168)	20±20
Beta Blocker (carvedilol equivalents, mg)	30±19	(28)	28±18	30±23	(206)	31±23
MRA (spironolactone equivalents, mg)	15±6	(23)	16±7	32±22	(90)	35±30
Loop Diuretic (furosemide equivalents, mg)	123±135	(27)	131±134	92±63	(201)	110±89

Data: mean±SD; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist. Doses: for ACE or ARB are enalapril equivalents; for Beta Blockers in carvedilol equivalents; for MRA in spironolactone equivalents; for Loop Diuretics in furosemide equivalents. CHAMPION data from Costanzo MR, Stevenson LW, Adamson PB, et al. JACC Heart Failure 2016;4:333-44.

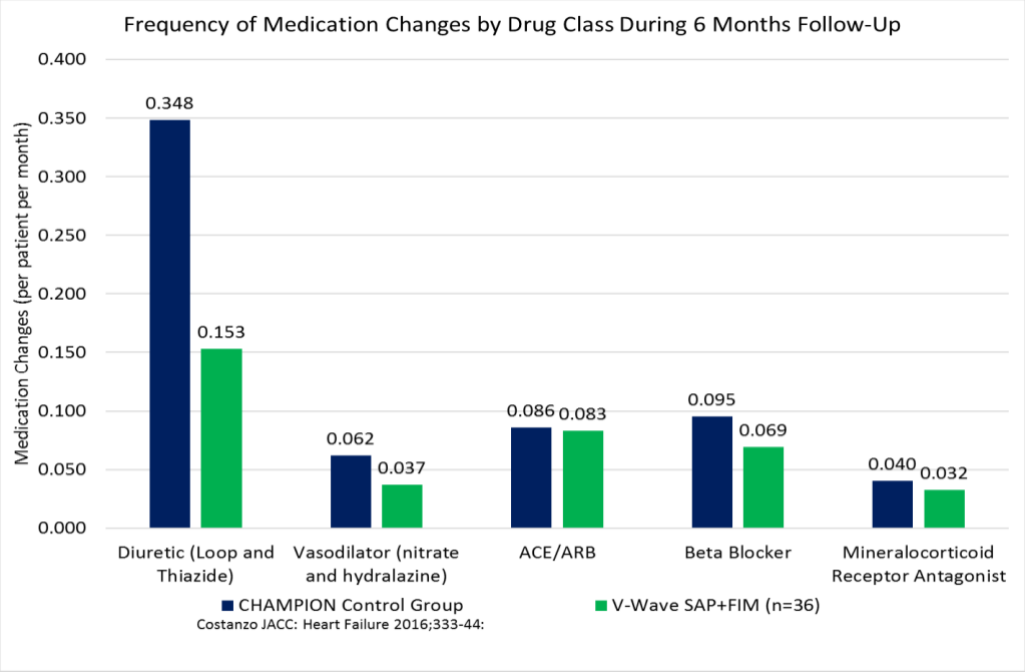


Figure 2. Medication Changes by Drug Class in CSAP+FIM vs. Champion Dataset

Hospitalization and Mortality: During the total follow-up of 12 months, there were 9 HF- hospitalizations. The annualized (Poisson) HF-hospitalization rate was 0.25 per patient per year and the mortality rate was 0.05 deaths per patient per year. For the purposes of developing exploratory effectiveness analyses, **Figure 3** compares these data with similar adjudicated endpoints from Champion at a mean duration of follow-up of 18 months. Shunt patient event rates are shown for the same

duration of follow-up. Shunt patients had annualized HF hospitalization rates or combined rates of death and HF-hospitalization that were significantly lower than CHAMPION Controls. Shunt patients also had consistently lower rates of non-HF-hospitalization, all-cause hospitalization, and death and all-cause hospitalization than either CHAMPION Controls or Treatment group patients.

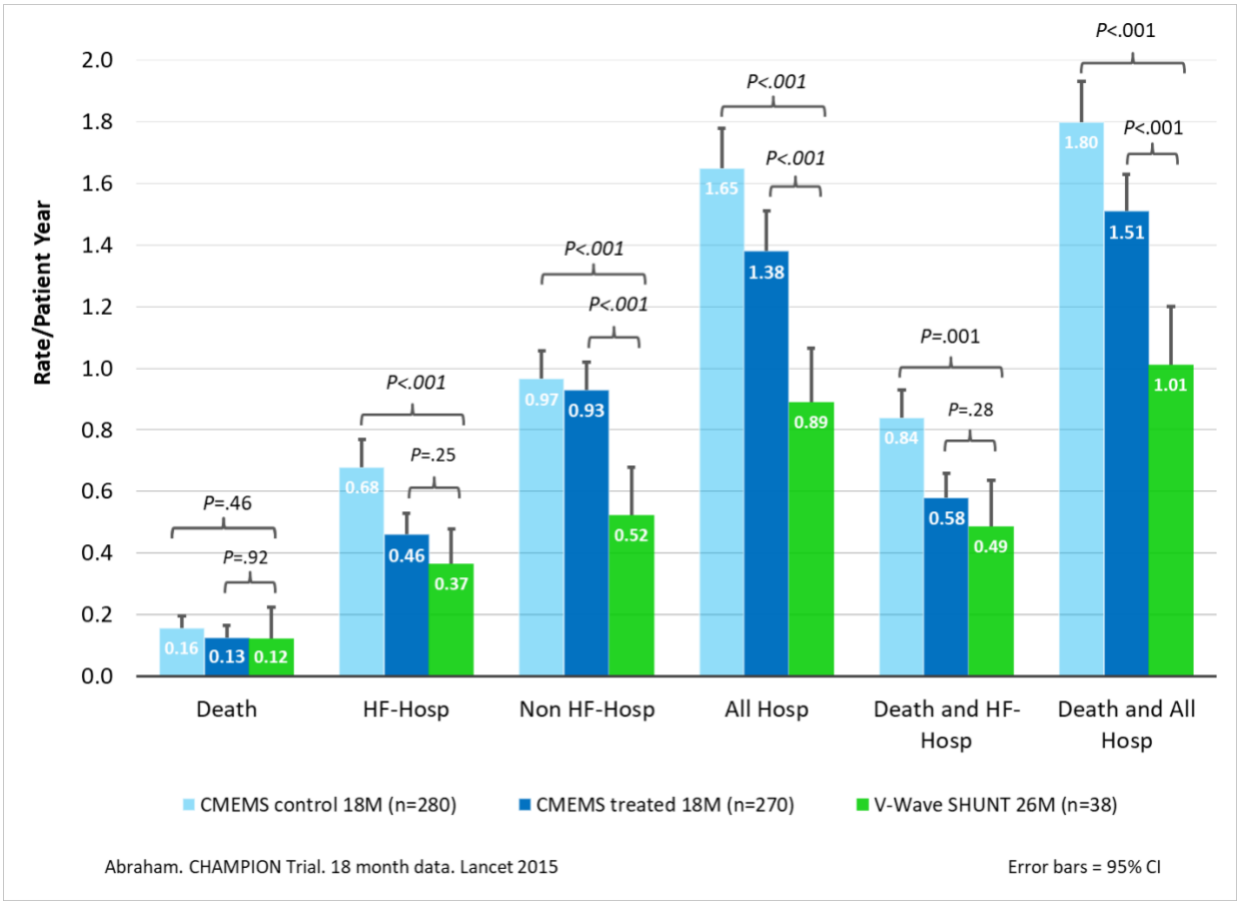


Figure 3. Hospitalization and Mortality of V-Wave Shunt vs. CHAMPION dataset

The overall experience with the V-Wave Interatrial Shunt System to date shows that it can be implanted with a high degree of reliability, safety and assurance of performance. The data from the feasibility studies shows multiple correlates of benefit over the span of more than one year in the setting of a high- risk population and the very low rates of death and HF-hospitalization in comparison with a well- matched population with advanced HF. These observations provide a reasonable assurance that the V- Wave Interatrial Shunt System is safe, meets satisfactory device performance criteria and likely has a device treatment effect.

There are currently studies underway with another investigational implantable interatrial shunt product manufactured by Corvia Medical Inc. (Tewksbury, MA), called the IASD II, short for interatrial shunt device II. This is also a self-expanding nitinol device that envelops the fossa ovalis leaving an 8-mm orifice for shunting. There is no encapsulation of the device with other biomaterials. The IASD II, has so far only been used in patients with HFpEF with EF ≥40%.

The REDUCE-LAP-HF Study, (NCT01913613) was a 66 patient non-randomized open label clinical trial that evaluated the safety and performance of the IASD II system outside of the US.[43,44] Key inclusion criteria included: LVEF ≥40%, symptomatic NYHA Class II/III/ambulatory class IV or HF hospital admission over past 12-months, PCWP >15 mmHg at rest and greater than CVP, or >25 mmHg during exercise. The primary outcome measure was periprocedural and 6 months Major Adverse Cardiac and Cerebrovascular Events (MACCE) and systemic embolic events (excluding pulmonary thromboembolism). Implantation was successful in 64 of 66 patients. There was no MACCE at 6 months. At 12 months, there were sustained significant improvements in New York Heart Association class (P<0.001), quality of life (Minnesota Living with Heart Failure) score (P<0.001) and 6-minute walk distance compared with baseline (363±93 versus 331±90 m; P=0.01; n=55).

The results of the REDUCE LAP-HF RANDOMIZED TRIAL I (NCT02600234) were recently reported (November 2017).[45] The primary effectiveness endpoint was exercise PCWP at 1 month. The primary safety endpoint was major adverse cardiac, cerebrovascular, and renal events (MACCRE) at 1 month. PCWP during exercise was compared between treatment groups using a mixed effects repeated measures model analysis of covariance that included data from all available stages of exercise. A total of 94 patients were enrolled, of which n=44 met inclusion/exclusion criteria and were randomized to the IASD (n=22) and control (n=22) groups. IASD resulted in a greater reduction in PCWP compared to sham- control (P=0.028 accounting for all stages of exercise). In addition, PCWP during passive leg raise and also during 20W of exercise decreased to a greater degree in the patients randomized to IASD compared to sham-control (*P*<0.05 for all comparisons). Peak PCWP decreased by 3.5±6.4 mmHg in the treatment group vs. 0.5±5.0 mmHg in the control group (P=0.14). There were no periprocedural or 1-month MACCRE in the IASD group and 1 event (worsening renal function) in the control group (P=1.0). The authors concluded that in patients with HF and LVEF ≥40%, IASD treatment unloads the left atrium and reduces PCWP during exercise.

Corvia is currently conducting a pivotal multicenter blinded randomized trial called REDUCE LAP-HF TRIAL II (NCT03088033), which began enrolling in June of 2017 and is expected to enroll approximately 380 patients.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Implanting permanent devices in the heart, especially within the left atrium and creating intracardiac shunts, carries with it known risks or complications, some of which may be severe, even at times fatal. Medical and/or surgical interventions may be required to correct clinical complications associated with the V-Wave Interatrial Shunt System and its implantation procedure. These known risks were considered with respect to severity and frequency and addressed by V-Wave according to its risk management procedures as specified under the EN ISO 14971:2012 standard. Specifically, a Failure Mode and Effects Analysis process was conducted beginning with design initiation and revised throughout the development process. Wherever possible, design changes, methods of use, and training, have been

adopted to mitigate the frequency and severity of these identified risks. As with any investigational device, there may be unforeseeable risks, which are not yet known at this time.

The potential risks associated with V-Wave System can be divided into three categories:

- The risks associated with the creation of an interatrial channel in the septum (similar to a small septal defect). These risks are known from ASD and PFO pathologies.
- Risks associated with the implantation of devices within the interatrial septum. These risks are not expected to substantively differ between currently marketed systems (e.g., Gore Helex, Amplatzer Septal Occluder) and the V-Wave Interatrial Shunt System.
- Finally, there are risks associated with the percutaneous implantation procedures (right heart catheterization, transesophageal or intracardiac echocardiography, and transfemoral transseptal cardiac catheterization with implantation of a device in the left atrium). These risks are also not expected to materially differ between marketed system (e.g., ASD closure devices, Left Atrial Appendage devices, Mitral valve treatment devices) and the V-Wave Interatrial Shunt System.

Foreseeable adverse events that may result from the V-Wave Shunt, its implantation, or ancillary investigational protocol specified procedures are summarized below:

- Acute decompensated heart failure
- Allergy, anaphylactic reaction, drug reaction, to contrast medium, anesthesia reaction, device components
- Arrhythmia
- Atrial septal defect (iatrogenic)
- Bleeding
- Cardiac arrest
- Cardiac or great vessel perforation
- Cardiac tamponade
- Coagulopathy
- Damage to adjacent cardiac structures
- Death
- Deep venous thrombosis (DVT)
- Device migration, embolization or erosion
- Device thrombosis
- Dislodgement of other previously implanted devices
- Effusion (e.g., pericardial, pleural, ascites)
- Emboli (air, thrombus, device)
- Emergency cardiac or vascular surgery
- Failure to deliver interatrial shunt to its intended site
- Failure to retrieve delivery system components
- Fever or hyperthermia
- Gastrointestinal disturbance (tear of bleeding of esophagus, peritonitis, infarction, ileus, nausea, vomiting, diarrhea)
- Hematuria
- Hemolysis
- Hemorrhage requiring transfusion
- Hypertension
- Hypotension
- Hypoxemia
- Infection (including septicemia and endocarditis)
- Interference with other implanted devices
- Loss of limb
- Myocardial infarction
- Nerve damage
- Pain
- Permanent disability
- Pneumothorax
- Psychological intolerance
- Pulmonary thromboembolism
- Radiation induced skin or tissue injury
- Reintervention/closure of shunt due to excessive shunting
- Removal of shunt due to infection
- Renal insufficiency
- Respiratory failure, atelectasis, pneumonia
- Seizure
- Shock (cardiogenic or anaphylactic)
- Skin irritation or inflammation
- Stridor
- Stroke or transient ischemic attack (TIA)
- Syncope
- Thrombosis
- Urinary retention
- Urinary tract infection
- Vascular trauma (dissection, occlusion, hematoma, arteriovenous fistula, pseudoaneurysm, perforation, spasm)
- Worsening right ventricular heart failure and pulmonary hypertension

The following discussion details some of the most severe and direct risks associated with the shunt and its implantation procedure.

2.3.1.1 RISKS ASSOCIATED WITH TRANSSEPTAL CARDIAC CATHETERIZATION

The V-Wave Shunt is placed following transseptal puncture from right femoral venous access using a market approved Brockenbrough needle/dilator/sheath or any other approved transseptal system such as a radiofrequency needle. Transseptal catheterization has been performed successfully in hundreds of thousands of patients for more than 50 years. Procedural safety has improved over time especially with better operator training, the proliferation of case experience, and the routine use of intracardiac or transesophageal echocardiography to assure the absence of left atrial thrombi, to puncture the interatrial septum in the proper location, and to prevent inadvertent puncturing of other cardiac structures. The improving safety can be assessed from studies of atrial fibrillation (AF) ablation and structural heart disease intervention in patients with elevated left atrial pressures. The risk of death generally ranges from 0.1% with AF ablation to 1% with mitral valve repair, and in both cases, the most common causes of death are complications of tamponade or stroke.[46,47,48] Although the literature does not break down if these adverse events were caused by the transseptal puncture or the subsequent intervention, they are likely a mixture of both.

De Ponti et al.,[49] published survey data from 5,520 transseptal catheterizations performed in 33 Italian centers spanning 12 years through 2004. Most of the procedures were for AF ablation. No deaths were reported. Cardiac perforation with tamponade occurred in 2 (0.1%) cases, needle puncture of the right atrium in 4 (0.2%) cases, puncture of the aortic root in 1 (0.05%) case and systemic thromboembolism in 1 (0.05%) case. These complication rates are likely artificially low due to the voluntary and retrospective data collection inherent in the study. The risk of cardiac tamponade increases to 0.4% to 1.3% when transseptal catheterization is followed by large bore sheaths to deliver structural heart therapies in higher risk populations including percutaneous mitral valve repair and left atrial appendage closure where more manipulation in the left atrium and its adjacent structures occurs.[50,51] In a series of left atrial appendage occlusion cases with the Watchman device, cardiac tamponade or other transseptal complications requiring surgical repair was 0.4%. Thus, the risks associated with transseptal device placement are generally known and appears to be acceptable relative to the natural history of the underlying disorders being treated.

2.3.1.2 RISK OF IMPROPER DEVICE PLACEMENT

Device maldeployment or improper device placement is defined as any device that is not seated across the interatrial septum with the intended inlet side in the left atrial chamber and the outlet side in the right atrial chamber. This includes instances of inadvertent deployment, maldeployment, device embolization, and inability to remove an improperly deployed or non-deployed device from the body without surgery. It can occur before or after the device is intended to be released from the Delivery Catheter. Improperly placed devices may impinge or erode into other adjacent cardiac structures or may cause fatigue or wear to the device resulting in strut fracture or device fragmentation.

ASD and PFO occlusion devices are the closest non-shunt predicate devices because they span the interatrial septum. The FDA conducted an extensive literature review of the Gore Helex Septal Occluder and the AGA Amplatzer Septal Occluder devices that was presented at the 24 May 2012 Circulatory Systems Advisory Panel meeting. They concluded that the embolization rates experienced in the clinical trials (~1-3%) were similar to those reported in the literature (~0.3-3.5%) and constitute the majority of adverse events reported to the MAUDE (Manufacturer and User Facility Device Experience) system. These events were not consistently associated with life-threatening sequela; however, they nonetheless require an additional procedure, percutaneous or surgical, for retrieval.

Erosion rate estimates from the literature and MAUDE system were also similar (~0.1-0.2%); however, these estimates are limited given the rarity of event and methodology used to capture data. Most erosions (60%) occur after discharge from the hospital and may occur more than one year after implantation. Although this type of event appears to be quite rare, the associated morbidity is considerable.

Fracture events with the Gore Helix Septal Occluder device were noted in the market entry clinical data (6-7%) and were similar to literature estimates (6-8%). Approximately 2% of post-approval study patients have undergone device explant due to device fracture.

2.3.1.3 RISKS OF THROMBOEMBOLISM AND STROKE

One potential risk of creating an interatrial shunt is paradoxical embolism. Paradoxical embolization refers to thromboembolism originating in the venous vasculature (venous thromboembolism or VTE) and traversing right-to-left through a cardiac shunt into the systemic arterial circulation. VTE in adults is almost exclusively the consequence of *in situ* thrombosis in the deep veins (deep venous thrombosis or DVT) of the lower extremities or pelvis. Heart failure is a well-recognized risk factor for DVT and VTE, especially in patients with reduced left ventricular systolic function.[52] About 3% of deaths in heart failure patients are due to VTE, usually associated with pulmonary emboli.[53]

There is evidence that the risk of paradoxical embolism is directly related to the orifice size of naturally occurring atrial level shunts such as ASD and PFO.[54] In patients with clinically significant ASD referred for closure, the incidence of paradoxical embolus has been reported to be up to 14%.[55,56]

It has been asserted that for VTE to enter the systemic circulation, the prevailing LA to RA pressure gradient seen in heart failure must be temporarily eliminated or reversed so that blood will flow retrograde across the shunt. In patients with existing ASD or PFO, bidirectional shunting can be best demonstrated when a subject performs a Valsalva maneuver, which causes the RA and LA pressures to equalize after several seconds and for the gradient to transiently reverse immediately upon secession of straining.[57] Intermittent bidirectional flow may also be observed at rest when the interatrial pressure gradient is low, or intermittently during the cardiac cycle when LA contraction is delayed compared to RA contraction (interatrial conduction delay). Bidirectional shunting can also be seen transiently during inspiration, when venous return to the RA is increased, during coughing, forced expiration, with abdominal compression, or in the presence of severe tricuspid valve regurgitation.

Any risk of stroke from paradoxical embolization must be weighed against the background rate of stroke in HF patients who have a 2- to 3-fold increased risk of stroke due to many risk factors, including LV apical dyskinesia, a high incidence of atrial fibrillation (typically 35-45%), hypercoagulable states, endothelial dysfunction, atherosclerosis, hypertension and diabetes.[58] Abdul-Rahim et al.,[59] reported the rates of stroke in the long term follow-up cohorts of the CORONA and GISSI-HF studies totaling 9,585 patients, 3,531 (37%) with any history of atrial fibrillation (AF) and 6,054 without AF. In patients with AF, the 1-, 2-, and 3-year cumulative incidence rates of stroke were 1.7%, 2.8%, and 4.2%, respectively. In patients without AF, the 1-, 2-, and 3-year rates of stroke were lower at 1.2%, 2.2%, and 3.1%, respectively. In a review of 402 patients with cardioembolic strokes, Arboix and Alio[60] reported that only 2(0.5%) patients were diagnosed as having paradoxical emboli. The overwhelming majority of cardioembolic strokes were associated directly with atrial arrhythmias or LV dysfunction. Cardioembolic stroke constitutes a minority of all strokes: about 15% of all strokes in patients 65 years old or younger, increasing to 36% of all strokes in patients 85 years or older. Atherothrombotic strokes, lacunar infarctions, and strokes of unknown causes make up the rest. These data suggest that although paradoxical embolic stroke may be associated with atrial shunting, it is likely to be very uncommon in relationship to the underlying rate of stroke in patients with advanced HF, especially in the setting of a predominately left-to-right shunt.

Another potential concern is thromboemboli originating from the surfaces of the shunt device itself. Krumsdorf et al.,[61] reviewed 1,000 consecutive ASD and PFO device closure cases with transesophageal echocardiography after 4 weeks and 6 months. The incidence of thrombus formation was highly device-dependent ranging from very low with ASD devices (0-0.8% at 4 weeks and 0-0.3% at 6 months) to generally higher early rates with PFO devices (5.7-7.1% at 4 weeks, 0-3.3% at 6 months). Risk factors for device thrombosis include atrial fibrillation, persistent atrial septal aneurysm, and coagulation disorders. The treatment for device thrombosis is anticoagulation; however, there is a risk of stroke when the thrombus is on the LA side, and surgical treatment might be considered for large, mobile thrombi.

2.3.1.4 RISK OF CREATING TOO LARGE A LEFT-TO-RIGHT SHUNT

There is wide consensus that atrial septal defects (ASDs) of more than 10 mm in diameter are associated with clinically significant left-to-right shunting where the pulmonary to systemic blood flow ratio (Qp:Qs) is greater than 1.5, or there is dilation of the right heart chambers.[62,63,64,65] ASDs that are between 5-10 mm in diameter, with smaller shunt ratios, generally have excellent outcomes and are not indicated for device or surgical closure. They are recommended to be followed every few years and ASDs with a diameter of 5 mm or less, Qp:Qs <1.5 and no RV dilation do not adversely impact the natural history of the patient and require no intervention.

Creation of iatrogenic ASD or iASD has become more common with the proliferation of percutaneous interventions using the transseptal approach including: electrophysiological ablation procedures, atrial appendage occlusion, percutaneous mitral valvuloplasty, and mitral valve repair with the MitraClip.[66,67,68] When these ASDs did not exceed a diameter of 5 mm (measured on 3-D echo) and had a Qp:Qs that did not exceed 1.4, these patients had no differences in clinical outcomes or pulmonary pressures compared to those without iASDs when followed for more than an average of 6 years.[69,70]

Persistent iASDs with shunt diameters of up to 6 mm in patients undergoing pulmonary vein isolation has demonstrated similar results with no worsening of symptoms or complications due to hemodynamically relevant interatrial shunting.[66,71]

There are cautionary reports suggesting that patients with residual iASDs larger than 8mm in diameter may be at risk to develop right-sided heart failure and may have a higher mortality rate than those with iASDs ≤8mm, thus requiring percutaneous ASD closure.[72,73] In summary, these observations, from a variety of experiences support that small ASDs or iASDs, in the range of 5-8 mm in diameter, appear to be well tolerated and may decompress the left atrium, reducing symptoms from LV dysfunction.
Conversely, larger shunts are associated with poorer outcomes due to right heart volume overload.

2.3.1.5 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

The V-Wave Shunt may interfere with catheter-based or surgical procedures which require access to the left atrium. These include but are not limited to: mitral valve repair or replacement, left atrial appendage occlusion, electrophysiological studies and ablation of structures in or near the left atrium, such as pulmonary vein isolation.

Shunted patients will be receiving antiplatelet or anticoagulant therapy. These may require interruption if certain surgical procedures are needed.

The Shunt may cause an artifact on MR imaging within a range of a centimeter surrounding the Shunt's location.

2.3.2 POTENTIAL BENEFITS

The potential benefits to patients implanted with the V-Wave Shunt include:

- Serial evaluation, close monitoring, and medical optimization by cardiologist and skilled heart failure team
- Reduction in the severity and frequency of heart failure symptoms such as dyspnea
- Improvement in quality of life
- Improvement in exercise capacity
- Reduction in the number of hospitalizations for worsening heart failure
- Reduction in the number of Emergency Room visits for worsening heart failure
- Reduction in the number of urgent clinic visits of worsening heart failure
- Prolongation of life

The potential benefits to patients not implanted with the Shunt (Controls) include:

- Serial evaluation, close monitoring, and medical optimization by cardiologist and skilled heart failure team
- Opportunity to receive the Shunt after unblinding (maximum of 24 months)

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

2.3.3.1 STEPS TO MITIGATE RISK

Special considerations have been taken in designing the V-Wave System for the purpose of achieving its safe and reliable performance. The risk management procedures and related documentation and activities were performed according to the EN ISO 14971:2012 standard. The program was designed to identify the sources of risk during the design, development, and production processes. Specifically, a Failure Mode and Effects Analysis table was created and periodically assessed and revised. Preventive and/or control actions were implemented into device development and manufacturing to eliminate or reduce potential failure modes wherever and whenever possible.

For example, the Shunt, its Delivery System, and the Instructions for Use have been designed to reduce the likelihood of cardiac perforation, and tamponade during the device implantation procedure. The potential risk of creating too large a shunt, resulting in right heart volume overload, pulmonary hypertension, right ventricular failure and increased mortality has been in part mitigated by fixing the shunt orifice size at 5.1 mm diameter, which is expected to limit shunt flow, with a resulting Qp:Qs of approximately 1.2. This is expected to reduce the chances of right heart deterioration.

The protocol, by way of inclusion/exclusion provisions, study design, and follow-up procedures is intended to minimize patient risks. Certain clinical, imaging, and laboratory inclusion/exclusion criteria at baseline screening and at final screening performed at the time of the Study Intervention Procedure are intended to maximize the patient population anticipated to benefit from shunting while minimizing the risk of device and procedure related complications. For example, the exclusion of patients with poor RV function and severe pulmonary hypertension is intended to reduce the potential of even modest volume left-to-right interatrial shunting to exaggerate these conditions. All potential patients considered for entry into the trial who pass initial non-invasive screening will be reviewed by a Sponsor- independent Central Eligibility Committee to ensure that appropriate patients are being enrolled.
Patients are evaluated for clinical, hemodynamic, heart rhythm, and respiratory stability just prior to randomization/enrollment to further assure their safety. Similarly, the peri- and post-procedural medication regimen is designed to minimize thromboembolic complications.

Site selection with only highly experienced multidisciplinary HF teams and two physician expert investigators is required. These include a HF cardiologist (*HF-Investigator*) and an implanting cardiologist (*Implanter-Investigator*). Only implanters with advanced experience in transseptal catheterization, structural heart disease therapeutic procedures such as MitraClip mitral valve repair, and left atrial appendage occlusion, or AF ablation will participate in the trial.

The Company will develop a site training program. All site investigation personnel will be thoroughly trained on the protocol and study procedures. Investigators will be trained in the selection of patients for potential participation in this study, ensuring that all patients meet all the inclusion criteria and none of the exclusion criteria. The *Implanter-Investigator* will by trained in the proper use of the Study Device, first on a bench-top model and then proctored during the first cases per the protocol requirements. The Sponsor will share its experience training implanters in “bailout” procedures that may be considered to retrieve a maldeployed or embolized shunt, or to close a Shunt that is not clinically tolerated. A trained and experienced company representative will be present to support all device implantation procedures.

Mandatory safety data events reporting, and regular clinical monitoring will ensure the timely awareness of untoward outcomes and compliance with protocol requirements that affect risk including patient eligibility criteria, study medications, follow-up schedule, and use of the Study Device according to the Instructions-for-Use (IFU). Unanticipated adverse events will be evaluated and reported as required per the protocol and local regulations. A Sponsor-independent Clinical Event Committee (CEC) will adjudicate all SAEs for device or procedure-relatedness. A Sponsor-independent Data Safety Monitoring Board (DSMB) will provide trial oversight to assure patient safety.

2.3.3.2 TABLE OF ANTICIPATED DEVICE AND PROCEDURE-RELATED MAJOR RISK FREQUENCIES VS. BACKGROUND RISK RATES

Table 5 lists the anticipated device and procedure-related major risks as well as expected event frequencies with respect to background rates.

Table 5. Anticipated Device and Procedure-Related Risks

Major Risk	Anticipated 30-day Device-Related Frequency	Background Rate/yr in Control group
Death	≤2%	15-20%
Stroke and systemic thromboembolism	≤1%	~2%
Tamponade/cardiac perforation requiring surgical repair	≤0.5%	-
Shunt embolization requiring surgery	≤0.5%	-
Need to remove or close shunt (infection, over-shunting)	≤1%	-
Vascular complication (requiring surgical repair)	≤2%	-

The major risks listed are the components of the Primary Safety Endpoint (see Section 3.1.1.). The anticipated rates are based on prior CSAP/FIM experience with the prior V-Wave Shunt and publicly available Watchman and MitraClip summary information presented at FDA Circulatory Systems Devices Panel Meetings of March 20, 2013 and October 8, 2014, respectively.[74,75] Other major risks including arrhythmias, myocardial infarction, and major bleeding, are not expected to be materially different between shunted and control patients based on the anticipated high background rates of ischemic heart disease, LV dysfunction, atrial fibrillation and widespread use of anticoagulation/antiplatelet agents in the target population.

Finally, the anticipated risks for the V-Wave Shunt are not expected to be substantively different than those observed in comparable marketed devices used to treat structural heart disease that are placed in the left atrium including mitral valve clips, appendage occluders and ASD/PFO occlusion devices. Moreover, based on our preclinical and preliminary clinical experience and those of the Corvia IASDII shunt, as detailed above, these risks will likely be outweighed by the potential benefits of interatrial shunting as a therapeutic option for patients with advanced HF that are currently poorly responsive to

optimal medical therapy, that have a guarded prognosis, and are subject to disease progression with accompanying deterioration of their general health status.

3 OBJECTIVES AND OUTCOME MEASURES

The objective of the RELIEVE-HF study is to provide reasonable assurance of safety and effectiveness of the V-Wave Interatrial Shunt System by improving meaningful clinical outcomes in patients with NYHA functional class III or ambulatory class IV heart failure, irrespective of left ventricular ejection fraction, who at baseline are treated with guideline-directed drug and device therapies.

3.1 PRIMARY ENDPOINTS

Detailed definitions of endpoints and statistical approaches will be defined in the separate Statistical Analysis Plan (SAP).

3.1.1 PRIMARY SAFETY ENDPOINT

The Primary Safety Endpoint is the percentage of Treatment Group patients experiencing any device-related Major Adverse Cardiovascular or Neurological Events (MACNE) during the first 30-days after randomization, compared to a pre-specified performance goal. MACNE is defined as all-cause death, stroke, systemic embolism, need for open cardiac surgery or major endovascular surgical repair. Specifically, percutaneous drainage of a pericardial effusion, percutaneous catheter snaring and removal of an embolized but otherwise uncomplicated Study Device and non-surgical treatment of access site complications are excluded from the definition of MACNE.

3.1.2 PRIMARY EFFECTIVENESS ENDPOINT

The Primary Effectiveness Endpoint is a hierarchical composite ranking of all-cause death, cardiac transplantation or left ventricular assist device (LVAD) implantation, recurrent HF hospitalizations (including Emergency Room HF Visits with duration >6 hours), and change in 6-minute walk test (6MWT) distance, comparing Treatment and Control groups. The analysis is based on the method of Finkelstein and Schoenfeld.[76]

3.2 SECONDARY OUTCOME MEASURES

3.2.1 HIERARCHICALLY TESTED SECONDARY EFFECTIVENESS ENDPOINTS

- 6MWT changes from Baseline to 12 months
- KCCQ changes from Baseline to 12 months
- All-cause mortality and heart failure hospitalizations
- Time to all-cause death, LVAD/Transplant or heart failure hospitalization
- Time to all-cause death or first heart failure hospitalization

- Cumulative heart failure hospitalizations
- Time to first heart failure hospitalization
- Modified Primary Effectiveness Endpoint including all-cause death, LVAD/Transplant and HF Hospitalizations but without 6MWT

3.3 ADDITIONAL MEASUREMENTS

Details of analyses, including time points where not specified, will be defined in the separate Statistical Analysis Plan.

3.3.1 EFFECTIVENESS

- NYHA Class
- Patient Global Assessment
- Combined all-cause death and all-cause hospitalizations
- All-cause death
- Time to all-cause death (KM analysis)
- Time to cardiovascular death (KM analysis)
- Time to all-cause death, transplant or LVAD (KM analysis)
- Time to cardiovascular death, transplant or LVAD (KM analysis)
- Days alive free from heart failure hospitalization
- Outpatient intensification of heart failure therapy
- Emergency room HF visits
- HF Clinical Composite Assessment (improved, unchanged, or worsened) as described by Packer comprised of all-cause mortality, HF hospitalization, and changes in NYHA functional class ranking and Patient Global Assessment
- Comparison of transthoracic echocardiographic parameters as listed in Echocardiography Core Laboratory Manual
- Incidence of loss of shunt flow as measured on TTE and/or TEE
- Changes in 6MWT
- Changes in KCCQ
- Death: All-cause; Cardiovascular cause (with breakdown by cause, e.g. sudden death, myocardial infarction, pump failure, stroke); Non-Cardiovascular cause; Undetermined cause; and relationship to device, study intervention or other cardiovascular procedure
- Hospitalization: All-cause; HF hospitalization, Non-HF hospitalization (with breakdown for cause including if associated with secondary worsening of HF)
- Change in renal function
- Medication utilization including type, dose, frequency and changes
- Cost and cost-effectiveness data
- Technical success
- Device success
- Procedural success
- For Roll-in patients, transesophageal or intracardiac echocardiography at 6 and 12 months to assess shunt patency and other parameters as listed in the Echocardiography Core Laboratory Manual

3.3.2 SAFETY DATA COLLECTION

- Major Adverse Cardiovascular and Neurological Events (MACNE) and Bleeding Academic Research Consortium (BARC) types 3 and 5 bleeding at 30 days
- Percentage of Treatment Group patients with device-related MACNE at 12 months
- Incidence of all Serious Adverse Events by type at study duration
- Incidence of cerebrovascular events at study duration with sub-classification of CNS infarction, CNS hemorrhage, and TIA and their relationship to device or study procedures (per NeuroARC)
- Incidence of MI events at study duration after implantation
- Incidence of systemic embolization events at study duration after implantation
- Incidence of pulmonary embolism events at study duration after implantation
- Incidence of shunt implant embolization at study duration
- Device-related MACNE annually through 5 years

3.4 EFFECTIVENESS QUALIFYING ENDPOINT DEFINITIONS

3.4.1 HOSPITALIZATION (ALL-CAUSE)

Defined as an admission to an acute care facility, inpatient unit, observation unit or emergency room, or some combination thereof, for at least 24 hours. Excludes hospitalizations planned for pre-existing conditions (elective admissions), unless there is worsening in the baseline clinical condition prior to the planned admission. Overnight stays at nursing home facilities, physical rehabilitation or extended care facilities, including hospice, do not meet the definition of hospitalization. Hospitalizations will be adjudicated by the Clinical Events Committee as Heart Failure Hospitalization, Other Cardiovascular Hospitalization, or Non-Cardiovascular Hospitalization.

3.4.2 HEART FAILURE HOSPITALIZATION

Meets the definition of Hospitalization above and the primary reason for admission is acute decompensated heart failure (ADHF) meeting the following criteria:

1) Patient has one or more symptoms of ADHF such as worsening or new onset of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, reduced exercise capacity and/or lower extremity/abdominal swelling;

AND

2) Patient has one or more signs or laboratory evidence of ADHF such as: rapid weight gain, pulmonary edema or rales, elevated jugular venous pressure, radiological signs of pulmonary congestion or increased pulmonary venous pressure, increasing peripheral edema or ascites, S3 gallop, hepatojugular reflux, and/or elevated BNP or NT pro-BNP above most recent baseline, right heart catheterization within 24 hours of admission showing elevated PCWP or low cardiac index;

AND

3) Admission results in the initiation of intravenous heart failure therapies such as diuretics, vasodilators, inotropes, or mechanical or surgical intervention (e.g., ultrafiltration, intra-aortic balloon pump, mechanical assistance) or the intensification of these therapies or at least doubling of the oral diuretic dose with the clear intent of promoting increased diuresis for the treatment of ADHF.

AND

4) No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

It is recognized that some patients may have multiple simultaneous disease processes. Nevertheless, for the endpoint event of heart failure requiring hospitalization, the diagnosis of HF would need to be the primary disease process accounting for the above signs and symptoms. All hospitalizations where the primary reason for admission is other than ADHF, if accompanied by worsening HF or subsequently complicated by ADHF, do not meet the criteria for HF Hospitalization. This includes the admission for the study intervention procedure. For example, patients admitted where the primary reason for admission is pneumonia, which are adjudicated to have secondary worsening of HF, would not be counted as HF Hospitalization.

Outpatient Intensification of Heart Failure Therapy (as defined in 3.4.6), whether managed in a Heart Failure clinic, other clinic setting, or done remotely, does not meet the definition of HF Hospitalization. However, these events will be collected and used in sensitivity analyses.

3.4.3 OTHER CARDIOVASCULAR HOSPITALIZATION

Meets the definition of Hospitalization in 3.4.1 for conditions such as coronary artery disease, acute coronary syndromes, hypertension, cardiac arrhythmias, pericardial effusion, atherosclerosis, peripheral vascular disease, pulmonary embolisms, stroke and aortic dissection.

3.4.4 NON-CARDIOVASCULAR HOSPITALIZATION

Meets the definition of Hospitalization in 3.4.1 and does not meet the definition of HF Hospitalization or Other Cardiovascular Hospitalizations.

3.4.5 EMERGENCY ROOM HEART FAILURE VISIT

Admission to an emergency room for less than 24 hours, where the primary reason for admission is ADHF otherwise meeting the same criteria defined for HF Hospitalization when the patient is not transferred to an inpatient unit or observation unit, but is discharged home.

3.4.6 OUTPATIENT INTENSIFICATION OF HEART FAILURE THERAPY

Requires that the patient has worsening symptoms, signs or laboratory evidence of worsening heart failure and the dose of diuretics was increased and sustained for a month, or intravenous treatment given for HF, or a new drug was added for the treatment of worsening HF.

3.4.7 HEART FAILURE ENDPOINT QUALIFYING EVENTS

Only Heart Failure Hospitalization and Emergency Room Heart Failure Visits lasting at least 6 hours as defined will be adjudicated by the CEC as Endpoint Qualifying Events for inclusion in the Primary Effectiveness Endpoint analysis.

3.4.8 TECHNICAL SUCCESS

Technical success will be measured at exit from cath lab and is defined as alive, with successful access, delivery and retrieval of the transcatheter V-Wave delivery system, with deployment and correct positioning of the single intended device and no need for additional emergency surgery or re- intervention related to either the device or the access procedure.

3.4.9 DEVICE SUCCESS

Device success will be measured at 30 days and all post-procedural intervals and is defined as alive and stroke free, with original intended device in place and no additional surgical or interventional procedures related to access or the device and intended performance of the device with no device migration, embolization, detachment, fracture, hemolysis or endocarditis, and expected hemodynamic performance including patent device with Qp:QS <1.5, and no detected para-device complications including device leak, erosion, systemic or pulmonary thromboembolization.

3.4.10 PROCEDURAL SUCCESS

Procedural success will be measured at 30 days and is defined as device success and no device or procedure related SAEs including life threatening bleeding (>4 units of packed red blood cells), acute kidney injury (stage 2 or 3, including renal replacement therapy), major vascular complications or tamponade requiring intervention, myocardial infarction or coronary ischemia requiring PCI or CABG, severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatment (e.g. ultrafiltration or hemodynamic assist devices including intra- aortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for ≥ 48 hours).

3.5 OTHER ENDPOINT DEFINITIONS

3.5.1 NEUROLOGICAL EVENTS

Neurological events will be classified according to Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative (NeuroARC).[77] Events will be

classified as CNS injury (Type 1) including ischemic stroke, with or without hemorrhagic conversion, along with other Type 1 subtypes, and neurological dysfunction without CNS injury (Type 3) including TIA.

Clinical assessment will include a neurological consultation, assessment of the National Institutes of Health Stroke Scale, and assessment of neurological deficits and cognitive function according to institutional standards. Patients experiencing a neurological event will have an MRI or a head CT (if MRI is contraindicated) and will undergo transesophageal echocardiography (TEE) to evaluate cardiac origin, device patency and involvement in their neurological event.

3.6 HEALTHCARE ECOMOMIC ANALYSES

The RELIEVE-HF trial will include a prospective health economic evaluation in order to provide rigorous, prospective data with respect to the cost-effectiveness of the interatrial shunt procedure compared with standard medical therapy. Resource utilization and cost data will be assessed for all patients in the trial from the time of randomization through a minimum of 1 and a maximum of 2 years of follow-up (at which point some patients assigned to the control group may cross over to the shunt procedure). These data will include hospital billing data (UB-04 summary bills and itemized hospital bills) for all U.S. patients, which will be used, along with supplementary material from the case report forms, to determine the initial treatment costs. Follow-up costs will be assessed from the perspective of the U.S. healthcare system based on resource utilization data including follow-up hospitalizations, office visits, medications, etc. At the completion of the trial, these data will be used in conjunction with quality of life and utility data collected from the trial to develop a long-term Markov model in order to project patient-level survival, quality-adjusted life expectancy, and costs beyond the time frame of the trial in order to estimate the incremental cost-effectiveness ratio for the interatrial shunt procedure compared with standard medical therapy for the trial population.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The RELIEVE-HF trial hypothesis is that the V-Wave Shunt System is a safe and effective method for improving clinically meaningful outcome measures in a population of patients with advanced, highly symptomatic HF, irrespective of left ventricular systolic function, who are at high risk for morbidity and mortality events. This is accomplished by achieving both the Primary Safety Endpoint, demonstrating an acceptably low level of device-related Major Cardiovascular and Neurological Events, and the Primary Effectiveness Endpoint, establishing superiority of interatrial shunting for a hierarchical composite ranking of death, cardiac transplantation or left ventricular assist device (LVAD) implantation, recurrent HF-hospitalizations (including Emergency Room HF Visits >6 hours), and change in 6-minute walk test (6MWT) distance.

RELIEVE-HF is a pivotal study (Schema Figure 1), comprising a prospective, multi-center, multinational, randomized, controlled, clinical assessor blinded and patient-blinded trial design. The study is

anticipated to include up to 60 centers in the United States and other countries with a majority of sites located in the US.

All patients will be screened for eligibility in a 3-stage process. After Preliminary Screening by the site, de-identified patient information including Echocardiographic Core Lab data will be reviewed by an independent *Eligibility Committee*, to confirm that inclusion/exclusion criteria are met and to minimize site selection bias. Final eligibility for study enrollment is then determined by the *Implanter-Investigator* in the Cardiac Catheterization Laboratory after a right heart catheterization and transesophageal echocardiographic (TEE) or intracardiac echocardiographic (ICE) imaging is performed to assess whether final hemodynamic and anatomic exclusion criteria are absent.

RELIEVE-HF is a 2-arm trial with roll-in patients. Sites will first familiarize themselves with the V-Wave system by implanting the shunt in up to 3 Roll-in patients and follow them in an open-label (unblinded) manner. Implantation performance during Roll-in will be assessed during the implant by a Sponsor provided qualified *Proctor*. The Roll-in arm is anticipated to enroll approximately 100 patients. Roll-in patients will otherwise be followed and analyzed identically as Randomized patients, but their study data will be presented separately. Roll-in patients will additionally undergo TEE imaging at 6 and 12 months to assess Shunt patency.

Once a site has successfully completed proctoring, they will begin the Randomized Access (blinded) phase of the study. Initiation of sites and patient randomization will be staged and controlled so that early safety data can be evaluated before opening all centers and fully enrolling the trial.

During the Randomized Access phase, approximately 400 patients will be randomized 1:1 into a Shunt Treatment arm or a Control arm, with a possible increase to approximately 600 total patients based on interim analysis results. Randomization will be stratified by site and left ventricular ejection fraction (HFrEF, LVEF≤40% or HFpEF, LVEF>40%) as determined by the Echocardiography Core Laboratory on the baseline transthoracic echocardiogram. Treatment arm patients will undergo transseptal catheterization and Shunt implantation. Control patients will not have transseptal catheterization or shunt placement but will undergo all other study procedures. All patients are blinded to study assignment in the Cath Lab (see Section 6.3.2 Blinding Procedures). After randomization, all patients and study personnel involved in endpoint collections will remain blinded until a maximum of 24 months or until the last enrolled patient reaches the 12-month follow-up, whichever occurs sooner. All patients will have the same in- clinic and telephone follow-up schedule as described in the Schedule of Activities (SoA, Section 1.2) and be treated with Guideline-Directed Medical Therapy. Patients who receive the shunt require adjunct antiplatelet or anticoagulant pharmacological treatment. Many HF patients are already taking these medications, but for those who are not, the study will supply antiplatelet medications for Treatment patients and placebo for Control patients to maintain blinding.

The Randomized Access phase incorporates an adaptive design that allows sample size adjustment upward to a maximum of 600 randomized patients if a one-time interim analysis, performed by the independent *Unblinded Statistician,* results in updates to the original planning assumptions for the

components of the composite primary effectiveness endpoint requiring a sample size change to maintain the original design statistical power.

Upon reaching 24 months of follow-up or at study unblinding, whichever occurs first, individual patients enter an Open Access phase where Control arm patients may cross over and receive a shunt if they consent and still meet eligibility criteria.

RELIEVE-HF uses standard trial methodologies to minimize patient risk and bias in interpreting the trial results. Risks are minimized by the selection of a defined patient population similar to that used in early feasibility studies and by the use of strictly enforced inclusion/exclusion criteria, including requiring data from invasive diagnostic procedures to help avoid patients at high risk for device-related complications, specifically those with severe pulmonary hypertension, significant RV failure, unstable hemodynamics, arrhythmias, or unsuitable anatomy. Patients are closely followed at regular intervals and observed for the detection and reporting of Serious Adverse Events (SAEs) and Serious Adverse Device Effects (SADEs). Standard sponsor-independent trial governance procedures including event endpoint adjudication by a Clinical Events Committee and trial oversight by the Data Safety Monitoring Board will also help assure patient safety.

Enrolling and randomizing patients immediately after diagnostic catheterization and invasive echocardiographic procedures (TEE or ICE) in the Cath Lab is also a means to prevent inadvertent selection bias at implant and to capture events that may occur between randomization and device implantation or control procedures. Randomization and blinding of patient, observers, and data analysis are the standard methods that will be used to reduce bias. The additional use of an Eligibility Committee, Echo Core Lab, and CEC is expected to reduce inter-site heterogeneity in applying inclusion/exclusion criteria and adverse event reporting. Finally, the sponsor will be blinded to all aggregate endpoint data in the Randomized Access cohort patients until the completion of the study.
However, some patient data may need to be unblinded to Sponsor to allow investigation of study safety and device performance concerns.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The multicenter, randomized, blinded, controlled design was selected to minimize institution, observational, and reporting bias. Although great care will be taken to assure patient and observer blinding, it cannot be guaranteed. The adequacy of blinding and the patients' perception as to whether they were treated with the shunt or remained in the control arm will be assessed in patients with a blinding questionnaire at the time of hospital discharge from the Study Intervention Procedure and at 1 year. A blinding manual will provide guidance for sites and blinding logs will be maintained for all site research personnel that are involved in performing study procedures that will be used to assess study endpoints.

The study will enroll patients irrespective of LV systolic function. Randomization will be stratified for patients by ejection fraction, with HFrEF (LVEF≤0.40) and HFpEF (LVEF>0.40). From prior studies of implantable hemodynamic monitoring that have enrolled similar patients, including COMPASS-HF,

CHAMPION, and LAPTOP-HF, it is anticipated that approximately 20-25% of patients meeting the enrollment criteria will qualify as HFpEF.[Error! Bookmark not defined.,78,79] Just as with implantable hemodynamic monitoring, the main treatment goal of interatrial shunting is to prevent the highest excursions of LAP. The use of combined HFrEF and HFpEF populations for evaluation of the shunt is justified, since the major clinical outcomes associated with the resulting episodes of acute decompensated heart failure from each are identical. These include mortality, HF hospitalization, and exercise capacity, all of which are likely to be either caused by, or correlated with, sustained elevations in LAP, irrespective of LVEF.[8] The safety and effectiveness of the shunt according to pre-specified LVEF subgroups will be assessed by interaction testing.

4.3 END OF STUDY DEFINITION

It is anticipated that the study will require approximately 9 years to complete. This includes the initial period for Roll-in patients, randomization and follow-up through unblinding and determination of the primary endpoints and then annual follow-up for 5 years after implantation for Roll-In, Treatment and Control arm patients that receive a shunt at the end of the blinded phase.

A participant is considered to have completed the study if they complete all phases of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.2).

After each scheduled review of the accumulating safety data, the DSMB will provide the Executive Committee and the Sponsor with a written recommendation whether to continue the study as planned, suspend enrollment, or terminate enrollment in the clinical investigation early for safety reasons. All DSMB recommendations will be reviewed by the Sponsor in consultation with the Executive Committee, with the Sponsor making the final determination about accepting, modifying, or rejecting the recommendations. If a decision is made to terminate the study early, the Sponsor will notify sites and develop a modified protocol for follow-up of implanted patients, which will be submitted to the appropriate regulatory authorities and Ethics Committees/IRBs. The Sponsor reserves the right to terminate the clinical investigation at any time and for any reason.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1) Ischemic or non-ischemic cardiomyopathy with either reduced or preserved LV ejection fraction and documented heart failure for at least 6 months.

2) NYHA Class III or ambulatory Class IV HF documented at Baseline Visit.

3) Receiving guideline directed medical therapy (GDMT) for heart failure which refers to those HF drugs carrying a Class I indication including the following for patients with reduced LVEF (≤40%):

    a) An inhibitor of the renin-angiotensin system (RAS inhibitor), including an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI) and a beta-blocker (BB), for at least 3 months prior to the Baseline Visit.

b) Other medications recommended for selected populations, e.g., a mineralocorticoid receptor antagonist (MRA) or nitrates/hydralazine, should be used in appropriate patients, according to the published guidelines.

c) Patient has been on stable medications optimized to the patient's tolerance of ACE or ARB or ARNI and MRA, if indicated, as determined by the investigator, for at least 1 month and BB for at least 3 months. Stable is defined as no more than a 100% increase or 50% decrease in dose within these periods.

d) Drug intolerance, contraindications, or lack of indications must be attested to by the investigator. Patients should be on appropriate doses of diuretics as required for volume control.

4) Receiving Class I recommended cardiac rhythm management device therapy. Specifically: if indicated by class I guidelines, cardiac resynchronization therapy (CRT), an implanted cardioverter-defibrillator (ICD) or a pacemaker should be implanted at least 3 months prior to enrollment. These criteria may be waived if a patient is clinically contraindicated for these therapies or refuses them and must be attested to by the investigator.

5) Has a minimum of:

a) One (1) prior Heart Failure Hospitalization with duration >24 hours or Emergency Room Heart Failure Visit with duration >6 hours, within the last 12 months.

b) If a CRT device was previously implanted, the heart failure hospitalization must be ≥ 1 month after CRT implantation.

c) Alternatively, if patients have not had a HF hospitalization or ER HF Visit within the prior 12 months, they must have a corrected elevated Brain Natriuretic Peptide (BNP) level of at least 300 pg/ml or an N-terminal pro-BNP (NT-proBNP) level of at least 1,500 pg/ml, according to local measurement, within 3 months of the Baseline Visit. (Note: "corrected" refers to a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m^2 in BMI above a reference BMI of 20 kg/m^2). If patient is on ARNI, NT-proBNP should be used exclusively.

6) Able to perform the 6-minute walk test with a distance ≥100 meters and ≤450 meters. The test will be performed twice separated by a minimum of 60 minutes between tests. The second test may be performed up to 7 days after the first test, if needed. The higher reading shall be used as the baseline value.

7) Provide written informed consent for study participation and be willing and able to comply with the required tests, treatment instructions and follow-up visits.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

5.2.1 PRELIMINARY EXCLUSION CRITERIA (PEC)

1) Age <18 years old.

2) BMI >40 or <18 kg/m^2.

3) Females of childbearing age who are not on contraceptives or surgically sterile, pregnant or lactating mothers.

4) Resting systolic blood pressure <90 or >160 mmHg after repeated measurements.

5) Baseline echocardiographic evidence of unresolved, non-organized or mobile intracardiac thrombus.

6) Severe pulmonary hypertension defined as PA systolic pressure >70 mmHg by echo/Doppler (or PVR >4.0 Wood Units by PA catheter measurement that cannot be reduced to ≤4 Wood Units by vasodilator therapy).

7) RV dysfunction defined as TAPSE <12mm or RVFAC ≤30%.

8) Left Ventricular End-Diastolic Diameter (LVEDD) >8cm.

9) Atrial septal defect (congenital or iatrogenic), patent foramen ovale, or anomalous pulmonary venous return, with more than trace shunting on color Doppler or intravenous saline contrast (bubble study) or prior surgical or interventional correction of congenital heart disease involving the atrial septum (excluding closure by suture only but including placement of a PFO or ASD closure device).

10) Untreated moderate to severe aortic or mitral stenosis.

11) Untreated severe (3+ to 4+) regurgitant valve lesions, which are anticipated to require surgical or percutaneous intervention within 12 months.

12) Untreated coronary stenosis which requires surgical or percutaneous intervention.

13) Acute MI, acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), rhythm management system revision, lead extraction, or cardiac or other major surgery within 3 months.

14) Active valvular vegetations, atrial myxoma, hypertrophic cardiomyopathy with significant resting or provoked subaortic gradient, acute myocarditis, tamponade, or large pericardial effusion, constrictive pericarditis, infiltrative cardiomyopathy (including cardiac sarcoidosis, amyloidosis, and hemochromatosis), or congenital heart disease, as cause of HF.

15) Stroke, transient ischemic attack (TIA), systemic or pulmonary thromboembolism, or deep vein thrombosis (DVT) within the last 6 months. Any prior stroke with permanent neurologic deficit. Any IVC filter.

16) Transseptal procedure for another indication (e.g. AF ablation, left atrial appendage occlusion, mitral valve repair/replacement) anticipated within 6 months.

17) Bradycardia with heart rate <45 bpm (unless treated with a permanent pacemaker) or uncontrolled tachyarrhythmias. This includes defibrillation shocks reported by the patient within the last 30 days.

18) Intractable HF with:

    a) Resting symptoms despite maximal medical therapy (ACC/AHA HF Stage D).

    b) Treatment with IV vasoactive medications (e.g., IV inotropes, IV vasodilators) within the last 30 days.

    c) Cardiac Index <1.5 L/min/m^2.

    d) Treated with a ventricular assist device (VAD).

    e) Listed for cardiac transplantation.

19) Prior cardiac transplantation.

20) Patients with HFrEF (LVEF ≤40%) who are intolerant to a RAS inhibitor including all of ACEI, ARB or ARNI, and intolerant to beta-blocker medical therapy.

21) Not eligible for emergency cardiothoracic or vascular surgery in the event of cardiac perforation or other serious complication during study intervention procedure.

22) Life expectancy <1 year due to non-cardiovascular illness.

23) Coagulopathy or is taking anticoagulation therapy which cannot be interrupted for the study intervention procedure, or has contraindications for heparin or for all of the study-mandated post implantation anticoagulation / antiplatelet regimens.

24) Estimated glomerular filtration rate (eGFR) <25 ml/min/1.73 m^2 by the MDRD method, or not responsive to diuretics, or is receiving dialysis.

25) Hepatic impairment with at least one liver function test (transaminases, total bilirubin, or alkaline phosphatase) ≥ 3 times upper limit of normal.

26) Severe chronic pulmonary disease requiring daytime home oxygen or chronic oral steroid therapy (Note: nighttime oxygen therapy and inhaled steroid therapy are acceptable).

27) Active infection requiring parenteral or oral antibiotics.

28) Known or suspected allergy to nickel.

29) Any condition that may interfere with compliance of all protocol procedures, such as history of active drug addiction, active alcohol abuse, or psychiatric hospital admission for psychosis within the prior year.

30) Currently participating in a clinical trial of any investigational drug or device that has not reached its primary endpoint, or any study that may interfere with the procedures or endpoints of this trial. Participation in an observational study or registry with market approved drugs or devices would not exclude a patient from participation in this trial.

31) Patient is otherwise not appropriate for the study as determined by the investigator or the Eligibility Committee, for which the reasons must be documented.

32) Patient belongs to a vulnerable population per investigator's judgment or patient has any kind of disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures.

5.2.2 FINAL EXCLUSION CRITERIA (FEC) ASSESSED DURING CARDIAC CATHETERIZATION, AT STUDY INTERVENTION VISIT, JUST PRIOR TO RANDOMIZATION

The FEC serves two important purposes: 1) to exclude patients with anatomy or physiology less suitable for interatrial shunt implantation; and 2) to exclude clinically and hemodynamically unstable patients.

1) Change in clinical status between baseline screening and Study Intervention visit that would no longer meet all of the inclusion/exclusion criteria.

2) Females with a positive pregnancy test on laboratory testing for FEC.

3) Unable to undergo TEE or ICE.

4) Unable to tolerate or cooperate with general anesthesia or conscious sedation.

5) Anatomical anomaly on TEE or ICE that precludes implantation of Shunt across fossa ovalis (FO) of the interatrial septum including:

   a) Minimal FO Thickness >3mm.

   b) Minimal FO Length <10mm.

   c) ASD or PFO with more than a trace amount of shunting.

   d) Intracardiac thrombus felt to be acute and not present on prior exams.

   e) Atrial Septal Aneurysm defined as ≥ 10 mm of phasic septal excursion either into either atrium or a sum total excursion of ≥ 15 mm during the cardiorespiratory cycle, with a base of ≥ 15 mm.

6) Inadequate vascular access for implantation of Shunt. Femoral venous or inferior vena cava (IVC) access for transseptal catheterization are not patent as demonstrated by failure to pass Swan-Ganz or ICE catheter from the right or left femoral vein to the right atrium.

7) Hemodynamic, heart rhythm, or respiratory instability at time of cardiac catheterization including:

   a) Mean PCWP <7 mmHg, not correctable by IV volume infusion (maximum 1,000 ml normal saline or equivalent).

   b) Mean PCWP >35 mmHg, not correctable by medical therapy (e.g. IV Furosemide, IV or sublingual nitroglycerin).

   c) Right Atrial Pressure (RAP) ≥ Left Atrial Pressure (LAP or PCWP) when LAP (PCWP) ≥7 mmHg.

   d) Cardiac Index (CI) <1.5 liters/min/m^2 after correction of volume depletion with IV fluids (maximum 1,000 ml normal saline or equivalent).

   e) Severe pulmonary hypertension defined as PASP >70 mmHg.

   f) PVR >4.0 Wood Units that cannot be reduced to ≤4 Wood Units by vasodilator therapy.

   g) Resting systolic Blood Pressure <90 or >160 mmHg, not corrected with IV fluid administration or vasodilators, respectively.

   h) Need for IV vasopressor or inotropic medication.

   i) Malignant arrhythmias such as ventricular fibrillation, ventricular tachycardia, atrial fibrillation/flutter with rapid ventricular response associated with hypotension and requiring cardioversion.

   j) Acute respiratory distress or hypoxemia.

8) Patient is otherwise not appropriate for study as determined by the Investigator.

Note: Patients excluded for any of the FEC criteria related to clinical or hemodynamic stability may be considered for repeat screening at a later date once the Investigator has determined the cause of the instability and patient has been shown to return to baseline stable status (see Section 5.3).

5.3 SCREEN FAILURES

Screen failures are defined as patients who sign informed consent to participate in the clinical trial but do not meet all inclusion/exclusion criteria. All AEs that occur after patient consent and before study enrollment will be reported and adjudicated for their relationship to study procedures.

All potential study patients will be tracked at each site with a *Site Screening Log*. The log documents each patient's study eligibility based on the 3-part screening process described in Section 4.1. The

reasons for non-eligibility will be documented. The log also informs the level of screening effort at each site and that consecutively eligible patients are enrolled.

Patients that fail screening may be re-screened after 30 days if the Investigators and the Sponsor agree (documented in writing). Rescreened participants should be assigned the same participant number as for the initial screening.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Please refer to the detailed Recruitment Plan in the manual of operations (MOP). In summary, the trial is expected to enroll approximately 100 patients in the Roll-in arm (maximum of 180 patients) and approximately 400 patients in the Randomized arms. The total number of randomized patients may be further increased to approximately 600 patients after a single interim analysis.

The target population includes adult male and female patients irrespective of age, race, and ethnicity. It is recognized that female patients have been traditionally underrepresented in HF trials for a variety of reasons. Similarly, minority populations have been under-represented in prior HF trials. To enhance enrollment of underrepresented groups this study plans to:

- Where appropriate, target investigational sites where recruitment of needed populations can be more easily facilitated (hospitals with women's clinics, urban facilities).
- Have tailored communication strategies for study recruitment including social media outreach.
- Have physician investigators involved in recruiting patients.
- Have flexibility in follow-up visit schedules including provision for transportation or elder care services during appointments.
- Perform periodic evaluation of Site Screening Logs to understand reasons for screen failures.

The study is anticipated to include up to 60 centers in the United States and other countries with a majority of sites located in the US. The anticipated accrual rate is approximately 0.6 patients per site per month. Sources for participant patients are expected to include inpatients, outpatient Heart Failure Clinics, and local community outreach programs. Patients will be approached by investigational site personnel only. Social media, patient advocacy groups or advertising may be used to attract potential patients to make inquiries at local sites or be approached by individual sites.

6 STUDY INTERVENTION

6.1 STUDY DEVICE

6.1.1 V-WAVE INTERATRIAL SHUNT SYSTEM INTENDED USE AND INDICATIONS FOR USE

The V-Wave Shunt System consists of the V-Wave Shunt and the V-Wave Delivery System. The V-Wave Shunt is a permanent implant, which is designed to enable shunting of blood from the left to the right

atrium and by that, improve symptoms in NYHA Class III and ambulatory Class IV heart failure patients with reduced or preserved left ventricular systolic function.

6.1.2 V-WAVE INTERATRIAL SHUNT SYSTEM

The V-Wave Interatrial Shunt System consists of two major components; (1) V-Wave Interatrial Shunt, Part Number 51140125 and (2) V-Wave Delivery System, Part Number 85014155. The Delivery System is introduced into the body through a 14-15 Fr inner diameter Delivery Sheath placed in the left atrium following a standard femoral venous access transseptal cardiac catheterization procedure.

The V-Wave Shunt is a permanent implant, which is designed to shunt blood from the left to right atrium thereby, improving symptoms in patients with advanced chronic heart failure. It is constructed on an hourglass-shaped, self-expanding Nitinol frame, with ePTFE encapsulation to block tissue ingrowth. The Shunt is implanted across the fossa ovalis of the interatrial septum. Once implanted, it protrudes into the left and right atria, with a total length of ~12mm. The external diameter at the right and left atrial ends are ~11 mm and ~14 mm, respectively. The implant is designed for single-use, and is sterilized using ethylene oxide.

The V-Wave Delivery System includes a Delivery Catheter and Loading Tools. The Loading Tools are used to compress the shunt for attachment to the distal end of the Delivery Catheter and for loading the Shunt/Catheter into the Delivery Sheath. The Delivery Sheath is a commercially available Cook Medical (Bloomington, IN) 14 Fr Mullins Introducer Sheath (Part Number RCFW-14.0-38-85-RB). The Delivery Catheter includes a handle to control the release of the Shunt, a flushing port and a safety clip to prevent unintended release of the Shunt. Detailed instructions for loading and implanting the Shunt with its dedicated Delivery System are included in the IFU.

6.1.3 SUMMARY OF NECESSARY TRAINING, EXPERIENCE AND FACILITIES NEEDED TO USE THE INVESTIGATIONAL DEVICE

Sites will be selected that have multidisciplinary HF teams and at least two physician expert investigators who are experienced in participating in randomized trials. Each site will include at least one cardiologist with expertise in the diagnosis and medical management of patients with severe HF (*HF-Investigators*) and at least one implanting physician (*Implanter-Investigators*). Implanting physicians may be interventional cardiologists highly experienced in ultrasound-guided transseptal catheterization and structural heart disease therapeutic procedures such as MitraClip mitral valve repair or left atrial appendage occlusion; or they may be electrophysiologists with similar transseptal experience who are skilled at AF ablation by pulmonary vein isolation. On-site cardiac surgery must be available. One of these physician investigators will be designated the Primary Investigator for each site.

All Investigators and trial personnel are required to attend Sponsor training sessions. Training of trial personnel will include the clinical investigation plan and its requirements, investigational device usage, case report form (CRF) completion and trial personnel responsibilities. All Investigators must be trained to the clinical investigation plan and trial procedures prior to consenting and enrolling patients.

Investigators will be specifically trained in the selection of patients for participation. The (*Implanter-Investigator*) will be trained in the proper use of the V-Wave Interatrial Shunt System, first on a bench-top model and then proctored during the first Roll-in cases per the protocol requirements.

6.1.4 PROCTORING

The RELIEVE-HF Study involves the use of new device implantation techniques and post implantation patient management. As such, resources must be available to sites for proctoring device implantation and sharing experience. The Sponsor will assign each site an experienced proctor for each V-Wave Interatrial Shunt implantation during Roll-in cases. The proctor may be an employee of the Sponsor or another investigator. A proctor will be present at implantations for each new implanting physician to assure adequate training and compliance with the protocol and the *Implant Guidelines* (refer to the MOP) until both the Sponsor and implanting physician feel it is no longer necessary. The proctor is asked to observe and advise but not to participate in the procedure in a hands-on fashion. Sites are encouraged to consult their proctor or other knowledgeable implanter with questions or concerns prior to, during, or after device implantations. Satisfactory completion of proctoring is certified by the proctor. This typically requires 1-2 implantation procedures, but no more than 3 cases. If a proctor has not certified an Implanter after 3 cases, a plan to either drop the site or Implanter, or add additional proctoring cases must be agreed to in written communications between the Investigators and the Sponsor.

6.2 PREPARATION/HANDLING/STORAGE/ ACCOUNTABILITY

6.2.1 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

The Sponsor must maintain device accountability, documenting all shipments and returns of investigational devices. Each device is traceable using the lot or serial numbers that is affixed to the device label.

Investigational product will be shipped only after site activation and shipping authorization is complete. The Sponsor will only ship the V-Wave Shunt and Delivery System to the site's *Primary-Investigator* (or designee). Storage locations for the devices at investigational sites will be locked with access restricted to investigators and authorized study personnel only. Alternatively, depending on individual site logistics, a Sponsor representative may hand-deliver devices to the sites as needed for case performance.

The Principal Investigator or an authorized designee must maintain records on the *Device Inventory Log* of the date of receipt, the identification of each investigational device (batch number, serial number or unique code), identification of participant receiving the device, the date of use, expiration date and final disposition. The *Implanter-Investigator* will also maintain adequate records on case report forms (CRFs), including date implanted, patient identification number and implanting Investigator.

Upon study enrollment completion, the *Primary-Investigators* at each site will be notified. All unused V-Wave products must be returned to the Sponsor when enrollment is complete according to the returned goods process. All V-Wave products or any remaining components that are associated with a device malfunction must be returned to the Sponsor.

The *Inventory Accountability Report* generated by the Sponsor must document the disposition of all investigational devices including those that have been returned to the Sponsor.

Use of any investigational device outside of the clinical investigation plan (e.g. compassionate use) is strictly forbidden and may constitute grounds for removal of the Investigator/Site from the trial.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All potentially eligible patients at approximately 75 sites will be approached for participation in the study. Baseline screening data from consented patients will be reviewed by the Eligibility Committee to ensure that inclusion/exclusion criteria are met. These measures will help minimize patient selection bias and assure that a breadth of patient demographic characteristics will be included in the study. In addition, these practices optimize the chances that trial inclusion/exclusion criteria are strictly adhered to and create a cadre of multiple heart failure specialists and implanter investigators who can critically evaluate their experience with interatrial shunting in general and the V-Wave System in particular.

6.3.1 RANDOMIZATION

Once a site has successfully completed Roll-in cases, the Sponsor will notify the site to begin the Randomized Access phase of the study. Patients who are eligible based on meeting Inclusion Criteria and Preliminary Exclusion Criteria during outpatient screening and after approval by the Eligibility Committee, will undergo cardiac catheterization and TEE or ICE for evaluation of the FEC. Randomization will occur if the right heart catheterization and the TEE or ICE demonstrate that the patient has no Final Exclusion Criteria as determined by the *Implanter-Investigator*. If necessary, randomization and the index procedure may be delayed for up to 24 hours for patient safety, but the reasons must be documented. In this situation, the patient may remain hospitalized until randomized.

Patient randomization will be via an automated interactive system, which will require entry of the site's ID, and the patient's participant number. The system will have knowledge of the site and the patient's LVEF as determined by the Echo Core Lab for stratification purposes. After data are verified, a randomization code will be given and recorded by the Site in a Site Randomization Log, which will be kept by the *Implanter-Investigator* or unblinded designate and kept separate from other study documents until the patient has been unblinded. Randomization will be 1:1 to the Shunt or the Control group. Unblinded cross-over of Control patients to receive a Shunt is allowed when the patient completes the Randomized Access period (at 24 months or when the last patient enrolled reaches 12 months of follow-up).

6.3.2 BLINDING PROCEDURES

RELIEVE-HF will be a double-blinded study with the patient and the physicians and research staff managing the patients after the Randomization/Study Intervention Procedure, including all those involved in conducting post-randomization evaluations or treatment decisions will be blinded to study assignment. Personnel at the site who will be unblinded include the implanting physician, research staff present during the implant procedure and the study pharmacist (responsible for maintaining and dispensing the study provided antiplatelet or placebo medications).

At the time of randomization in the Cath Lab, any staff members present who are designated as blinded personnel will be instructed to leave the area. The *Implanter-Investigator* will be the responsible local authority throughout the trial for maintaining the blind and managing the blinding procedures of the *HF-Investigator* and blinded research staff. The *Study Pharmacist*, will also be unblinded and be responsible for administering the medications or placebos in the study. Selected members of the echocardiography department will similarly have to be unblinded.

Patient blinding begins in the Cath Lab with general anesthesia or sedation. Patients who receive sedation for the procedure will be provided earphones to wear with music playing to preclude hearing procedural discussions. A blindfold or other shielding may be used to prevent the patient from viewing the imaging screens during the procedure

Patients randomized to the Control arm will not undergo transseptal catheterization and Shunt placement. The *Implanter-Investigator* will perform a mock transseptal catheterization and device placement from a script provided in the manual of operations. After approximately 15 minutes have passed, the echo probes and right heart catheter will be removed, and the skin incisions closed. Treatment and Control patients may transition from general anesthesia to conscious sedation during the study intervention procedure as soon the indication for general anesthesia no longer exists.

At the completion of the intervention procedure, the *Implanter-Investigator* will read a script to the patient, informing them that they qualified for the study, that they were treated according to their randomization assignment, and they will remain unaware of whether they received the Study Device or were a Control, until the end of the Randomized Access phase of the study. All Site personnel who have knowledge of the patient study assignment will be instructed to maintain blinding of study assignment to patient, treating clinicians and blinded research staff. Randomization assignment should not be recorded in the patient medical record. All hospital notes should state that the patient was enrolled in the RELIEVE-HF Trial only, that it is a blinded trial of an implanted interatrial shunt device and not include information regarding whether a shunt was implanted.

The managing *HF-Investigator* and blinded research staff that have patient contact after the intervention procedure will be blinded to the patient's randomization assignment. They will remain blinded until the completion of each patient’s Randomized Access phase of the study. This is to ensure that all patients have equal interactions with study personnel and procedures and be maintained on GDMT throughout the study.

Blinded research staff will perform in-clinic follow-up visits at 1, 3, 6, 12, 18, and 24 months and telephone contact visits at 2 weeks and 9, 15, and 21 months. Only a blinded staff member should perform study evaluations including:

- 6MWT
- KCCQ, EQ-5D
- NYHA classification
- Physical Exam (including those related to assessments for potential LVAD use or heart transplant)

The unblinded staff members are responsible from preventing patient and blinded staff members from observing imaging screens during imaging studies or image review sessions.

To determine the effectiveness of blinding procedures, patients will be asked to complete a *Blinding Questionnaire* shortly after their study intervention procedure and at 1 year to determine if they had knowledge or belief of their randomized group assignment. All Staff will complete a *Blinding Log* and if they become unblinded to an individual patient they must be replaced with another blinded staff member for subsequent interactions with that patient.

All hospital notes, office notes, letters to referring physicians, procedure notes, billing information, and other related patient information must refer to the assigned treatment as “study procedure” or other non-revealing language, to maintain the blind.

All request for unblinding before the scheduled date of unblinding must be submitted in writing by a treating physician to the study sponsor. The request will be evaluated by the Chief Medical Officer or designee to determine if unblinding is justified to ensure patient safety.

Individual patient study assignment will be known to Sponsor’s Field Engineers supporting the study intervention procedures, the Field Monitors and the in-house personnel required to evaluate possible device-related safety events and report them to FDA and other required authorities. To further minimize the potential for bias, Field Clinical Engineers and/or Field Monitors shall not have communication with any patient once enrolled in the study. Any questions or comments received from patients should be referred to site personnel. In addition, Field Clinical Engineers and/or Field Monitors shall have no contact with site personnel while they are conducting study-related activities involving Randomized patients (e.g. when a patient is performing a 6MWT).

Sponsor personnel and the trial Executive and Steering Committees will be blinded to all Randomized Access Phase combined and individual assignment group outcome measures, until the time of primary-endpoint unblinding and database lock is complete. This does not include baseline demographics for the combined randomized cohort or recommendations from the DSMB regarding the interim analysis.

To further minimize bias, the CEC will be blinded to patient, site, and operator when performing SAE and endpoint adjudications. CEC may subsequently become unblinded for specific adjudications where knowledge of procedures performed is required. The echocardiographic core laboratory cannot be

blinded to individual patient study assignment. The Independent Statistician(s) will generate blinded tables for review as requested by the DSMB to evaluate safety and for the planned interim analysis.

6.3.3 ASSESSMENT OF BLINDING AND PERCEPTION BIAS

Patients' perception as to whether they received the control or test device may affect the outcomes of the study. As described throughout the protocol, comprehensive efforts will be undertaken to maintain patient blinding. Nonetheless, for a variety of reasons patients may develop a belief as to the Randomization Group they were assigned, even if the blind is maintained.

To assess blinding and any potential perception bias on the endpoints of the study, information will be collected in a brief patient blinding and perception assessment questionnaire administered by the research coordinator post-procedure in the hospital prior to discharge (≥ 4 hours to ≤7 days after the procedure) and at 1 year. Subjects will be asked for their perception of what treatment they believe they might have received, and the basis of this perception (see MOP for the questionnaire). Analysis of the primary and secondary effectiveness endpoints will be performed in subgroups according to the results of this survey.

6.3.4 ECHOCARDIOGRAPHY CORE LABORATORY

Echocardiographic imaging, whether transthoracic (TTE), transesophageal (TEE) or intracardiac (ICE) will provide essential data to evaluate cardiac structure and function before and after interatrial shunting (as well as changes over time in the control group) and to examine the function of the shunt itself. To enhance the accuracy of study results, an independent core laboratory will be assigned to evaluate all echo imaging studies performed during the study. The Echocardiography Core Laboratory will:

- Develop an *Echo Core-Lab Manual* to be included in the MOP.
- Certify each site prior to first enrollment.
- Provide echo-based Inclusion/Exclusion parameters to sites and *Eligibility Committee*.
- Analyze all echocardiographic data per the Echo Core-Lab Manual.
- Provide quality assurance.
- Provide information technology services, image management - digitization, transfer, storage and summary data management.
- Consult with and provide services to the study Executive Committee, as necessary.

6.4 STUDY INTERVENTION COMPLIANCE

The V-Wave Interatrial Shunt is a passive device that shunts blood between the atria in relation to the pressure gradient across the device. To use the device requires no action by the patient other than to take their daily prescribed adjunct anticoagulant/antiplatelet therapy described in Section 6.5. Medication compliance will be clinically assessed at each study visit through questioning by research staff. Non-compliance with study medications will be noted in the CRF and standard clinical means

including patient education, administration of medications by a caregiver, pill counts, etc., will be instituted by the site on an as needed basis. See MOP for further details.

6.5 CONCOMITANT THERAPY

All patients should continue to receive medical therapy for heart failure. Prior to enrollment the central eligibility committee will confirm that all patients eligible for enrollment are on GDMT. After randomization and during the follow-up phase of the study the types and doses of HF medications should not be changed, unless required for clinical or symptomatic changes or side effects. Any changes in dose or medication type will be documented in the Case Report Form.

Patients with HFrEF should be:

a) Maintained on tolerated doses of an inhibitor of the renin-angiotensin system either an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI)) and a beta-blocker (BB). Doses should be adjusted per published guidelines and clinical conditions. Such changes will be documented in the Case Report Form.

b) Other medications recommended for selected populations, e.g., a mineralocorticoid receptor antagonist (MRA) or nitrates/hydralazine, should be used in appropriate patients, according to the published guidelines.

c) Diuretics should be used to relieve symptoms due to volume overload.

d) Receive any cardiovascular devices (e.g. pacemaker, cardiac resynchronization therapy, implantable defibrillator) for which they develop a class I indication.

e) Drug intolerance, new contraindications or other reason for changes in drug dose should be attested to by the investigator in the CRFs.

GDMT for patients with HFpEF generally includes:

a) Systolic and diastolic blood pressure should be controlled in accordance with current clinical practice guidelines.

b) Patients with atrial fibrillation should have adequate rate control

Diuretics should be used to relieve symptoms due to volume overload in both HFrEF and HFpEF patients. All medications including doses and dose changes will be recorded in the *Medication Log* at the time of baseline and follow-up visits.

Additionally, for all patients:

Due to the creation of an artificial interatrial shunt, there is the possibility of right-to-left (paradoxical) embolization of thromboemboli, fat, and air emboli. These events are anticipated to be rare. They may

however be more likely if or when the normally present left-to-right interatrial pressure gradient is reversed. The most likely situations for this to occur are straining with stool, strong coughing and purposefully Valsalva maneuvers in the presence of occult right-sided emboli. Therefore, consideration should be given to prudent general medical measures to prevent constipation, use of antitussives during upper respiratory illness, prevention of deep venous thrombosis, prevention of air injection in intravenous lines, and careful observation after falls or fractures.

6.5.1 REQUIRED ANTIPLATELET/ANTICOAGULATION AND OTHER MEDICATIONS

A. Implantation. During the Implant of the Shunt, patients should be anticoagulated with unfractionated heparin per institutional standard of care to maintain the ACT >250. Other anticoagulants are not permitted to be utilized in this protocol.

B. Chronic Therapy. All patient who receive a shunt must be treated with a 6-month course of either 1) aspirin (≥75 mg daily) and a P2Y12 inhibitor (clopidogrel, ticagrelor or prasugrel at clinically indicated doses), or 2) warfarin or a direct acting oral anticoagulant (dabigatran, apixaban, rivaroxaban or edoxaban or other approved agent at clinically indicated doses). Patients who are already receiving one of these regimens for a clinical indication unrelated to the shunt implant (e.g. prior stent or atrial fibrillation) should remain on their medications as clinically indicated. Patients who are not on either of these regimens will be treated with dual antiplatelet therapy. Control patients should remain on any clinically indicated antiplatelet/anticoagulant agents.

To maintain patient and study site personnel blinding all patients (regardless of treatment assignment) who are not on an antiplatelet/anticoagulant for a clinical indication will be provided study medications. Clopidogrel 75mg and Placebo clopidogrel 75mg will be provided to the site for maintenance and management by a site pharmacist. Aspirin 75-100 mg will be provided to patients by sites.

The clopidogrel provided by sponsor to all participating sites, including US and International sites, will be commercially available clopidogrel sourced in the US (Clopidogrel Bisulfate 75 mg tablets, Teva Pharmaceuticals USA, Inc., NDC 0093-7314-98). A matching placebo, manufactured under GMP in the US (Sharp Clinical Services, Inc.) will be provided. Both clopidogrel and placebo will be properly labeled to maintain the blinding.

Specific study required medications for all patients are shown in **Table 6**:

Table 6. Study Required Medications

Medication	Patients	Pre-Index Procedure	Post-Procedure
Oral anticoagulant	Those taking Warfarin, Warfarin analogue or NOAC	Holding dose per institutional standard of care	Continue oral anticoagulant at dose indicated by pre-existing condition.
Dual Agent Antiplatelet Therapy (DAPT)	All others	Loading/holding of P2Y12 inhibitor*/ aspirin per institutional standard of care with transseptal procedure	**Treatment Arm:** Continue P2Y12 inhibitor* already in use for 6 months or longer if clinically indicated, otherwise, clopidogrel 75 mg daily for 6 months. All Treatment Arm patients should be on aspirin 75-100 mg daily indefinitely. **Control Arm:** Continue P2Y12 inhibitor* already in use for 6 months or longer if clinically indicated, otherwise, Placebo for clopidogrel for 6 months. All Control Arm patients should be on aspirin 75-100 mg daily for duration of blinding.

*P2Y12 inhibitors include clopidogrel, ticagrelor and prasugrel.

If during the course of therapy patient develops a contraindication to their anticoagulation/antiplatelet regimen, manage per local standards and consult with Sponsor's Medical Director regarding alternative regimens.

C. Endocarditis prophylaxis. All patients should receive infective endocarditis prophylaxis as per institutional standards for a permanently implanted device for coverage of the Study Intervention Procedure. Endocarditis prophylaxis is specifically indicated before dental procedures with manipulation of gingival tissue, periapical region of teeth or perforation of oral mucosa or other procedures with high risk of bacterial seeding for a duration of six months after randomization in all Treatment and Control patients. Choice of drug and dosage are per institutional standards.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Each enrolled patient should agree at the time of consent to remain in the study until completion of the 5-year follow-up period. However, a patient's participation in any clinical trial is voluntary and the patient has the right to withdraw at any time without penalty or loss of benefit. Withdrawal is defined as termination of participation of a patient from a clinical trial. Reasonable efforts should be made to retain the patient in the clinical trial until completion of the clinical trial. Reasons for withdrawal include, but are not limited to the following:

- Withdrawal of informed consent by patient or family request (if patient unable to communicate their preference). No reason for withdrawal need be given.
- If any adverse event whether anticipated or not, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would, in the opinion of the Investigator, endanger the patient if study treatment were to continue.
- Disease progression which requires discontinuation of the study intervention (e.g. heart transplant). Patients treated with a VAD should continue to be followed in the trial but will be censored from all study endpoints from date of VAD hospitalization.
- Non-compliance with the clinical investigation procedures or study protocol deemed by the Investigator to be sufficient to impact patient outcomes
- Lost to follow-up (as defined in Section 7.2)
- Patient death

The reason for participant discontinuation or withdrawal from the study will be recorded on the appropriate Case Report Form (CRF). Patients who sign the informed consent form but are not randomized may be replaced. Patients who sign the informed consent form, and are randomized (regardless of treatment assignment), and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

Patients who do not want to continue clinical follow up visits will be asked if they will continue to permit: 1) telephone follow up 2) medical record follow up 3) vital status follow up.

Withdrawn patients will be followed according to the standard of care existing at their care facilities.

7.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for three contiguous study scheduled contacts (in-clinic or telephonic) and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant as below:
  - 2 documented telephone calls
  - a certified letter to the participant's last known mailing address with return receipt documented (or local equivalent methods).
- After the above steps are taken, the patient will be considered withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 STUDY ASSESSMENTS: EFFECTIVENESS AND SAFETY

8.1.1 SCREENING / BASELINE VIST

Once informed consent has been obtained and documented with a signed and dated Informed Consent Form, screening procedures may begin.

The following activities are performed as part of the screening process:

- **Obtain Patient Informed Consent.** A copy of the informed consent must be retained in the patient medical record and study file.
- **Demographics and Medical History:** Includes age, sex, etiological factors for HF, all hospitalizations and Emergency Department visits during the prior 12 months, relevant co-morbidities, previous cardio-pulmonary procedures/surgeries.
- **Vital Signs and Physical Examination**: includes height, weight, blood pressure, temperature, pulse oximetry, heart rate and rhythm, and cardiovascular focused physical examination for assessing heart failure and performing study intervention procedure.
- **Medications**
- **Laboratory Tests:** to include Na, K, HGB, HCT, PLTS, WBC, Cr, BUN, AST, ALT, T Bili, BNP or NT-pro BNP.
- **12-Lead ECG**
- **Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE)** with color Doppler, tissue Doppler, and optional 3D assessment of atrial septum. Elements per Core Laboratory Manual.
- **NYHA Functional Class and Patient Self-Assessment**
- **KCCQ and EQ-5D Quality of Life assessments**
- **6MWT:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Inclusion/ Preliminary Exclusion Criteria (PEC) Review**
- **Complete CRFs**

Patients who do not meet all the inclusion criteria or who meet any of the exclusion criteria will be considered screening failures; however, patients may be re-screened after 30 days if the *HF-Investigator* and the Sponsor agree that he/she has a reasonable likelihood to subsequently become eligible (see Section 5.3). A *Screening/Baseline CRF* will be completed for all screened patients and submitted to the Sponsor. The *Screening/Baseline CRF* and the *Screening Log* will indicate the inclusion/exclusion criteria that were not met.

8.1.2 FINAL SCREENING / STUDY INTERVENTION VISIT

Once the investigator has reviewed the baseline screening information and has determined that the patient meets the Inclusion and without Exclusion criteria, the information from the baseline visit will be submitted to the *Eligibility Committee.* The baseline TTE will be read by the Echo Core Lab and the pertinent results passed on to the *Eligibility Committee*. The *Eligibility Committee* will review the records to assure eligibility for the final screening phase. If clarifications are required, the site will be contacted by the Sponsor for the required information. Once approved by the Eligibility Committee, the Sponsor will notify the site and the Final Screening/Study Intervention Visit should be scheduled within 45 days of the baseline visit.

CAUTION: To assure the patient's wellbeing during the *Final Screening/Study Intervention Visit,* it is critical that the Investigator has determined and is satisfied that the patient is clinically compensated prior to that visit. If not, the patient should be medically stabilized prior to scheduling the Final Screening/Intervention Visit. This can reduce the risk of study-related complications or the need to cancel procedures. This includes a physical examination with a careful assessment of volume status with consideration of diuresis prior to the procedure, or consultation with an anesthesiologist if patient has orthopnea or sleep disordered breathing. Chronic oral anticoagulation should be discontinued prior to the Study Intervention Visit per the site's standard of care.

Note: If after Eligibility Committee approval but before cardiac catheterization and randomization a major change is required in HF study medications (either increase in dose by >100%, reduction in dose by >50%, or introduction of a new study medication (RAS inhibitor, beta-blocker or MRA), or the patient receives a new ICD or CRT device, the patient should be stabilized for >30 days and presented again to the Eligibility Committee for de novo consideration after this time. However, the procedure does not need to be delayed for changing diuretic doses of other HF medications not mentioned in this paragraph, as long as the patient is clinically stabilized.

8.1.2.1 FINAL ELIGIBILITY DETERMINATION

Final eligibility is determined in the Cardiac Catheterization Laboratory from the right heart catheterization and ICE or TEE measurements. The Implanting Physician will determine if the patient meets the Final Exclusion Criteria (FEC). After confirmation that the patient does not have any FEC, the randomization will proceed. **The patient will be considered enrolled in the study when the patient is randomized after confirmation by the *Implanting-Investigator* to have none of the FEC**.

Patients will be evaluated when presenting for the Study Intervention Visit. The following assessments will be performed prior to the Intervention Procedure, During and Post Procedure:

- **Vital Signs and Physical Examination**: includes weight, temperature, blood pressure, pulse oximetry, heart rate and rhythm, and focused cardiovascular physical examination pertinent to heart failure and study intervention procedure.
- **Medication review**: Include chronic cardiac, pulmonary and antiplatelet/anticoagulants and all medications taken during last 72 hours.
- **Blood tests:** PT, PTT, INR, Hgb, HCT, Cr and Pregnancy-urine or blood (if applicable).
- **Intracardiac or Transesophageal echocardiogram/Doppler examination (ICE/TEE):**

Elements per Core Laboratory Manual.

- **Right Heart Catheterization (RHC):** Per RHC manual conducted at the beginning of the procedure in both Treatment and Control patients.
- **Assessment of AEs** that occurred during implantation and all hospitalizations and Emergency Department visits since the Baseline visit.
- **Cost Effectiveness**
- **Complete CRFs**

During the Randomized Access phase, once the patient is placed on the cardiac catheterization table, strict blinding procedures must be followed and maintained until the patient has reached the designated time for unblinding. Please see Section 6.3.2 detailing blinding procedures.

TEE or ICE must be used for confirming the FECs and guiding the implantation procedure. If TEE is used, general anesthesia administered by a dedicated anesthesiologist or equivalent is required. ICE can be performed under conscious sedation as required for patient comfort when patient cooperation is expected.

Participants who have one or more FEC will be considered a screening failure and will not be randomized. These patients may remain in the hospital overnight for observation at the investigator's discretion. They will be followed for 30 days to determine if there are procedure-related adverse events. They may be considered for rescreening after 30 days if the Investigator and Sponsor agree (see Section 5.3). A *Screening/FEC CRF* will be completed for all screened patients and submitted to the Sponsor. The *Screening/FEC CRF* and the *Screening Log* will indicate the inclusion/exclusion criteria that were not met.

8.1.2.2 PATIENT ENROLLMENT IN THE STUDY AND RANDOMIZATION

After patient blinding procedures have been instituted and Final Eligibility Criteria are confirmed by the *Implanter-Investigator* (see Section 5.2.2), the patient is then randomized (see Section 6.3.1). With randomization, the patient is enrolled in the study.

8.1.2.3 STUDY INTERVENTION PROCEDURE

Patients randomized to the Shunt arm will undergo transseptal catheterization and Shunt placement as described below.

The V-Wave Shunt will be inspected and prepared for implantation according to the *Instructions for Use.*

A Sponsor representative will be available during the implantation procedure to support the study staff with device set-up and implantation processes and any training needs they may have.

In brief, the implantation procedure of the Shunt includes:

- TEE or ICE measurements and fluoroscopically guided transseptal puncture near the mid fossa ovalis with left atrial access.
- System set-up in accordance with the IFU
- Placement of Delivery Introducer Sheath
- Delivery and deployment of the Shunt in the target site in accordance with IFU
- TEE or ICE confirmation of successful Shunt placement and function
- Vascular access site care - introducer sheath removal immediately after completion of the intervention procedure. Other care per institutional standards

CAUTION: Introducer sheath must be removed immediately after completion of the intervention procedure. Failure to do so may increase the risk of potential paradoxical embolus and/or pulmonary embolism.

Treatment patients may transition from general anesthesia to conscious sedation during the study intervention procedure as soon the indication for general anesthesia no longer exists.

Implant data including procedure times, fluoroscopy time, radiation dose and contrast dose will be collected and reported on the *Intervention Procedure CRF*. Investigational products that are opened during a procedure and not used shall be recorded on a CRF.

All AEs during intervention procedure including date and time are to be documented.

Every effort should be made to maintain patient and medical staff blinding. Entries into the patient's clinical chart and disclosure to the patient should not reference the result of the randomization or whether a shunt was implanted. They should only reference that the patient was enrolled in a blinded study of interatrial shunting.

8.1.2.4 UNSUCCESSFUL IMPLANT

Implantation failure is defined when a patient enrolled in either the Roll-in or randomized to the Treatment arm does not have a successful device implantation. **At the *Implanter-Investigator's* discretion, several attempts to implant the device may be made during a single Study Intervention Procedure. Patients that fail implantation during this single procedure may not undergo a second**

Study Intervention Procedure attempt. In all cases, randomized patients will remain blinded to study assignment and be followed for the study duration and analyzed on an Intention to Treat basis starting from the time of Enrollment/Randomization.

If the implantation failure is due to a suspected device malfunction, the occurrence will be documented in the CRF. Devices, Delivery Systems and Tools that malfunction during the procedure will be returned to the sponsor for analysis.

8.1.2.5 CONTROL PROCEDURE

Patients randomized to the Control arm will not undergo transseptal catheterization and Shunt placement. For patients undergoing ICE with moderate sedation, the *Implanter-Investigator* will perform a mock transseptal catheterization and device placement from a script provided in the MOP. After approximately 15 minutes have passed, the echo probe and any remaining catheters will be removed, and hemostasis obtained at vascular access sites.

Control patients may transition from general anesthesia to conscious sedation during the study intervention procedure as soon the indication for general anesthesia no longer exists.

Implant data including procedure times, fluoroscopy time, and contrast dose will be collected and reported on an Index Procedure CRF. CRFs will be sent to the Sponsor.

All AEs during hospitalization including date and time are to be documented.

Every effort should be made to maintain patient and medical staff blinding. Entries into the patient's clinical chart and disclosure to the patient should not reference the result of the randomization or whether a shunt was implanted. They should only reference that the patient was enrolled in a blinded study of interatrial shunting.

8.1.2.6 POST PROCEDURE & DISCHARGE EVALUATION

Following the intervention procedure, the patient shall be admitted to the hospital and not discharged until the *Implanter-Investigator* deems the patient clinically stable. If not, appropriate clinical work-up should be performed.

Patients will be evaluated at hospital discharge and the following assessments will be performed:

- **Assure blinding procedures**
- **Vital Signs and Physical Examination**: includes weight, temperature, blood pressure, pulse oximetry, heart rate and rhythm and cardiovascular focused physical examination pertinent to assessing heart failure and study intervention procedure complications including vascular access sites, pulses and extremities.
- **Medication review**: All discharge medications including antiplatelet therapy per protocol.
- **Blood test:** HGB, HCT, Cr

- **Chest X-Ray:** Attention should be paid to complications of procedure (e.g. pneumothorax). No reference should be made in the patient's clinical chart on whether a Shunt is present or not. Patient blinding should be maintained.
- **Assessment of AEs** that occurred in the hospital.
- **Cost Effectiveness**
- **Complete CRF**

Note: The unblinded Implanter-Investigator should specifically review the Chest X-Ray and TTE prior to discharge to confirm there are no procedure-related complications and to facilitate maintenance of patient and research staff blinding.

8.1.3 2-WEEK TELEPHONIC FOLLOW UP (± 7 DAYS)

- **Assure blinding procedures**
- **Medications:** Confirm antiplatelet/anticoagulation medications as per protocol.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Complete CRFs**

8.1.4 ONE (1) MONTH IN-CLINIC FOLLOW UP (± 7 DAYS)

Patients will be evaluated at 1-month (±7 days) post implantation, and the following assessments will be performed:

- **Assure blinding procedures**
- **Vital Signs and Physical Examination**: includes weight, blood pressure, heart rate and rhythm and cardiovascular focused physical examination pertinent to assessing heart failure status and study intervention procedure complications.
- **Medications:** Confirm antiplatelet/anticoagulation medications as per protocol.
- **Blood test:** HGB, HCT, Cr
- **Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE):** Elements per Core Laboratory Manual. No reference should be made in the patient's clinical chart on whether the Shunt is present or not. Patient blinding should be maintained.
- **NYHA Functional Class by blinded assessor**
- **KCCQ and EQ-5D Quality of Life assessments by blinded assessor**
- **6MWT by blinded assessor:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Cost Effectiveness**
- **Complete CRFs**

8.1.5 THREE (3) MONTHS IN-CLINIC FOLLOW UP (± 14 DAYS)

Patients will be evaluated at 3 months (±14 days) post implantation, and the following assessments will be performed:

- **Assure blinding procedures**
- **Vital Signs and Physical Examination**: includes weight, blood pressure, heart rate and rhythm, and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications**: Confirm antiplatelet/anticoagulation medications as per protocol.
- **NYHA Functional Class by blinded assessor**
- **KCCQ and EQ-5D Quality of Life assessments by blinded assessor**
- **Patient Global Assessment**
- **6MWT by blinded assessor:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Cost Effectiveness**
- **Complete CRFs**

8.1.6 SIX (6) MONTHS IN-CLINIC FOLLOW UP (± 30 DAYS)

Patients will be evaluated at 6 months (±30 days) post implantation, and the following assessments will be performed:

- **Assure blinding procedures**
- **Vital Signs and Physical Examination**: includes weight, blood pressure, heart rate and rhythm, and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications**: Confirm antiplatelet/anticoagulation medications as per protocol.
- **Blood test:** HGB, HCT, Cr
- **Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE):** Elements per Core Laboratory Manual. No reference should be made in the patient's clinical chart as to whether the Shunt is present or not. Patient blinding should be maintained.
- ***For Roll-In Patients Only* - Transesophageal 2-dimansional echocardiogram/Doppler examination (TEE):** Elements per Core Laboratory Manual.
- **NYHA Functional Class by blinded assessor**
- **KCCQ and EQ-5D Quality of Life assessments by blinded assessor**
- **Patient Global Assessment**
- **6MWT by blinded assessor:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.

- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Cost Effectiveness**
- **Complete CRFs**

8.1.7 NINE (9) MONTHS TELEPHONIC FOLLOW UP (± 30 DAYS)

Patients will be evaluated at 9 months (±30 days) post implantation by blinded research staff with telephonic contact, and the following assessments will be performed:

- **Assure blinding procedures**
- **Medications: all medications including anticoagulants.**
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Complete CRFs**

8.1.8 TWELVE (12) MONTHS IN-CLINIC FOLLOW UP (± 30 DAYS)

Patients will be evaluated at 12 months (±30 days) post implantation, and the following assessments will be performed:

- **Assure blinding procedures**
- **Vital Signs and Physical Examination**: includes weight, , blood pressure, heart rate and rhythm, and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications**
- **Blood test:** HGB, HCT, Cr
- **Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE):** Elements per Core Laboratory Manual. No reference should be made on the patient's clinical chart as to the presence or absence of the Shunt. Patient blinding should be maintained.
- **For Roll-In Patients Only - Transesophageal 2-dimansional echocardiogram/Doppler examination (TEE):** Elements per Core Laboratory Manual.
- **NYHA Functional Class by blinded assessor**
- **KCCQ and EQ-5D Quality of Life assessments by blinded assessor**
- **Patient Global Assessment**
- **6MWT by blinded assessor:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Cost Effectiveness**
- **Complete CRFs**

8.1.9 FIFTEEN (15) MONTHS TELEPHONIC FOLLOW UP (± 30 DAYS)

Patients will be evaluated at 9 months (±30 days) post implantation by blinded research staff with telephonic contact, and the following assessments will be performed:

- **Assure blinding procedures**
- **Medications**
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Complete CRFs**

8.1.10 EIGHTEEN (18) MONTHS IN-CLINIC FOLLOW UP (± 30 DAYS)

Patients will be evaluated at 18 months (±30 days) post implantation, and the following assessments will be performed:

- **Assure blinding procedures**
- **Vital Signs, and Physical Examination:** includes weight, blood pressure, heart rate and rhythm, and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications**
- **NYHA Functional Class by blinded assessor**
- **KCCQ and EQ-5D Quality of Life assessments by blinded assessor**
- **Patient Global Assessment**
- **6MWT by blinded assessor:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Cost Effectiveness**
- **Complete CRFs**

8.1.11 TWENTY-ONE (21) MONTHS TELEPHONIC FOLLOW UP (± 30 DAYS)

Patients will be evaluated at 9 months (±30 days) post implantation by blinded research staff with telephonic contact, and the following assessments will be performed:

- **Assure blinding procedures**
- **Medications**
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Complete CRFs**

8.1.12 TWENTY-FOUR (24) MONTHS IN-CLINIC FOLLOW UP (± 30 DAYS)

Patients will be evaluated at 24 months (±30 days) post implantation, and the following assessments will be performed:

- **Assure blinding procedures**
- **Vital Signs and Physical Examination**: includes weight, blood pressure, heart rate and rhythm and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications**
- **Blood test:** HGB, HCT, Cr.
- **Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE).** Elements per Core Laboratory Manual. No reference should be made on the patient's clinical chart as to the presence or absence of the Shunt. If no flow seen through Shunt, patient to be referred for TEE evaluation.
- **NYHA Functional Class by blinded assessor**
- **KCCQ and EQ-5D Quality of Life assessments by blinded assessor**
- **Patient Global Assessment**
- **6MWT by blinded assessor:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits.**
- **Cost Effectiveness**
- **Complete CRFs**
- **Unblind patient**

For patients finishing the blinded phase prior to the 24 months visit, a blood test collecting HGB, HCT and Cr should be performed.

8.1.13 CLOSE-OUT TELEPHONIC VISIT

The primary endpoint analyses of the study will be conducted after the last patient enrolled completes the 12-month follow-up, which is defined as the close-out date. Sponsor will inform sites of this close-out date in advance.

Where possible, patients due with 18- and 24-month in-clinic follow-up should be schedule during the one month before the close-out date, which will serve as their close-out visit. Otherwise, all patients that have not reached 24 months follow-up, or cannot return to clinic will have a telephonic close-out visit within one month of the close out date. The elements of the close-out visit include:

- **Assure blinding procedures**
- **Medications**

- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Complete CRFs**
- **Unblind patient**

If patients randomized to the Control group who are followed telephonically for their close-out visit are interested in receiving a shunt, they will be invited to return to the clinic to be re-consented and to evaluate if they currently meet the baseline inclusion/exclusion criteria before scheduling a Final Screening/Intervention Procedure.

8.1.14 FOLLOW-UP SCHEDULE FOR CONTROL PATIENTS THAT CROSS-OVER AND RECEIVE A SHUNT IMPLANT

Cross-over patients who receive the Shunt will be followed for 12 months according to the follow-up schedule described above for the first 12 months post randomization (see Sections 8.1.2.6 - 8.1.8).

8.1.15 UNSCHEDULED CLINIC VISITS

Unscheduled clinic visits are defined as any clinic visit relating to the protocol that is not a required protocol visit. **If an unscheduled clinic visit occurs, patient blinding should be maintained.** If patient has an unscheduled clinic visit, the clinical information should be captured on the *Unscheduled Clinic Visit CRF*. Unscheduled visits will be classified by type according to the reason for the visit according to the following categories:

- Worsening HF status according to the definitions of Intensification of Heart Failure Therapy described in Section 3.4.6:
  - signs or laboratory evidence of worsening heart failure
  - if the dose of diuretics was increased and if sustained for a month or more
  - if intravenous treatment given for HF
  - if a new HF drug class was added for the treatment of worsening HF
- Worsening clinical status not related to HF
- Stable clinical status for medication change/titration
- Patient education
- Elective follow-up of previous visit or recent hospital discharge
- Other, (specify)

8.1.16 YEARLY IN-CLINIC FOLLOW-UP YEARS 3, 4, AND 5 YEARS (± 60 DAYS) IN IMPLANTED PATIENTS

All patients who receive an implant (Roll-Ins, Randomized to Therapy or Controls that cross-over and receive an implant) will be evaluated in-clinic at years 2 (if blinded ended prior to this time point), 3, 4 and 5 (±60 days) post implantation, and the following assessments will be performed:

- **Vital Signs and Physical Examination**: includes weight, blood pressure, heart rate and rhythm and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications**
- **Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE).** Elements per Core Laboratory Manual. No reference should be made on the patient's clinical chart as to the presence or absence of the Shunt. If no flow seen through Shunt, patient to be referred for TEE evaluation.
- **NYHA Functional Class by blinded assessor**
- **KCCQ and EQ-5D Quality of Life assessments by blinded assessor**
- **Patient Global Assessment**
- **6MWT:** The test should be performed only once. Obtain Borg score.
- **Assessment of AEs that occurred during the last one year (since last contact) including Hospitalization and Emergency Room visits.** Current health status and obtain information about any treatment for heart failure including hospitalizations or emergency room visits, procedures or surgeries
- **Complete CRFs**

8.1.17 HOSPITALIZATIONS

All events that result in ER visits, outpatient short stays or hospitalizations shall be reported on a Hospitalization CRF. Additionally, an Adverse Event CRF must be completed. The following information will be documented: primary diagnosis requiring hospitalization (e.g. ADHF, pneumonia, AMI, etc.), length of stay, days in ICU/CCU (if applicable) and all therapies for HF treatment including specifying parenteral therapies. Deidentified source records related to a patient's hospitalization must be obtained and submitted to the sponsor for review by the CEC. For prolonged hospitalizations, an investigator summary note should accompany the event. Source documentation includes:

- Emergency department notes
- Physician consultation notes
- Medication records and logs
- Admission notes (required for all hospitalizations)
- Laboratory results and summary details
- Discharge summary (required for all hospitalizations)
- Operative reports
- Clinician progress notes
- X-ray reports
- Diagnostic test reports
- Death summary written by Investigator including: date and time of death, place death occurred, if death was witnessed, heart rhythm at time of death (if known), cause of death, classification of death (HF related, cardiovascular, non-cardiovascular), time interval to death from initiating event, autopsy report (if available), relationship to device or study procedures and any other comments regarding the death.

8.2 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCES

Adverse events will be reported to the Sponsor by the Investigator. The Investigator will classify events by diagnosis or by specific signs, symptoms or abnormal laboratory values, if no medical diagnosis is available. Definitions and safety reporting requirements for Investigators in the US follows the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice (ICH/GCP), and outside of the United States (OUS) the event definitions are based on ISO 14155:2011. The Sponsor is responsible for determining which adverse events are required to be reported to regulatory authorities and for submitting such reports within the required time periods.

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

8.2.1.1 US SAFETY REPORTING

Adverse event: Any untoward or physical or psychological occurrence or undesirable and unintended effect for a participant that may present during interventions and interactions used in the research or from the collection of identifiable private information under the research, whether or not there may be a relationship to the individual's participation in the research.

Anticipated problem/adverse event: Any foreseen or expected problem or event which was described in the general investigational plan, the current application, the current investigator brochure, or in the informed consent document submitted to the IRB.

Related to the research: An event is related to the research if, in the opinion of the investigator, it was, more likely than not, the result of the interventions or interactions used in the research or the result of the collection of identifiable private information in the research (i.e., there is a reasonable possibility that the event may have been caused by participation in the research).

Serious Adverse Event: An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected adverse event: Any adverse event occurring in one or more participants in a protocol when the nature, severity, or frequency is not consistent with either:

- the known or foreseeable risk of adverse events associated with the research procedures that are described in (a) the protocol-related documents (i.e., the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document) and (b) other relevant sources of information (i.e., product labeling and package inserts); or

- the expected natural progression of any underlying disease, disorder, or condition of the individuals(s) experiencing the adverse event and the individual's predisposing risk factor profile for the adverse event.

Unanticipated adverse device effect (UADE): Any serious effect on health or safety or any life- threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

Device Deficiency: A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Malfunction: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or protocol.

Use Error: Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

Notes: Use error includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.

8.2.1.2 OUTSIDE US SAFETY REPORTING

Adverse Event: Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

Note 1: This includes events related to the investigational device or the comparator.
Note 2: This includes events related to the procedures involved (any procedure in the clinical investigation plan).
Note 3: For users or other persons this is restricted to events related to the investigational medical device.

Serious Adverse Event: Adverse event that:

- Led to a death,
- Led to a serious deterioration in health that either:
  - resulted in a life-threatening illness or injury, or
  - resulted in a permanent impairment of a body structure or a body function, or
  - required in-patient hospitalization or prolongation of existing hospitalization, or
  - resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.
Note 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

Adverse Device Effect: Adverse event related to the use of an investigational medical device.

Note 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
Note 2- This includes any event that is a result of a use error or intentional misuse.

Serious Adverse Device Effect: Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE): Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

8.2.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.2.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.2.2.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the study investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other procedures or medications.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other procedures or medications.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

For the purposes of endpoints and outcome measures that involve device relatedness assessments, only AEs classified as definitely or probably related by the CEC will be included for analysis. AEs categorized as potentially, unlikely or not related will be tabulated and reported separately.

8.2.2.3 EXPECTEDNESS

The CEC will be ultimately responsible for determining whether an adverse event (AE) is expected or unexpected as it pertains to the analysis of the endpoints in this study. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.2.3 LIST OF FORESEEABLE ADVERSE EVENTS AND ANTICIPATED ADVERSE DEVICE EFFECTS

Risk analysis was used as a basis for identifying anticipated adverse device effects characterized by their nature, incidence, severity and outcome. An anticipated adverse event is an event that has been reported in the literature. A list of adverse events which may result from these percutaneous procedures, as well as those clinical adverse events identified as unique to the study device can be found in Section 2.3 Risk/Benefit Assessment as well as in the Investigators Brochure.

8.2.4 HANDLING OF ADVERSE EVENTS

Investigator will report "to the sponsor, without unjustified delay, all serious adverse events and device

deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports" (ISO 14155:2011 § 9.8 b and 21 CFR 812.150). Device malfunctions and use errors should also be reported without unjustified delay.

Reporting all Serious Adverse Events (SAEs and SADEs), including all device deficiencies should be done by completing the CRF (AE/SAE and Device Deficiency forms) within 24 hours of event knowledge. Investigator should return the entire delivery system, and if available, the implant involved in potential deficiency to V-Wave for analysis.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while in the study must be documented appropriately regardless of relationship, seriousness, intensity, outcome or casualty. All AEs will be followed to adequate resolution.

In case of a patient death, the Study Investigator will determine the mode and cause of death and its relationship to the investigational device. In addition, the Study Investigators will make reasonable efforts to obtain an autopsy and provide an autopsy report to the Sponsor. In all cases of death, the Investigator will provide a signed narrative description of the events surrounding the death including the cause of death and relationship to the study device.

The Investigator will monitor the occurrence of adverse events or device deficiencies for each patient during the course of the trial. All adverse events (AEs) reported by the patient, observed by the Investigator, or documented in medical records will be recorded on the adverse event CRF, whether believed by the Investigator to be related or unrelated to the study device. Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Report Form and followed as appropriate. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Principal Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.2.5 SERIOUS ADVERSE EVENT REPORTING

The following section describes the roles and responsibilities for serious adverse event reporting to regulatory authorities, IRBs and ECs.

8.2.5.1 REPORTING ADVERSE EVENTS TO THE ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD (EC/IRB)

It is the responsibility of each investigator to report all Serious Adverse Events and/or Serious Adverse Device Effects to the Ethics Committee/Institutional Review Board, according to local and national regulations and Ethics Committee requirements. A copy of the Ethics Committee report should be shared with V-Wave.

8.2.5.2 REPORTING ADVERSE EVENTS (OUS)

V-Wave is responsible for the classification and reporting of adverse events and ongoing safety evaluation of the clinical investigation in line with ISO 14155:2011 and regulatory requirements. V-Wave will assure that all Serious Adverse Events are reported to the Competent Authorities in accordance with European Medical Device Directives and all applicable National Regulations.

8.2.5.3 REPORTING UADE(S) TO IRB/FDA

The definition for Unanticipated Adverse Device Effect (UADE) from the Investigational Device Exemption (IDE) regulations is provided in Section 8.2.1.1.

- An investigator is required to submit a report of UADE to the sponsor and to the reviewing Ethics Committee/Institutional Review Board as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)).
- Sponsors must immediately conduct an evaluation of UADE and must report the results of such evaluation to the FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.150(b)(1)).

9 STATISTICAL CONSIDERATIONS

The following sections summarize statistical considerations for the RELIEVE-HF study. Additional details will be provided in the Statistical Analysis Plan (SAP) for the study.

9.1 STATISTICAL HYPOTHESES

9.1.1 SAFETY

The safety endpoint will be compared to a pre-specified Performance Goal (PG) of 11%. The expected rate (R) of observed Device/Procedure-related MACNE is 5% of patients at 30 days.

The hypothesis for safety is:

$$H_0: R \geq PG \quad H_1: R < PG$$

Where, PG = 11%. The hypothesis will be tested with an exact binomial test, with a one-sided significance level of 0.025.

9.1.2 EFFECTIVENESS

The hypothesis for effectiveness is:

$$H_0: \ T_{Shunt} \leq 0$$
$$H_1: \ T_{Shunt} > 0$$

Where, T_{Shunt} = sum of ranks in the Shunt group and the hypothesis is evaluated using the method of Finkelstein and Schoenfeld with a one-sided significance level of 0.025.

9.2 SAMPLE SIZE DETERMINATION

9.2.1 FOR SAFETY

Assuming an alpha level of 0.025 (one-sided), a sample size of 200 evaluable Treatment group patients from the Randomized cohort would achieve a power of 87% to detect a difference between the expected safety endpoint rate of 5% and a Performance Goal of 11%. Primary safety endpoint analysis will be conducted in all patients implanted with the device using an intention to treat analysis including patients randomized to Therapy only.

9.2.2 FOR EFFECTIVENESS

Primary effectiveness endpoint analysis will be performed on a combined HFrEF and HFpEF population. The homogeneity of the treatment effect will be examined in an analysis of the interaction between treatment effect and the HFrEF/HFpEF subpopulations. It is estimated that 20%-25% of the total study population will be HFpEF patients. Based on 10,000 simulated trials, a study of 400 patients (200 per arm) would achieve an expected power of 90% to detect a sum of ranks greater than zero in the treatment group, with a one-sided alpha of 0.025. Details about specific assumptions used for each of the composite endpoint components in the HFrEF and HFpEF subpopulations will be provided in the SAP.

9.3 POPULATIONS FOR ANALYSES

The following populations are defined for study analyses:

Safety Population: Subjects who met the initial inclusion and exclusion criteria, signed an Informed Consent form, and underwent any invasive procedure associated with evaluation of the final exclusion criteria.

Intention-to-Treat (ITT): Subjects who were randomized to the Shunt Implant or Control study arms.

Per Protocol (PP): Randomized subjects who met all initial and final inclusion/exclusion criteria, had no major protocol deviations which may have impacted study outcomes, and had sufficient data to be considered evaluable for the primary safety and effectiveness endpoints.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

1. Descriptive statistics will be used to summarize all subject Baseline and outcome data collected during the study. Continuous variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized in frequency distributions.
2. Statistical analyses will be performed by validated software (e.g., SAS, IBM/SPSS, or Cytel Software)
3. Statistical tests appropriate to the endpoint being examined will be used and identified. The non-parametric Finkelstein-Schoenfeld test will be used for the evaluation of the primary effectiveness endpoint. Parametric tests (e.g., Student's t-tests) will be utilized for other endpoints, if the distributional properties of the data are suitable. If parametric tests are not indicated, the associated non-parametric tests (e.g., Mann-Whitney tests, Fisher's Exact Tests) will be used.
4. A one-sided p-value of 0.025 or less for tested primary and secondary endpoints will be considered evidence of statistical significance. Reported p-values for all other tests will be considered nominal and unadjusted for multiple testing, without conclusions regarding statistical significance levels.
5. Copies of databases used to prepare clinical report summaries will be archived to enable any statistical analyses performed to be replicated.
6. A full data listing will be prepared, including an electronic version in a standard computer-accessible format (e.g., SAS) at the completion of the study. Listings of data represented on the case report forms (eCRF) will be provided for all key baseline, demographic and outcome variables to facilitate further investigation of tabulated values and to allow for clinical review of safety variables.

9.4.2 ANALYSIS OF THE PRIMARY SAFETY ENDPOINT(S)

The Primary Safety Endpoint is the percentage of Treatment Group patients experiencing any device-related Major Adverse Cardiovascular and Neurological Events (MACNE) during the first 30-days after randomization. The proportion of subjects with MACNE events will be tested against a Performance Goal of 11% with an exact binomial test, with a one-sided significance level of 0.025. The Intention-to- Treat population randomized to the Shunt implant is the primary analysis population for this safety analysis.

9.4.3 ANALYSIS OF THE PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint will be evaluated with a sum of ranks (T_{Shunt}) test statistic in the Shunt group using the method of Finkelstein and Schoenfeld. All subjects have a scheduled minimum follow-up period of 12 months, and all data collected through 24 months of follow-up will be included in the final analyses. The ITT population is the primary analysis population for the primary effectiveness endpoint, with supportive analyses in the PP population.

The ranks are based on a hierarchical evaluation of the components of the composite primary effectiveness endpoint across the total evaluable study population (Shunt and Control groups) in the following order:

1. Death (all-cause)
2. Heart transplant or LVAD implant
3. HF hospitalizations (including ER visits > 6 hours)
4. Six-Minute Walk Distance Test (6MWT, measured as % change from baseline)

The rank of a subject relative to other subjects is based on consideration of the following factors: level of an observed event in above hierarchical list, the time of the event(s) after randomization, the number of events, the observed time in study, and 6MWT performance. Details of the hierarchical ranking procedure will be provided in the SAP.

The sum of ranks (T_{Shunt}) under the null hypothesis of no difference between study groups has an expected mean value of zero and a variance equal to:

$V = [N (N – m) / N (N -1)] (\sum U_i^2)$

Where,

N = total sample size
m = number of shunt patients U_i
= rank of patient (i)
$\sum U_i^2$ represents a summation across all shunt and control patients

The hypothesis will be tested by comparing the test statistic ($T_{Shunt} / V^{½}$) to the normal distribution, with a one-sided significance level of 0.025. Multiple imputation methods will be used to address any missing data for the primary effectiveness endpoint.

9.4.4 ANALYSIS OF HIERARCHICALLY TESTED SECONDARY EFFECTIVENESS ENDPOINTS

The difference between study groups will be hierarchically tested for the following secondary effectiveness endpoints in the order shown below, if the primary effectiveness endpoint is met. The same significance level (one-sided, alpha = 0.025) used for the primary effectiveness endpoint will be applied at each step in the hierarchical testing. The PP population is the primary analysis population for these secondary endpoints.

Where indicated, the analyses of secondary endpoints will be covariate adjusted. The final list of pre-specified covariates will be described in the SAP, but will include:

- Stratification factor of HFrEF and HFpEF
- Sex
- Age

The secondary endpoints are:

1. 6MWT changes from Baseline to 12 months

Analysis: Two-group Student's t-test of mean percentage changes from baseline

2. KCCQ changes from Baseline to 12 months

Analysis: Two-group Student's t-test of mean score changes from baseline

3. All-cause mortality and heart failure hospitalizations at study duration

Analysis: Negative binomial or Cox regression (Anderson-Gill) with covariates, as appropriate for the data collected

4. Time to death, LVAD/Transplant, or heart failure hospitalization

   Analysis: Cox regression with covariates

5. Time to death or first heart failure hospitalization

   Analysis: Cox regression with covariates

6. Cumulative heart failure hospitalizations at study duration

Analysis: Non-parametric Kolmogorov-Smirnov comparison of cumulative curves

7. Time to first heart failure hospitalization

   Analysis: Cox regression with covariates

8. Modified Primary Effectiveness Endpoint including mortality, LVAD/Transplant, and HF Hospitalizations but without 6MWT

Analysis: Finkelstein-Schoenfeld analysis of primary effectiveness endpoint without 6MWT

9.4.5 ANALYSIS OF THE ADDITIONAL SAFETY DATA

The following additional safety data will be evaluated. There are no tests of hypotheses associated with these analyses.

- Comparison of Major Adverse Cardiovascular and Neurological Events (MACNE) and Bleeding Academic Research Consortium (BARC) types 3 and 5 bleeding at 30 days

This endpoint will be evaluated by estimating the rates of MACNE and BARC events at 30 days, together with the associated exact, 95% confidence intervals.

- Percentage of Treatment Group patients with device-related MACNE at 12 months.

This endpoint will be evaluated by estimating the MACNE rate at 12 months, together with its exact, 95% confidence intervals and a Kaplan-Meier analysis of the time-to-events.

9.4.6 PLANNED INTERIM ANALYSES

A single, midpoint interim analysis with adaptive sample size re-estimation is planned at the point when approximately 50% of the study population (200 subjects) have completed at least 8 months of follow- up, but no later than 3 months prior to completion of enrollment of the original 400 subjects. This interim analysis would consider only data collected for the composite primary effectiveness endpoint and be based on validation of the original planning assumptions for the components of the endpoint.
The interim analysis would be performed by an independent third party, who would communicate results only to the study DSMB. The interim analysis plan is summarized below, with final details of plan and a full description of the adaptive design to be found in the SAP.

The interim analysis will be limited to data collected in an identified study cohort (e.g., the first 200 evaluable subjects). Using the analysis method specified for evaluation of the primary effectiveness endpoint (Finkelstein-Schoenfeld), the unconditional power to meet the endpoint at the conclusion of the study will be re-estimated.

Increases in study sample size will occur only if updated estimates for the composite endpoint components require an increase to maintain the original design goal of 90% power. The increase, if any, would be limited to a relative increase cap of 50% of the original study size: from 400 to 600 evaluable subjects.

Based on the interim analysis results, the DSMB would be expected to make one of the following recommendations to the Sponsor, who will make the final decision regarding actions to be taken in response to the recommendation:

- Continue the study as originally planned,
- Increase the study sample size, or,
- Terminate the study early for futility.

The first DSMB recommendation option (Continue the study as originally planned) would be made if it is determined that no increase in sample size is required or that an increase of 200 subjects would not meaningfully change the estimated power achieved. The DSMB will also have an ongoing responsibility to monitor the study for patient safety, and so, may consider safety issues in making recommendations at the time of the interim analysis, or independently, make recommendations concerning safety issues at any time during the conduct of the study.

The interim results leading to any potential increase in the required study sample size would be known to only the independent party performing the interim analysis and DSMB members, with the Sponsor and other study participants blinded to this information.

If the study continues after the interim analysis as originally planned, with no sample size increase, then the Finkelstein-Schoenfeld analysis on the total study population would be performed at the completion of the study. If a sample size increase occurs, then the results from the first cohort of subjects used in the interim analysis would be combined with the results from subsequent subjects using the method of

Cui et al.[80] (i.e., pre-specified weights assigned to the two stages). In addition, the DSMB may entertain a supplementary interim analysis designed to restore power to certain hierarchical secondary effectiveness clinical event and functional parameter endpoints.

9.4.7 SUB-GROUP ANALYSES

The consistency of the primary safety endpoint and primary effectiveness endpoint will be examined in subgroups defined by sex, LVEF stratification factor of HFrEF and HFpEF, and clinical sites. A complete listing and methodology for sub-group analyses will be included in the Statistical Analysis Plan.

Sex: The primary safety endpoint of MACNE rates at 30 days will be compared by sex using a Fisher's Exact test. The primary effectiveness endpoint will be compared using Z-test based on the Finkelstein-Schoenfeld estimates of the test statistic and its variance in the sex subgroups.

LVEF Stratification: The primary safety endpoint of MACNE rates at 30 days will be compared between HFrEF and HFpEF subjects using a Fisher's Exact test. The primary effectiveness endpoint will be compared using Z-test based on the Finkelstein-Schoenfeld estimates of the test statistic and its variance in the HFrEF and HFpEF subgroups.

Sites: The primary safety endpoint of MACNE rates at 30 days will be compared between study sites (poolability) using a Mantel-Haenszel analysis to examine the homogeneity of the odds ratios at sites. The consistency of the primary effectiveness endpoint across sites will be examined by summarizing the distribution of the within-site Finkelstein estimates of the test statistic and its variance.

Additional sub-group analyses will be specified in the SAP.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

A listing by subject of key demographic and study outcome data (MACNE and SAE events, components of the primary effectiveness endpoint) will be prepared.

9.4.9 ADDITIONAL ANALYSES

The following additional analyses will be summarized using descriptive measures appropriate to the endpoint (e.g., rates, mean and standard deviations, frequency distributions, time-to-events). There are no tests of hypotheses associated with these endpoints. Any reported p-values associated with statistical tests comparing results between study groups are considered nominal, unadjusted for multiple testing, and without assignment of statistical significance levels. The PP population is the primary population for examining these additional endpoints.

Effectiveness

- NYHA Class
- Patient Global Assessment
- Combined all-cause death and all-cause hospitalizations
- All-cause death
- Time to all-cause death (KM analysis)

- Time to cardiovascular death (KM analysis)
- Time to all-cause death, transplant or LVAD (KM analysis)
- Time to cardiovascular death, transplant or LVAD (KM analysis)
- Days alive free from heart failure hospitalization
- Outpatient intensification of heart failure therapy
- Emergency room HF visits
- HF Clinical Composite Assessment (improved, unchanged, or worsened) as described by Packer comprised of all-cause mortality, HF hospitalization, and changes in NYHA functional class ranking and Patient Global Assessment
- Comparison of transthoracic echocardiographic parameters as listed in Echocardiography Core Laboratory Manual
- Incidence of loss of shunt flow as measured on TTE and/or TEE
- Changes in 6MWT
- Changes in KCCQ
- Death: All-cause; Cardiovascular cause (with breakdown by cause, e.g. sudden death, myocardial infarction, pump failure, stroke); Non-Cardiovascular cause; Undetermined cause; and relationship to device, study intervention or other cardiovascular procedure
- Hospitalization: All-cause; HF hospitalization, Non-HF hospitalization (with breakdown for cause including if associated with secondary worsening of HF)
- Change in renal function
- Medication utilization including type, dose, frequency and changes
- Cost and cost-effectiveness data
- Technical success defined as successful delivery and deployment of the device and retrieval of the delivery catheter
- For Roll-in patients, transesophageal or intracardiac echocardiography at 6 and 12 months to assess device patency and other parameters as listed in the Echocardiography Core Laboratory Manual

<u>Safety</u>

- Incidence of all Serious Adverse Events at study duration
- Incidence of cerebrovascular events at study duration with sub-classification of CNS infarction, CNS hemorrhage, and TIA and their relationship to device or study procedures (per NeuroARC)
- Incidence of MI events at study duration after implantation
- Incidence of systemic embolization events at study duration after implantation
- Incidence of pulmonary embolization events at study duration after implantation
- Implant embolization at study duration
- Device-related MACNE annually through 5 years

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 INFORMED CONSENT PROCESS

10.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention or administering study intervention.

10.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided to the prospective patients in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document, including the date of consent, and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The investigator or an authorized member of the research team who has witnessed the prospective patient's signature must also sign and date the informed consent, prior to enrollment of the prospective patient. A copy of the completed informed consent form must be provided to the patient. Local EC regulations regarding obtaining informed consent must be followed. The patient's medical record should have a notation regarding the signing of the informed consent.

If records are consistent with Inclusion/Exclusion criteria, patients will then be approached to undergo the informed consent process and only then the Baseline Visit.

Informed consent will be completed by research personnel trained on the study background and requirements prior to performing any study specific testing. Patients will be introduced to the scope, purpose, rights and duties of the study. Study background information, study requirements, potential

risks and benefits will be explained to the patient. After receiving complete information about the study, both orally and in writing, the patient will have to confirm their consent in writing.

Patients who provide a written informed consent will be assigned a study identification number, which will consist of a code indicating the site identification and a sequential number.

After written informed consent is obtained, patients will undergo additional evaluation and testing that is required to determine their study eligibility.

Clinical study specific procedures or alterations of patient care must not be performed until the prospective patient has provided a signed informed consent. The informed consent will be in the prospective patient's native language and will contain non-technical language to describe the investigational procedures. The informed consent should also include a clause that ensures important new information will be provided to the patient throughout the clinical investigation.

The Primary-Investigator is ultimately responsible for the achievement of written consent from the prospective patient before they are included in the trial. All patients must provide informed consent in accordance with the local EC requirements, using EC-approved informed consent forms. Figure 4 below outlines the screening process and illustrates the point where informed consent should be obtained. The final eligibility for the clinical trial will be confirmed based during the study intervention visit using right heart catheterization and intracardiac or transesophageal imaging.

10.1.3 INFORMED CONSENT PROCESS WHEN PATIENT IS UNABLE TO GIVE IT

It is anticipated that the patients enrolled in this trial will not be requiring emergency treatments as part of the clinical investigation. Therefore, there will be sufficient time to obtain proper written informed consent without emergency measures being taken.

It is possible that prospective patients may be unable to provide written consent due to limitations in their ability to read or write. In this case, informed consent shall be obtained through a supervised oral process of a prospective patient. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective patient and, whenever possible, the patient shall sign and personally date the informed consent form. The witness must also sign and personally date the informed consent form attesting that the information was accurately explained, and that informed consent was freely given.

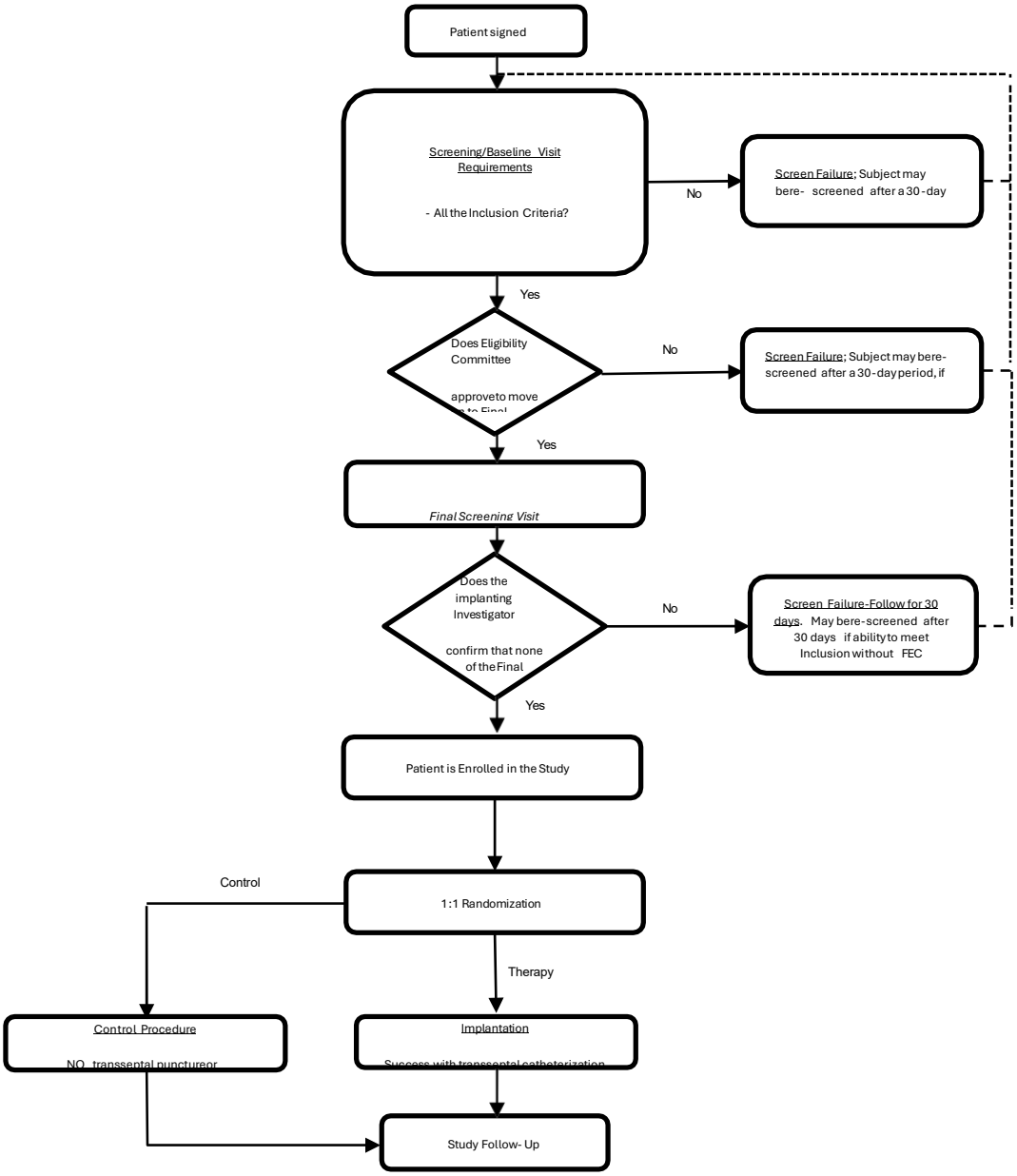


Figure 4. Screening and enrollment process.

10.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and regulatory authorities. If the study is prematurely terminated or suspended by the sponsor, the PI will be responsible for promptly notifying the study participants and IRB/ECs. Sponsor will provide the reason(s) for the termination or suspension.

10.2.1 CRITERIA AND ARRANGEMENTS FOR SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION OR OF THE CLINICAL INVESTIGATION IN ONE OR MORE SITES

In case one or more sites are incapable of continuing to follow the patients in accordance with GCP (e.g. failure to comply with the study protocol), the site may be temporarily suspended or terminated by the Sponsor. Arrangements will then be made to reassign patients to a nearby site, conditional to consent by the affected patients.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA) and other regulatory agencies.

Specifically, placing a prosthetic device that creates an interatrial communication may have a risk of thrombotic events including stroke and systemic embolization. For that reason, formal suspension criteria have been developed to be applied to the Roll-in cohort. A plan to rapidly and thoroughly evaluate strokes associated with device occlusion was defined using the NeuroARC evaluation protocol. If two or more strokes adjudicated to be probable or definitely device-related and associated with a device occlusion in the first 45 Roll-in patients during the first 6 months after implantation, randomization will be put on hold, pending regulatory review.

10.2.2 CRITERIA FOR ACCESS TO AND BREAKING THE BLINDING CODE IN THE CASE OF SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL

The trial is a double-blind study and every effort should be made to maintain the blinding so as not to compromise the integrity of the trial. In the unlikely event that it becomes medically necessary to unblind the patient, the site will request written permission to unblind from the Sponsor, with explanation of the circumstances requiring unblinding. If the Sponsor agrees to unblind, the site as the treatment facility will

provide the information to the patient and/or treating physician. The site will also notify the sponsor that unblinding has occurred.

10.2.3 REQUIREMENTS FOR SUBJECT FOLLOW-UP

All patients will continue to receive standard of care follow-up in the event of suspension or premature termination of the clinical investigation.

10.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or Sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital), pharmacy records and billing records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, sponsor requirements and local regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Data Coordinating Center (DCC). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Study Sponsor.

10.3.1 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored by the Study Sponsor. After the study is completed, the de-identified, archived data will be transmitted to and stored by the Sponsor, which may be used by other researchers including those outsides of the study. Permission to transmit data to the Sponsor will be included in the informed consent.

10.4 KEY ROLES AND STUDY GOVERNANCE

The names and contact information of the Executive Committee Investigators is provided in **Table 7**. Medical Monitor details will be contained in the Manual of Operation (MOP).

Table 7: Executive Committee Investigators' name and contact information

Stefan D. Anker MD, PhD, FESC	**Josep Rodés-Cabau, MD, FHSA**
University Medical Center Gottingen, Germany	Université Laval (CRIUCPQ-ULaval)
Robert-Koch-Straße 40 37075 Göttingen Briefpostadresse 37099 Göttingen, Germany	2725, Chemin Sainte-Foy, U-2755 Québec (Québec) G1V 4G5, Canada
s.anker@cachexia.de	Josep.Rodes@criucpq.ulaval.ca
JoAnn Lindenfeld, MD	**Gregg W. Stone, MD**
Vanderbilt University	Colombia University Medical Center
1215 21st Ave S Nashville, TN 37212	161 Ft. Washington Ave. Herbert Irving Pavilion, 6th Floor. New York NY 10032
joann.lindenfeld@vanderbilt.edu	gstone@crf.org

10.5 STUDY LEADERSHIP COMMITTEE

The RELIEVE HF study uses four committees to oversee safety and proper conduct of the trial. Charters of committees (DSMB and CEC) will be included in trial master file (TMF). In addition, a list of study team roles and responsibilities of those involved in the conduct, management, or oversight of the trial is included in the manual of operation binder (MOP).

10.5.1 EXECUTIVE COMMITTEE

The Executive Committee is comprised of the Trial Chairmen (Sponsor CEO and CMO), Principal Investigators, Medical Monitor, and a representative of the Sponsor (Biostatistician and Echocardiographic Core Laboratory Director). This committee will oversee general aspects of the trial. This oversight includes review of the final clinical investigation plan, ongoing monitoring of the general data collection, as well as review and consideration of implementation of operational issues that may arise and warrant a clinical investigation plan amendment or other corrective action. This committee will review recommendations from the DSMB and determine policy regarding publication. The Executive Committee will also approve policy regarding presentations and/or publications. It is recommended that the Committee will meet at least twice yearly. Meeting minutes from this committee will be filed with the sponsor.

10.5.2 ELIGIBILITY COMMITTEE

The Eligibility Committee is comprised of at least 2 members (cardiologists) who are not directly involved in the conduct of the trial. The Eligibility Committee will review each patient baseline clinical information prior to final eligibility check and randomization. Baseline clinical information will include at a minimum medical history, Guideline Directed Medical Therapy (GDMT), previous HF hospitalization in

the prior year, blood tests results, echocardiography report and other relevant clinical data for purposes of determining enrollment eligibility.

10.5.3 CLINICAL EVENT COMMITTEE

The Clinical Events Committee (CEC) will be comprised of cardiologists who are not participants in the trial and who have no conflict of interest with the trial or the trial sponsor. The CEC will retain a consultant neurologist to assist with these adjudications. All members of the CEC will be blinded to the primary results of the trial.

The CEC will be responsible for the adjudication of the clinical trial events. At the onset of the trial, the CEC will establish explicit rules outlining the process for adjudication and the algorithms followed, in order to classify a clinical event. The CEC will also review and rule on all deaths that occur throughout the blinded phase of the trial. In addition, the CEC will review and adjudicate all clinical endpoints events during the blinded phase of the trial. Definitions are provided in Section 3.4. The CEC will employ a 2- step adjudication process: first, blinded to randomization, and then if an endpoint event is positively adjudicated, the CEC will be unblinded to determine the likelihood of the event being related to the study device.

Once the specific criteria for clinical endpoints are established by the CEC, the independent DCC will be responsible for preparing all clinical endpoint event dossiers and for the conduct of the CEC meetings.

10.5.4 DATA SAFETY MONITORING BOARD (DSMB)

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB). The Data Safety Monitoring Board (DSMB) is comprised of at least three members with the appropriate expertise (heart failure, interventional cardiology and biostatistics), who are not directly involved in the conduct of the trial, independent from the study conduct and free of conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study sponsor.

All adverse events will be reported to the DSMB and reviewed on an on-going basis throughout the subject enrollment and follow-up period as specified in the DSMB charter, to ensure the safety of subjects enrolled in this trial. The DSMB may request additional information as needed. Based on safety data, the DSMB may recommend that the Executive Committee modify or discontinue the trial. All final decisions, regarding trial modifications, however, rest with the Study Executive Committee and the Sponsor.

10.6 CLINICAL MONITORING

The sponsor will manage the monitoring and data collection of this study per ISO 14155:2011, E6: ICH GCP Guideline, and 21 CFR 812. Study monitoring representatives with adequate medical experience and training to perform the assigned tasks to ensure that the study is performed as defined and to ensure that the required data is accumulated, will monitor this study. An Executive Committee has been assembled and assigned the tasks of maintaining the quality of study conduct.

Prior to initiating the study, the Sponsor will ensure that the appropriate personnel at each site are adequately trained in study procedures and in the proper use of the study device, and that the study protocol, patient informed consent form, Investigator and site agreements, and the case report forms are in place.

Review of study required documentation including signed agreements, protocol, required institutional approvals, Ethics Committee/Institutional Review Board Approval will be conducted. The investigator guarantees direct access to source documents by the sponsor and regulatory bodies. Source data verification is performed in accordance with data protection regulations and guidelines and all information reviewed will be kept confidential.

Participant data will be documented in the CRF. CRFs will be periodically monitored and 100% of primary safety and effectiveness endpoints, hierarchically tested secondary effectiveness endpoints and SAEs will be verified. Risk-based monitoring will be applied for all other elements of the study. The investigator is responsible for completing the CRFs in a timely manner and the monitor is responsible for reviewing them and clarifying and resolving any data queries. The monitor will ensure the case report forms and patient informed consent forms are completed as required and will verify that the appropriate personnel (i.e. Sponsor) are informed of any adverse events. At the conclusion of the study, the monitor will ensure all forms are completed and collected.

All deviations from the protocol that occur during the study will be captured and the impact of each deviation on the validity and integrity of the data collected will be evaluated.

Data in the study will be collected on all participants until study termination. Data collection will be terminated if the patient withdraws their consent.

Investigational device and medication accountability records will be reviewed including devices and medications received, receipt dates, quantity, lot numbers, identification of patient and date of implantation of the device, storage and signature of study personnel responsible for accountability.

10.6.1 MONITORING PLAN

Sponsor and/or designee will monitor the trial over its duration according to the pre-specified monitoring plan. The trial monitor will visit each site at appropriate intervals to review investigational data for accuracy and completeness and ensure compliance with the clinical investigation plan. The trial monitor may inspect all documents and required records that are maintained by the Investigator/Site,

including medical records (office, clinic, or hospital) for the subjects in this trial. Source documentation must be available to substantiate proper informed consent procedures, adherence to clinical investigation plan procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information. A monitoring visit sign-in log will be maintained at the site. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator/Site will provide the trial monitor with a suitable working environment for review of study-related documents.

10.6.1.1 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator and the associated institution will permit direct access to source data/documents for study-related monitoring, audits, IRB review and regulatory inspections.

Patients providing informed consent agree to allow the Sponsor or designee access and copying rights to pertinent information in their medical and billing records concerning their participation in this trial. The Investigator will obtain, as part of the informed consent, permission for trial monitors or regulatory authorities to review, in confidence, any records identifying the patients in this trial. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the patient's personal and private information.

10.7 SOURCE DATA

10.7.1 DEFINITION AND RESPONSIBILITY

Source data includes all information in original records, certified copies of original records (including imaging records) and original data recorded on worksheets, and includes all original recordings or certified copies of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the study.

The Investigator is responsible for maintaining complete and accurate documentation of the trial including but not limited to medical records, trial progress records, laboratory results, case report forms, signed informed consent forms, device accountability records, correspondence with the IRB as well as trial monitors and sponsor, adverse event reports, and information regarding subject discontinuations.

The Investigator is required to maintain information in the subject’s medical records which documents and corroborates data entered in the case report forms. As a minimum, the subject record should contain:

- Documentation of subject’s consent and subject ID number in the trial
- Medical history/physical exam documenting that subject meets inclusion/exclusion criteria
- Dated and signed notes from each subject visit

- Adverse events reported and their resolution or lack thereof including supporting documents such as hospital records, discharge summaries, catheterization reports, ECGs, etc.
- Record of clinical investigation plan required medications during the trial
- Record of the subject's condition upon completion of or withdrawal from the trial.

10.7.2 SOURCE DATA VERIFICATION

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits reported data are reviewed for accuracy, completeness and will be verified from source documents (e.g. patient files, physician notes, discharge summaries, imaging reports etc.). All data reported in CRFs should be supported by source documents unless otherwise specified.

Patient follow-up form on hospitalizations and survival documenting the follow-up call conducted by the study personnel will be considered as a source document.

10.7.3 RECORDS RETENTION

ICH guidelines require that essential documents be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

To comply with these requirements, the investigator will not dispose of any records relevant to this trial without either (1) written permission from the Sponsor, or (2) providing an opportunity for the Sponsor to archive the records. The investigator shall take responsibility for maintaining adequate and accurate source documents of all observations and data generated as required during this trial, including any data clarification forms received from the Sponsor or its designees. Such documentation is subject to inspection by the Sponsor or its agents, the IRB/EC, or other regulatory agencies.

The Investigator will be notified by the Sponsor of the date of marketing approval or discontinuation of the trial. The Investigator will obtain permission from the Sponsor in writing before destroying or transferring control of any trial records.

10.8 SELECTION OF CLINICAL SITES AND INVESTIGATORS

The sponsor will select Investigators who are qualified by training and experience, and are legally entitled to perform clinical research and to participate in the investigation of the study device. Sites will be selected based upon review of a recent site assessment and the qualifications of the Primary Investigator at the site.

10.9 TRAINING

10.9.1 SITE TRAINING

All Investigators and trial personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions including training utilizing electronic media. Training of Investigators and trial personnel will include, but is not limited to, the investigational plan, investigational device usage, clinical investigation plan requirements, case report form completion and trial personnel responsibilities. All Investigators and trial personnel who are trained must sign a training log (or an equivalent) upon completion of the training. Investigator and trial personnel must not perform any trial-related procedures prior to being trained. All Investigators must be trained to the clinical investigation plan and trial procedures prior to enrolling patients.

10.9.2 TRAINING OF SPONSOR'S MONITORS

The trial monitors will be trained to the clinical investigational plan, case report forms, and investigational device usage in accordance with the Sponsor's and/or designee's standard procedures.

10.10 QUALITY ASSURANCE ASSESSMENTS

The Sponsor and/or designee may conduct periodic compliance assessments (on-site audits) at the investigational study sites. A Sponsor representative or designee may request access to all trial records, including source documentation, for inspection and duplication during a compliance assessment. The Investigator and research coordinator must be available to respond to reasonable requests and queries made during the compliance assessment process.

10.11 REGULATORY AGENCY INSPECTION

In the event that an Investigator is contacted by a Regulatory Agency in relation to this trial, the Investigator will notify the Sponsor immediately. The Investigator and research coordinator must be available to respond to reasonable requests and inspection queries made during the inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of this trial. The Sponsor will provide any needed assistance in response to regulatory inspections.

10.12 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. A quality management plan will be developed to describe a study's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated and collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.13 PROCEDURES USED FOR DATA REVIEW, DATABASE CLEANING, AND ISSUING AND RESOLVING DATA QUERIES

Cardiovascular Research foundation (New York, NY) will provide the electronic data capture (EDC) services for the trial. The sites are responsible for completing the clinical electronic CRF (eCRF) from the EDC clinical database. The data cleaning routines are performed during data entry through automatic edit checks that occur during data entry by the sites into the EDC system. The auto-queries are generated by the EDC system and are resolved by the site. Those auto-queries will be cleared when the revised data entry meets the edit check criteria, or the monitor accepts the revised entry. The manual queries are created by the site monitors. The Data Manager from Cardiovascular Research Foundation can create manual queries on data as well for the sites to review. The EDC system flags the records with data queries which are resolved by the site, and the manual queries are cleared by the originating personnel. Tracking of data cleaning query status is facilitated by listings from the EDC system. Data listings needed for data review are also created within the EDC system. Refer to the separate Data Management Plan for specific details.

10.13.1 PROCEDURES FOR VERIFICATION, VALIDATION, AND SECURING OF ELECTRONIC CLINICAL DATA SYSTEMS

The trial website will be managed by Cardiovascular Research Foundation (New York, NY). The EDC will meet patient confidentiality requirements consistent with applicable regulations such as the US HIPAA (Health Insurance Portability and Accountability Act). The trial website will enforce restricted access control mechanisms under the management of Cardiovascular Research Foundation and will incorporate encrypted point-to-point data transfer via secure HTTP protocols. Trial Investigators/sites will enter data online; data will be stored at a secure and confidential location, and will be reviewed and analyzed on a regular basis. Further details of verification, validation, and securing of electronic clinical data systems can be found in the trial specific Data Management Plan.

10.14 PROTOCOL DEVIATIONS

10.14.1 STATEMENT SPECIFYING THAT THE INVESTIGATOR IS NOT ALLOWED TO DEVIATE FROM THE CIP

No investigative procedures other than those defined in this clinical investigational plan will be undertaken on the enrolled subjects without the written agreement of the IRB and Sponsor.

It is the Investigator's responsibility to ensure that there are no deviations from the clinical investigational plan and full compliance with all established procedures of the IRB is maintained. The Investigator will not deviate from the clinical investigational plan for any reason except in cases of medical emergencies, when the deviation is necessary to protect the life or physical well-being of the subject. Such deviations must be reported to IRBs/ECs and Sponsor within 24 hours from the time of the deviation.

10.14.2 PROCEDURES FOR RECORDING, REPORTING, AND ANALYZING CIP DEVIATIONS

A deviation is an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the Clinical Investigation Plan. All deviations must be reported to the Sponsor. The occurrence of clinical investigational plan deviations will be monitored by the Sponsor or designee. It is the Investigator's responsibility to inform their IRB of clinical investigational plan deviations in accordance with their specific IRB reporting policies and procedures.

In the event that a study site does not comply with the Investigator Agreement or Clinical Investigational Plan, the Sponsor will notify the Investigator of the site’s non-compliance. Continued non-compliance may result in further escalation in accordance with the Sponsor’s standard procedures.

10.14.3 NOTIFICATION REQUIREMENTS

Major protocol deviations shall be reported to the trial Sponsor and IRB. Sponsor approved personnel will also observe and record any protocol deviations during routine monitoring visits and follow up accordingly.

10.14.4 CORRECTIVE AND PREVENTATIVE ACTIONS AND PRINCIPAL INVESTIGATOR DISQUALIFICATION CRITERIA

Protocol deviations and site/Primary-Investigator non-compliance will be closely monitored by the Sponsor and appointed sponsor personnel. Identifying deviations and taking corrective actions at the earliest possible stage will increase the potential for clinical trial success and reduced patient risk. The initiation of a corrective and preventative action (CAPA) to investigate and establish corrective actions may be required in some cases. The Sponsor reserves the right to close a clinical study site or replace a PI if non-compliance is observed.

10.14.5 PUBLICATION AND DATA SHARING POLICY

The Sponsor of this trial, recognizing the seminal importance of this investigation, is committed to the unrestricted and widespread dissemination of all primary and secondary endpoint results and tertiary analyses. At the conclusion of the trial, a multicenter abstract reporting the primary results will be prepared by the Executive Committee Investigators and presented at an annual scientific meeting. A multicenter publication will similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the trial is not allowed until both the presentation and publication of the multicenter results.

10.14.6 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Executive Committee have established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11 ABBREVIATIONS

6MWT	6-Minute Walk Test
ACE	Angiotensin Converting Enzyme Inhibitor
ADHF	Acute Decompensated Heart Failure
AE	Adverse Event
AF	Atrial Fibrillation
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor-Neprilysin Inhibitor
ASD	Atrial Septal Defect
BARC	Bleeding Academic Research Consortium
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CSAP	Canadian Special Access Program
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
DVT	Deep Venous Thrombosis
EC	Ethics Committee
eCRF	Electronic Case Report Forms
eGFR	Estimated Glomerular Filtration Rate
EQ-5D	EQ-5D is a standardized measure of health status developed by the EuroQol Group
FDA	Food and Drug Administration
FIM	First-in-Man
FO	Fossa Ovalis
GCP	Good Clinical Practice
GDMT	Guideline-directed Medical Therapy
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HCN	Hyperpolarization-activated Cyclic Nucleotide Channel Blocker
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICD	Implantable Cardioverter/Defibrillator
ICE	Intracardiac Echocardiogram
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IFU	Instructions-for-Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention-To-Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire

LAP	Left Atrial Pressure
LV	Left Ventricle
LVAD	Left Ventricular Assist Device, including any form of Mechanical Circulatory Support
LVEF	Left Ventricular Ejection Fraction
MACNE	Major Acute Cardiovascular or Neurological Event
MAUDE	Manufacturer and User Facility Device Experience
MOP	Manual of Operations
MRA	Mineralocorticoid Receptor Inhibitor
NCT	National Clinical Trial
NIH	National Institutes of Health
NYHA	New York Heart Association Functional Class
OUS	Outside of the United States
PAP	Pulmonary Artery Pressure
PFO	Patent Foremen Ovale
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
Qp:Qs	Pulmonary to Systemic Blood Flow Ratio
RV	Right Ventricle
RVFAC	Right Ventricular Factional Area Change
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
TAPSE	Tricuspid Annular Plane Systolic Excursion
TEE	Transesophageal Echocardiogram
TMF	Trial Master File
TTE	Transthoracic Echocardiogram
US	United States
VTE	Venous Thromboembolism

12 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
0.0	February 13, 2018	N/A	Initial Release

13 REFERENCES

1 Adams KF, Lindenfeld J, Arnold J M. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. J Heart Failure 2006; 12:10-38.

2 Ambrosy P, Fonarow GC, Butler J, et al. The Global Health and Economic Burden of Hospitalizations for Heart Failure. Lessons Learned From Hospitalized Heart Failure Registries. J Am Coll Cardiol. 2014;63:1123–1133.

3 Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics-2009 Update. A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009; 119:e1-e161.

4 Butler J, Braunwald E, Gheorghiade M. Recognizing worsening chronic heart failure as an entity and an end point in clinical trials. JAMA. 2014;312(8):789-90.

5 Schiff GD, Fung S, Speroff T, et al. Decompensated heart failure: symptoms, patterns of onset, and contributing factors. The American journal of medicine 2003;114(8):625-30.

6 Adamson PB, Magalski A, Braunschweig F, et al. Ongoing right ventricular hemodynamics in heart failure: clinical value of measurements derived from an implantable monitoring system. Journal of the American College of Cardiology 2003;41(4):565-71.

7 Fonarow GC, Adams KF, Abraham WT, et al. Risk Stratification for in-hospital mortality in acutely decompensated heart failure. JAMA 2005;293:572-580.

8 Ritzema J, Troughton R, Melton I, Crozier I, Doughty R, Krum H, Walton A, Adamson P, Kar S, Shah PK, Richards M, Eigler NL, Whiting JS, Haas GJ, Heywood JT, Frampton CM, Abraham WT; Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) Study Group. Physician-directed patient self-management of left atrial pressure in advanced chronic heart failure. Circulation. 2010 Mar 9;121(9):1086-95.

9 Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119(14):e391-479.

10 McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–1847.

11 Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. New Engl J Med. 2006;355:251-259.

12 Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Current heart failure reports. 2013;10(4):401-410.

13 Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. Journal of the American College of Cardiology. 2004;43(3):317-327.

14 Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240-e327. DOI: 10.1161/CIR.0b013e31829e8776.

15 Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;000:e000–e000. DOI: 10.1161/CIR.0000000000000509.

16 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016 Aug;18(8):891-975. doi: 10.1002/ejhf.592. Epub 2016 May 20.

17 Abraham WT1, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomized controlled trial. Lancet. 2011 Feb 19;377(9766):658-66. doi: 10.1016/S0140-6736(11)60101-3.

18 Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2015 Update: A Report From the American Heart Association. Circulation. 2014.

19 Popovic JR, Kozak LJ. Vital and health statistics from the Centers for Disease Control and Prevention/National Center for Health Statistics: national hospital discharge survey annual summary, 1998.

20 Adams KF, Fonarow GC, Emerman CL, et. al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: Rationale, design and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National registry (ADHERE). Am Heart J 2005; 149: 209-216.

21 Fonarow GC, Gattis Strough W, Abraham WT. et. al. Characteristics, Treatments and Outcomes of Patients with Preserved Systolic Function Hospitalized for Heart Failure. JACC 2007; 50(8): 768-777.

22 Gheorghiade M, Zannad FZ, Sopko G, et. al. Acute Heart Failure Syndromes, Current State and Framework for Future Research. Circulation 2005; 112: 3958-3968.

23 Chen J, Norman SLT, Wan Y, Krumhollz HM, National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. JAMA 2011;306:1669-1678.

24 Owan TE, Hodge DO, Herges RM, Jacobsen SJ, et al. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. N Engl J Med 2006;355:251-9.

25 Krumholz HM, Merrill AR, Schone EM, Schreiner GC, Chen J, Bradley EH, Wang Y, Wang Y, Lin Z, Straube BM, Rapp MT, Normand SL, Drye EE. Patterns of hospital performance in acute myocardial infarction and heart failure 30-day mortality and readmission. Circ Cardiovasc Qual Outcomes. 2009;2:407–413.

26 Chun S, Tu JV, Wijeysundera HC, Austin PC, Wang X, Levy D, Lee DS. Lifetime analysis of hospitalizations and survival of patients newly-admitted with heart failure. Circ Heart Fail. May 2, 2012.

27 Cleland JGF, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme--a survey on the quality of care among patients with heart failure in Europe: Part 1: patient characteristics and diagnosis. Eur Heart J 2003;24:442-463.

28 Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of Tolvaptan, a Vasopressin Antagonist, in Patients Hospitalized With Worsening Heart Failure: A Randomized Controlled Trial. JAMA 2004;291:1963-1971.

29 Setogoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. Am Heart J 2007;154:260-266.

30 Ritzema J, Troughton R, Melton I, Crozier I, Doughty R, Krum H, Walton A, Adamson P, Kar S, Shah PK, Richards M, Eigler NL, Whiting JS, Haas GJ, Heywood JT, Frampton CM, Abraham WT; Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) Study Group. Physician-directed patient self-management of left atrial pressure in advanced chronic heart failure. Circulation. 2010 Mar 9;121(9):1086-95.

31 Abraham WT, Stevenson LW, Bourge RC, et al. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomized trial. Lancet. 2016 Jan 30;387(10017):453-61. doi: 10.1016/S0140-6736(15)00723-0. Epub 2015 Nov 9.

32 Adamson PB, Abraham WT, Bourge RC et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail 2014;7:935-944.

33 Abraham WT, Stevenson LW, Bourge RC, et al. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomized trial. Lancet. 2016 Jan 30;387(10017):453-61. doi: 10.1016/S0140-6736(15)00723-0. Epub 2015 Nov 9.

34 Adamson PB, Abraham WT, Bourge RC et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail 2014;7:935-944.

35 Drazner MH, Hamilton MA, Fonarow G, et al. Relationship between right and left-sided filling pressures in 1000 patients with advanced heart failure. J Heart Lung Transplant 1999;18:1126-1132.

36 Viaene D, Vermeersch P, Van den Branden F. Pulmonary oedema after percutaneous ASD-closure. Acta Cardiol. 2010 Apr;65(2):257-60.

37 Beyer J, Brunner L, Hugel W, Kreuzer E, Reichart B, Sunder-Plassmann L, et al. Acute left heart failure following repair of atrial septal defects. Its treatment by reopening. Thoraxchir Vask Chir 1975; 23: 346-349.

38 Schubert S, Peters B, Abdul-Khaliq H, Nagdyman N, Lange PE, Ewert P. Left ventricular conditioning in the elderly patient to prevent congestive heart failure after transcatheter closure of atrial septal defect. Catheter Cardiovasc Interv 2005; 64: 333-337.

39 Seib PM, Faulkner SC, Erickson CC, Van Devanter SH, Harrell JE, Fasules JW, Frazier EA, Morrow WR. Blade and balloon atrial septostomy for left heart decompression in patients with severe ventricular dysfunction on extracorporeal membrane oxygenation. Catheter Cardiovasc Interv. 1999 Feb;46(2):179-86.

40 Burkhoff D, Mirsky I, Suga H, Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Phsiol Heart Circ Physiol 2005;289:H501-H512.

41 Eigler NL, del Rio CL, Verheye S. et al. Cardiac unloading with an implantable interatrial shunt in heart failure: serial observations in an ovine model of ischemic cardiomyopathy. Structural Heart 2017; 1:1-2, 40-48.

42 Del Trigo M, Bergeron S, Bernier M, et al. Unidirectional left-to-right interatrial shunting for treatment of patients with heart failure with reduced ejection fraction: a safety and proof-of-principle cohort study. The Lancet;387:1290-1297.

43 Hasenfuß G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, Malek F, Van der Heyden J, Lang I, Petrie MC, Cleland JG, Leon M, Kaye DM; REDUCE LAP-HF study investigators. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. Lancet. 2016 Mar 26;387(10025):1298-304. doi: 10.1016/S0140-6736(16)00704-2.

44 Kaye DM, Hasenfuß G, Neuzil P, Post MC, Doughty R, Trochu JN, Kolodziej A, Westenfeld R, Penicka M, Rosenberg M, Walton A, Muller D, Walters D, Hausleiter J, Raake P, Petrie MC, Bergmann M, Jondeau G, Feldman T, Veldhuisen DJ, Ponikowski P, Silvestry FE, Burkhoff D, Hayward C. One-Year Outcomes After Transcatheter Insertion of an Interatrial Shunt Device for the Management of Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2016 Dec;9(12). pii: e003662.

45 Feldman T, Komtebedde J, Burkhoff D, Massaro J, Maurer MS, Leon MB, Kaye D, Silvestry FE, Cleland JG, Kitzman D, Kubo SH, Van Veldhuisen DJ, Kleber F, Trochu JN, Auricchio A, Gustafsson F, Hasenfuβ G, Ponikowski P, Filippatos G, Mauri L, Shah SJ. Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure: Rationale and Design of the Randomized Trial to REDUCE Elevated Left Atrial Pressure in Heart Failure (REDUCE LAP-HF I). Circ Heart Fail. 2016 Jul;9(7). pii: e003025. doi: 10.1161/CIRCHEARTFAILURE.116.003025.

46 Cappato R, Calkins H, Chen SA, et al. Prevalence and causes of fatal outcome in catheter ablation of atrial fibrillation. J Am Coll Cardiol 2009;53:1798-803.

47 Belhassen B. A 1 per 1,000 mortality rate after catheter ablation of atrial fibrillation, an acceptable risk? J Am Coll Cardiol 2009;804-8-5.

48 Feldman T, Foster E, Glower DD, et al, for the EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. J Engl J Med 2011;364:395-406.

49 De Ponti R, Cappato R, Curnis A, et al. Trans-septal catheterization in the electrophysiology laboratory, data from a multicenter survey spanning 12 years. J Am Coll Cardiol 2006;47:1037-1042.

50 Holmes DR, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy. J Am Coll Cardiol 2014;64:1-12.

51 Percutaneous mitral valve repair with the MitraClip clip delivery system in high surgical risk patient. Briefing document for the Circulatory Systems Device Panel Advisory Committee. 20 March 2013.

52 Howell MD, Geraci JM, Knowlton AA. Congestive heart failure and outpatient risk of venous thromboembolism: a retrospective, case-control study. J Clin Epidemiol. 2001;54:810–816.

53 Beemath A, Skaf E, Stein PD. Pulmonary embolism as a cause of death in adults who died with heart failure. Am J Cardiol. 2006;98:1073–1075.

54 Chiche O, Castellani M, et al. E. Prevalence of patent foramen ovale and stroke in pulmonary embolism patients. Eur Heart J. 2013;34:1142.

55 Bannan A, Shen R, Silvestry FE, et al. Characteristics of adult patients with atrial septal defects presenting with paradoxical embolism. Catheter Cardiovasc Interv 2009;74:1066–9.

56 Geva T, Martins JD, Wald RM. Atrial septal defects. Lancet 2014;383:1921–32.

57 McClean D, Aragon J, Jamali A, et al. Noninvasive calibration of cardiac pressure transducers in patients with heart failure: An aid to implantable hemodynamic monitoring and therapeutic guidance. J Card Fail 2006;12:567-576.

58 Haeusler KG, Laufs U, Endres M. Chronic heart failure and ischemic stroke. Stroke 2011;42:2977-2982.

59 Abdul-Rahim AH, Perez AC, Fulton RL et al. Risk of stroke in chronic heart failure patients without atrial fibrillation. Analysis of the controlled Rosuvastatin in multinational trial heart failure (COROMA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) trial. Circulation 2015;131:1486-1494.

60 Arboix A, Alio J. Cardioembolic stroke: clinical feature, specific cardiac disorders and prognosis. Current Cardiol Rev 2010:6:150-161.

61 Krumsdorf U, Ostermayer S, Billinger K, et al. Incidence and clinical course of thrombus formation on atrial septal defect and patent foramen ovale closure devices in 1,000 consecutive patients. J Am Coll Cardiol 2004;43:302–9.

62 Baumgartner H, Bonhoeffer P, Groot NMS, et al. ESC guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 2010;31:2915-2957.

63 Therrien J, Warnes C, Daliento L, et al. Canadian Cardiovascular Society Consensus Conference 2001 update: recommendations for the management of adults with congenital heart disease part III. Can J Cardiol. 2001;17:1135–1158.

64 Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society,

International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008 Dec 2;52(23):e143-263.

65 Webb G, Gatzoulis MA. Atrial septal Defects in the Adult: Recent progress and overview. Circulation 2006;114:1645:1653.

66 Chan NY, Choy CC, Lau CL, et al. Persistent iatrogenic atrial septal defect after pulmonary vein isolation by cryoballoon: an under-recognized complication. Europace 2011 Oct;13(10):1406-10.

67 Rillig A, Meyerfeldt U, Kunze M, et al. Persistent iatrogenic atrial septal defect after a single-puncture, double-transseptal approach for pulmonary vein isolation using a remote robotic navigation system: results from a prospective study. Europace 2010 Mar;12(3):331-6.

68 McGinty PM, Smith TW, Rogers JH. Transseptal left heart catheterization and the incidence of persistent iatrogenic atrial septal defects. J Interv Cardiol. 2011 Jun;24(3):254-63.

69 Hoffman R, Altiok E, Rieth S. Functional effect of new atrial septal defect after percutaneous mitral valve repair using the MitraClip device. Am J Cardiol 2014;113:1228-1233.

70 Korkmaz S, Demirkan B, Guray Y, et al. Long-term follow-up of iatrogenic atrial septal defect: after percutaneous mitral balloon valvuloplasty. Tex Heart Inst J. 2011;38(5):523-7.

71 Hammerstingl C, Licfett L, Jeong KM, et al. Persistence of iatrogenic atrial septal defect after pulmonary vein isolation—an underestimated risk? Am Heart J 2006;152:e1-362.e5.

72 Yousuf MA, Haqwue S, O'donnell R, et al. Right heart failure from persistent iatrogenic atrial septal defect following atrial fibrillation ablation. J Am Coll Cardiol 2014;63:A661.

73 Shueler R, Ozturk C, Wedekind JA, et al. Persistence of iatrogenic atrial septal defect after interventional mitral valve repair with the MitraClip system, A note of caution. J Am Coll Cardiol Intv 2015;8:450-459.

74 FDA. FDA Executive Summary P130013 Boston Scientific Watchman Left Atrial Appendage Closure Therapy. 2013;

75 Percutaneous mitral valve repair with the MitraClip clip delivery system in high surgical risk patient. Briefing document for the Circulatory Systems Device Panel Advisory Committee. 20 March 2013.

76 Finkelstein DM, Shoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Statistics in Medicine. 1999;18:1341-1344.

77 Lansky AJ, et al. J AM Coll Cardiol. 2017;69(6):679-691. doi.org/10.1016/j.jacc.2016.11.045.

78 Bourge RC, Abraham WT, Adamson PB, et al. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure. The COMPASS-HF Study. JACC 2008;51:1073-9.

79 Abraham WT, Adamson PB, Constanzo MR, et al. Hemodynamic Monitoring in Advanced Heart Failure: Results from the LAPTOP-HF Trial. Journal of Cardiac Failure: 22(11):940.

80 Cui L, Hung HMJ, Wang S-J. Modification of sample size in group sequential clinical trials. Biometrics 1999;55:853-857.

RELIEVE-HF TRIAL:
REducing Lung congestIon symptoms using the v-wavE shunt in adVancEd Heart Failure

Protocol Number: CL7018

National Clinical Trial (NCT) Identifier Number: NCT03499236 Executive

Committee Investigators:

Stefan D. Anker, MD, PhD, JoAnn Lindenfeld, MD Josep Rodés-Cabau, MD,

Gregg W. Stone, MD

IDE Sponsor: V-Wave, Ltd.

EU Sponsor Representative: genae Belgium nv Version Number: v.7.0

September 27, 2021

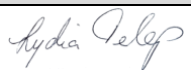
Sponsor	V-Wave, Ltd. POB 3076, 5 Tarshish Street, Caesarea Industrial Park (North), 3088900, Israel
Medical Monitoring Oversight	Details will be provided upon request
European Sponsor Representative	genae Belgium nv Justitiestraat 6B 2018 Antwerp, Belgium
Site Monitoring/Safety/Regulatory	Details will be provided upon request
Echocardiography Core Laboratory	Details will be provided upon request
Clinical Investigation Plan Version and Date	Version 7.0, September 27, 2021

This Clinical Investigation Plan has been written in accordance with Annex A of EN ISO 14155 (2011): Clinical investigations of medical devices for human subjects – Good Clinical Practice and ICH E6 Guidelines. In accordance with EN ISO 14155, where information is held within other trial documentation, e.g. in the Investigator Brochure, this is referenced where appropriate.

Compliance Statement

The trial will be conducted in accordance with the design and specific provisions of this clinical investigation plan, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP), EN ISO 14155, ICH E6, and the applicable regulatory requirements. The trial will also be conducted according to applicable Code of Federal Regulations including 21 CFR parts 50, 56 and 812 for U.S. sites and 812.28 (a)(1) for international sites.

PREPARED AND APPROVED BY:

NAME	TITLE, DATE, SIGNATURE
Lydia Telep	Electronically signed by: Lydia Telep Reason: I have reviewed and approve this document Date: Nov 9, 2021 20:40 EDT **Signature:**  **Email:** lydia@vwavemedical.com **Title:** VP Regulatory Affairs
Lori DonDiego	Electronically signed by: Lori DonDiego Reason: I have reviewed and approve this document Date: Nov 9, 2021 20:40 EDT **Signature:**  **Email:** lori@vwavemedical.com **Title:** Director, RA
Karen Foley	Electronically signed by: Karen Foley Reason: I have reviewed and approve this document Date: Nov 9, 2021 20:40 EDT **Signature:**  **Email:** Karen@vwavemedical.com **Title:** Sr Director Clinical Operations
Neal Eigler	Electronically signed by: Neal Eigler Reason: I have reviewed and approve this document Date: Nov 9, 2021 20:40 EDT **Signature:**  **Email:** neal@vwavemedical.com **Title:** CEO
William Abraham	Electronically signed by: William T Abraham, MD Reason: I have reviewed and approve this document Date: Nov 9, 2021 23:40 EST **Signature:**  **Email:** bill@vwavemedical.com **Title:** CMO
Gali Tzury	Electronically signed by: Gali Tzury Reason: I have reviewed and approve this document Date: Nov 9, 2021 20:40 GMT+2 **Signature:**  **Email:** gali@vwavemedical.com **Title:** VP QA
Olivia Mishall	Electronically signed by: Olivia Reason: I have reviewed and approve this document Date: Nov 9, 2021 21:29 GMT+2 **Signature:** Olivia **Email:** olivia@vwavemedical.com **Title:** Sr. Director Clinical Operations IL/EU

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

REducing Lung congestIon symptoms using the v-wavE shunt in adVancEd Heart Failure

CIP No: CL7018

I have read this clinical investigation plan and appendices and agree to adhere to the requirements. I will provide copies of this clinical investigation plan and all pertinent information to the trial personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the device and the conduct of the trial.

I will conduct the trial in accordance with the clinical investigation plan, , in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and consistent with Good Clinical Practice guidelines, EN ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice), ICH E6, as well as all applicable local regulations. I also accept respective revisions to the clinical investigation plan approved by authorized personnel of the Sponsor and by regulatory authorities.

The trial will also be conducted according to applicable U.S. Code of Federal Regulations including 21 CFR parts 50, 56 and 812 for U.S. sites and part 812.28(a)(1) for international sites. As an investigator in this study, and in accordance with the U.S. 21 CFR Part 812.43(c) (4), I commit to:

i. Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB/Ethic Committee, or US FDA;
ii. Supervise all testing of the device involving human subjects; and
iii. Ensure that the requirements for obtaining informed consent are met.

_____	_____
Principal Investigator Name	Signature and Date
_____	_____
Institution Name	Location
_____	_____
Sub-Investigator Name	Signature and Date

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable ISO standards and United States (US) Code of Federal Regulations (CFR) including 21 CFR parts 50, 56 and 812 for US sites and 812.28.a.1 for international sites. The Principal Investigator(s) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational Device Exemption (IDE) sponsor and FDA/Competent Authority review, and documented approval from the Institutional Review Board (IRB) or Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the trial participants. All site personnel will complete Human Subjects Protection and ICH GCP Training prior to be involved in the conduct of this study.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB/EC for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB and FDA/Competent Authority review before the changes are implemented to the study. All changes to the consent form will be IRB/EC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:

RELIEVE-HF TRIAL: REducing **L**ung congest**I**on symptoms using the v-wav**E** shunt in ad**V**anc**E**d **H**eart **F**ailure

Study Description:

The Study Device, the V-Wave Interatrial Shunt System, includes a permanent implant—the Shunt, placed during a minimally invasive cardiac catheterization procedure using its dedicated Delivery Catheter. By transferring blood from the left to the right atrium, the Shunt is intended to reduce excessive left-sided cardiac filling pressures in patients with advanced heart failure (HF). The anticipated outcomes are a reduction in symptoms related to pulmonary congestion including breathlessness, improved exercise capacity, and reduced need for hospitalization or emergency treatment for acute decompensated heart failure (ADHF).

The study is a prospective, multi-center, 1:1 randomized, patient and observer blinded trial, with a Shunt Treatment arm and a non-implant Control arm. A total of approximately 400 patients will be randomized, with a possible increase up to a total of approximately 600 patients based on the results of a planned interim analysis. Each site may implant up to 2

Roll-in patients before randomizing to become familiar with the device and procedures. The primary analysis will be performed when the last enrolled patient has been followed for a minimum of 12 months from randomization. The duration of follow-up evaluated by the primary effectiveness endpoint will range from a minimum of 12 to a maximum of 24 months. All implanted patients (Roll-Ins, Randomized to Treatment and Control patients that cross-over and receive the shunt) will be followed for a total of 5 years from the time of the Study Device implantation.

Objective:

The objective of this study is to provide reasonable assurance of safety and effectiveness of the V-Wave Interatrial Shunt System to improve clinical outcomes in a certain high-risk subset of symptomatic patients suffering from HF.

Endpoints:

Primary Safety Endpoint

The percentage of Treatment Group patients experiencing device-related Major Adverse Cardiovascular and Neurological Events (MACNE) during the first 30-days after randomization, compared to a pre-specified Performance Goal.

Primary Effectiveness Endpoint

Comparison between Treatment and Control groups of the hierarchical composite ranking of all-cause death, cardiac transplantation or left ventricular assist device (LVAD) implantation, recurrent HF hospitalizations (including Emergency Room HF Visits with duration ≥6 hours), recurrent worsening HF events treated as an outpatient (including ER visits < 6 hours), and change in KCCQ overall score. The analysis is based on the method of Finkelstein and Schoenfeld.

Hierarchically Tested Secondary Effectiveness Endpoints

- KCCQ changes from Baseline to 12 months
- Heart failure hospitalizations adjusted for all-cause mortality
- Time to all-cause death, LVAD/Transplant, or heart failure hospitalization
- Time to all-cause death or first heart failure hospitalization
- Cumulative heart failure hospitalizations
- Time to first heart failure hospitalization
- Modified Primary Effectiveness Endpoint including all-cause death, LVAD/Transplant, HF Hospitalizations, and worsening HF events treated as an outpatient but without KCCQ

- 6MWT changes from Baseline to 12 months

Additional Effectiveness Outcome Measurements

- NYHA Class
- Patient Global Assessment
- Combined all-cause death and all-cause hospitalizations
- All-cause death
- Time to all-cause death (KM analysis)
- Time to cardiovascular death (KM analysis)
- Time to all-cause death, transplant or LVAD (KM analysis)
- Time to cardiovascular death, transplant or LVAD (KM analysis)
- Days alive free from heart failure hospitalization
- Outpatient clinic HF visit and /or intensification of heart failure therapy
- Emergency room HF visits
- HF Clinical Composite Assessment (improved, unchanged, or worsened) as described by Packer comprised of all-cause mortality, HF hospitalization, and changes in NYHA functional class ranking and Patient Global Assessment
- Comparison of transthoracic echocardiographic parameters as listed in Echocardiography Core Laboratory Manual
- Incidence of loss of shunt flow as measured on TTE and/or TEE
- Changes in 6MWT
- Death: All-cause; Cardiovascular cause (with breakdown by cause, e.g. sudden death, myocardial infarction, pump failure, stroke); Non-Cardiovascular cause; Undetermined cause; and relationship to device, study intervention or other cardiovascular procedure
- Hospitalization: All-cause; HF hospitalization, Non-HF hospitalization (with breakdown for cause including if associated with secondary worsening of HF)
- Change in renal function
- Medication utilization including type, dose, frequency, and changes
- Cost and cost-effectiveness data
- Technical success defined as successful delivery and deployment of the shunt and removal of the delivery catheter
- Technical success
- Device success
- Procedural success

- For Roll-in patients, transesophageal or intracardiac echocardiography at 6 and 12 months to assess shunt patency and other parameters as listed in the Echocardiography Core Laboratory Manual

Additional Safety Data Collection

- Major Adverse Cardiovascular and Neurological Events (MACNE) and Bleeding Academic Research Consortium (BARC) types 3 and 5 bleeding at 30 days
- Percentage of Treatment Group patients with device related MACNE at 12 months
- Incidence of all Serious Adverse Events by type at study duration
- Incidence of cerebrovascular events at study duration with sub-classification of CNS infarction, CNS hemorrhage, and TIA and their relationship to device or study procedures (per NeuroARC)
- Incidence of MI events at study duration after implantation
- Incidence of systemic embolization events at study duration after implantation
- Incidence of pulmonary embolism events at study duration after implantation
- Incidence of shunt implant embolization at study duration
- Device-related MACNE annually through 5 years
- Study device related MACNE in Shunt treated patients receiving LVADs for 5-year post study device implantation.

Study Population:

NYHA functional class II, class III or ambulatory class IV HF irrespective of left ventricular ejection fraction, who have a history of hospitalization for worsening HF or BMI corrected elevated levels of BNP/NT-proBNP, in the setting of guideline-directed HF medical (including drug and device) therapy (GDMT).

Inclusion Criteria:

1. Ischemic or non-ischemic cardiomyopathy with either reduced or preserved LV ejection fraction and documented heart failure for at least 6 months from Baseline Visit.
2. NYHA Class II, Class III, or ambulatory Class IV HF (historical assessment documented at the Baseline Screening visit).
3. Receiving guideline directed medical therapy (GDMT) for heart failure which refers to those HF drugs carrying a Class I indication:
   a) Patients with reduced LVEF (≤40%): An inhibitor of the renin-angiotensin system (RAS inhibitor), including an angiotensin-

converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI) and a beta-blocker (BB), for at least 3 months prior to the Baseline Visit.

b) Patients with reduced LVEF (≤40%): Other medications recommended for selected populations, e.g., mineralocorticoid receptor antagonist (MRA) or nitrates/hydralazine should be used in appropriate patients, according to the published guidelines.
c) All patients: Patient has been on stable HF medications as determined by the investigator, for at least 1 month, with the exception of diuretic therapy. Stable is defined as no more than a 100% increase or 50% decrease in dose within these periods.
d) All patients: Drug intolerance, contraindications, or lack of indications must be attested to by the investigator. Patients should be on appropriate doses of diuretics as required for volume control.

4. Receiving Class I recommended cardiac rhythm management device therapy. Specifically: if indicated by class I guidelines, cardiac resynchronization therapy (CRT), implanted cardioverter-defibrillator (ICD) or a pacemaker should be implanted at least 3 months prior to Baseline Visit. These criteria may be waived if a patient is clinically contraindicated for these therapies or refuses them and must be attested to by the investigator.
5. NYHA Class II must meet both 5a **AND** 5b. NYHA Class III and ambulatory Class IV must meet 5a **OR** 5b.
   a) One (1) prior Heart Failure Hospitalization with duration >24 hours or Emergency Room Heart Failure Visit with duration ≥6 hours, or Heart Failure Clinic ADHF Visit with duration ≥6 hours, within 12 months from Baseline Visit.
      i) If a CRT device was previously implanted, the heart failure hospitalization must be ≥ 1 month after CRT implantation.
      ii) If a mitral valve repair device (e.g. MitraClip) was previously implanted, the heart failure hospitalization must be ≥ 1 month after mitral valve repair implantation.
   b) Alternatively, if patients have not had a HF hospitalization or ER HF Visit within the prior 12 months, they must have a corrected elevated Brain Natriuretic Peptide (BNP) level of at least 300 pg/ml or an N-terminal pro-BNP (NT-proBNP) level of at least 1,500 pg/ml, according to local measurement, within 3 months of the Baseline Visit during a clinically stable period and at least 1 month after implantation of a CRT or mitral valve repair devices. (Note: "corrected" refers to a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m^2 in BMI above a reference BMI of 20 kg/m^2). If patient is on ARNI, NT-proBNP should be used exclusively.

6. Able to perform the 6-minute walk test with a distance ≥100 meters and ≤450 meters. The test will be performed twice separated by a minimum of 60 minutes between tests. The second test may be performed up to 7 days after the first test, if needed. The higher reading shall be used as the baseline value.
7. Provide written informed consent for study participation and be willing and able to comply with the required tests, treatment instructions and follow-up visits.

Exclusion Criteria:

Preliminary Exclusion Criteria at Baseline

1. Age <18 years old.
2. BMI >45 or <18 kg/m^2.
3. Females of childbearing age who are not on contraceptives or surgically sterile, pregnant or lactating mothers.
4. Resting systolic blood pressure <90 or >160 mmHg after repeated measurements.
5. Baseline echocardiographic evidence of unresolved, non-organized or mobile intracardiac thrombus.
6. Severe pulmonary hypertension defined as PA systolic pressure >70 mmHg by echo/Doppler (or PVR >4.0 Wood Units by PA catheter measurement that cannot be reduced to ≤4 Wood Units by vasodilator therapy).
7. RV dysfunction defined as TAPSE <12mm or RVFAC ≤25% as assessed on Baseline TTE.
8. Left Ventricular End-Diastolic Diameter (LVEDD) >8cm as assessed on Baseline TTE.
9. Atrial septal defect (congenital or iatrogenic), patent foramen ovale, or anomalous pulmonary venous return, with more than trace shunting on color Doppler or intravenous saline contrast (bubble study) or prior surgical or interventional correction of congenital heart disease involving the atrial septum (excluding closure by suture only but including placement of a PFO or ASD closure device).
10. Untreated moderately severe or severe aortic or mitral stenosis.
11. Untreated severe or greater regurgitant valve lesions, which are anticipated to require surgical or percutaneous intervention within 12 months.
12. Mitral valve repair device (e.g. MitraClip) implanted within 3 months prior to Baseline Visit.
13. Untreated coronary stenosis which requires surgical or percutaneous intervention.

14. Acute MI, acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), rhythm management system revision, (not including generator change), lead extraction, or cardiac or other major surgery within 3 months of Baseline Visit. Rhythm management system generator change within 1 month of Baseline Visit.
15. Known active valvular vegetations, atrial myxoma, hypertrophic cardiomyopathy with significant resting or provoked subaortic gradient, acute myocarditis, tamponade, or large pericardial effusion, constrictive pericarditis, infiltrative cardiomyopathy (including cardiac sarcoidosis, amyloidosis, and hemochromatosis), or congenital heart disease, as cause of HF.
16. Stroke, transient ischemic attack (TIA), systemic or pulmonary thromboembolism, or deep vein thrombosis (DVT) within 6 months of Baseline Visit. Any prior stroke with permanent neurologic deficit. Existing IVC filter.
17. Transseptal procedure for another indication (e.g. AF ablation, left atrial appendage occlusion, mitral valve repair/replacement) anticipated within 6 months.
18. Bradycardia with heart rate <45 bpm (unless treated with a permanent pacemaker) or uncontrolled tachyarrhythmias. This includes defibrillation shocks reported by the patient within 30 days of Baseline Visit.
19. Intractable HF with:
    a) Resting symptoms despite maximal medical therapy (ACC/AHA HF Stage D).
    b) Treatment with IV vasoactive medications (e.g., IV inotropes, IV vasodilators) within the last 30 days.
    c) Cardiac Index <1.5 L/min/m^2.
    d) Treated with a ventricular assist device (VAD).
    e) Listed for cardiac transplantation.
20. Prior cardiac transplantation.
21. Patients with HFrEF (LVEF ≤40%) who are intolerant to a RAS inhibitor including all of ACEI, ARB or ARNI, and intolerant to beta-blocker medical therapy.
22. Not eligible for emergency cardiothoracic or vascular surgery in the event of cardiac perforation or other serious complication during study intervention procedure.
23. Life expectancy <1 year due to non-cardiovascular illness.
24. Coagulopathy or is taking anticoagulation therapy which cannot be interrupted for the study intervention procedure, or has contraindications for all of the study mandated post implantation anticoagulation / antiplatelet regimens or known hypersensitivity, or contraindication to procedural medications which cannot be adequately managed medically.
25. Estimated glomerular filtration rate (eGFR) <25 ml/min/1.73 m^2 by the MDRD method, or not responsive to diuretics, or is receiving dialysis.

26. Hepatic impairment with a documented liver function test result (transaminases, total bilirubin, or alkaline phosphatase) ≥ 3 times upper limit of normal.
27. Severe chronic pulmonary disease requiring daytime home oxygen or chronic oral steroid therapy (Note: nighttime oxygen therapy and inhaled steroid therapy are acceptable).
28. Active infection requiring parenteral or oral antibiotics.
29. Known allergy to nickel.
30. Any condition that may interfere with compliance of all protocol procedures, such as active drug addiction, active alcohol abuse, or psychiatric hospital admission for psychosis within the prior year.
31. Currently participating in a clinical trial of any investigational drug or device that has not reached its primary endpoint, or any study that may interfere with the procedures or endpoints of this trial. Participation in an observational study or registry with market approved drugs or devices would not exclude a patient from participation in this trial.
32. Patient is otherwise not appropriate for the study as determined by the investigator or the Eligibility Committee, for which the reasons must be documented.
33. Patient belongs to a vulnerable population per investigator's judgment or patient has any kind of disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures.

<u>Final Exclusion Criteria (FEC): Assessed during cardiac catheterization, at Study Intervention Visit, just prior to Randomization</u>

1. Change in clinical status between baseline screening and Study Intervention visit such that the patient is not stable to undergo the Intervention Procedure.
2. Females with a positive pregnancy test on laboratory testing for FEC.
3. Unable to undergo TEE or ICE.
4. Unable to tolerate or cooperate with general anesthesia or conscious sedation.
5. Anatomical anomaly on TEE or ICE that precludes implantation of Shunt across fossa ovalis (FO) of the interatrial septum including:
   a) Minimal FO Thickness >6mm.
   b) Minimal FO Length <10mm.
   c) ASD or PFO with more than a trace amount of shunting.
   d) Intracardiac thrombus felt to be acute and not present on prior exams.
   e) Atrial Septal Aneurysm defined as ≥ 10 mm of phasic septal excursion into either atrium or a sum total excursion of ≥ 15 mm during the cardiorespiratory cycle, with a base of ≥ 15 mm.
6. Inadequate vascular access for implantation of Shunt. Femoral venous or inferior vena cava (IVC) access for transseptal catheterization are

not patent as demonstrated by failure to pass Swan-Ganz or ICE catheter from the right or left femoral vein to the right atrium.

7. Hemodynamic, heart rhythm, or respiratory instability at time of cardiac catheterization including:
   a) Mean PCWP <7 mmHg, not correctable by IV volume infusion (maximum 1,000 ml normal saline or equivalent).
   b) Mean PCWP >35 mmHg, not correctable by medical therapy (e.g. IV Furosemide, IV or sublingual nitroglycerin).
   c) Right Atrial Pressure (RAP) ≥ Left Atrial Pressure (LAP or PCWP) when LAP (PCWP) ≥7 mmHg.
   d) Cardiac Index (CI) <1.5 liters/min/m^2 after correction of volume depletion with IV fluids (maximum 1,000 ml normal saline or equivalent).
   e) Severe pulmonary hypertension defined as PASP >70 mmHg associated with PVR >4.0 Wood Units, that cannot be reduced to PVR ≤4 Wood Units by acute vasodilator therapy.
   f) Resting systolic Blood Pressure <90 or >160 mmHg, not corrected with IV fluid administration or vasodilators, respectively.
   g) Need for IV infusions of vasopressor or inotropic medication. Transient hypotension or bradycardia during anesthesia or catheterization, manifest as a vagal or similar acute episode or dehydration, responding promptly to IV fluid boluses or IV push vasopressors or chronotropic agents is not an exclusion criterion.
   h) Malignant arrhythmias such as ventricular fibrillation, ventricular tachycardia, atrial fibrillation/flutter with rapid ventricular response associated with hypotension and requiring cardioversion.
   i) Acute respiratory distress or hypoxemia.
8. Patient is otherwise not appropriate for study as determined by the Investigator.

Study Duration:

The study duration from first patent enrolled until completion of the last follow-up is expected to take approximately 9 years.

Participant Duration:

Primary analysis will occur when the last patient enrolled completes 12 months of follow-up. Patients will be followed for the primary data analysis a minimum of 12 months and a maximum of 24 months from the time of randomization at the Study Intervention Procedure. Patients with less than 24 months of follow-up will complete randomized blinded follow- up when the last randomized patient has completed the 12-month visit.
Patients reaching 24 months prior to the last enrolled patient reaching 12 months will be unblinded. Patients randomized to the Control group who still meet inclusion/exclusion criteria will have the opportunity to cross- over and receive a shunt implant when they are unblinded. All implanted patients (Roll-Ins, Randomized to Treatment and Control patients that cross-over and receive the shunt) will be followed for a total of 5 years

from the time of the Study Device implantation. Control group patients who do not cross-over to receive a shunt implant, will cease to be followed once unblinding has occurred.

1.2 SCHEMA

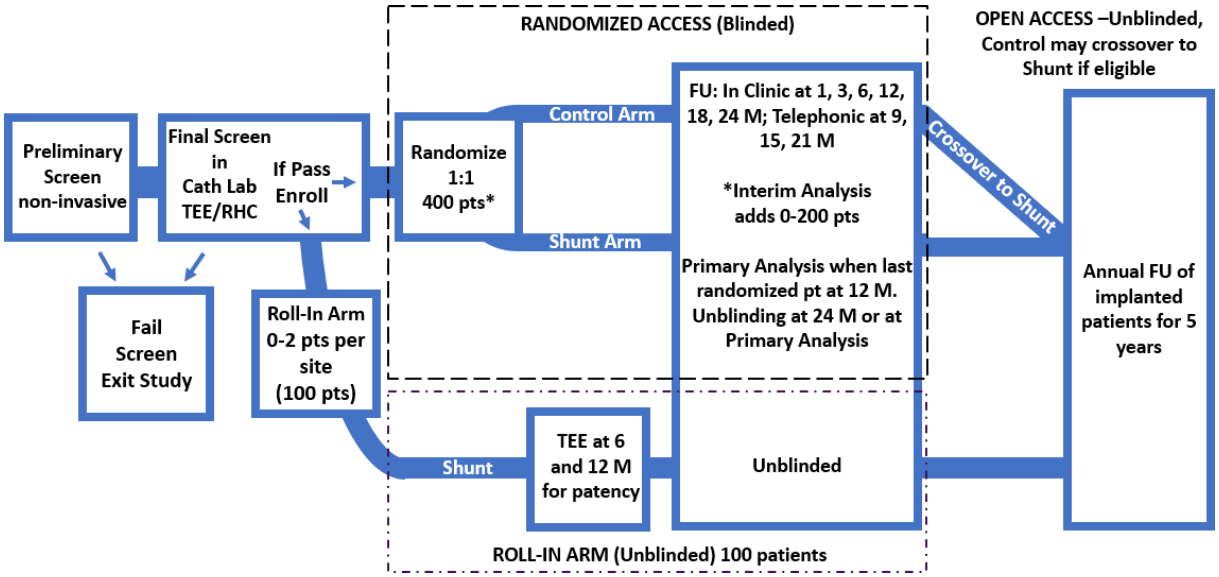


Figure 1. Patients are enrolled after successful two-phase screening. Up to 2 patients per site are enrolled into the open-label Roll-in arm where they are implanted with shunts, cases are proctored, and patients are followed as per the Randomized cohort with the addition of TEEs done at 6 and 12 months to evaluate shunt patency.
One to one patient randomization begins into the Shunt and Control arms. All patients receive GDMT. Control patients may receive the shunt device at the end of their 24-month follow-up or when the last patient reaches 12 months, if they consent and meet all study eligibility criteria again. Cross-over patients who receive the Shunt will be followed for 12 months according to the follow-up schedule described for the first 12 months post randomization. All patients implanted with shunts are followed annually for a total of 5 years from time of enrollment.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Visit Assessment	BASELINE SCREENING	FINAL SCREEN-STUDY INTERVENTION Implant or control	POST ENROLLMENT PRIOR TO DISCHARGE	2 WEEKS (telephone)	1, 24 MONTHS (in-clinic)	3, 18 MONTHS (in-clinic)	6, 12 MONTHS (in-clinic)	9, 15, 21 MONTHS (telephone)	ANNUAL years 3-5 (in-clinic)
Informed Consent	✓								
Demographics & Medical History	✓								
Vital signs, including weight and pulse oximetry	✓[1]	✓[1]	✓[1]		✓	✓	✓		✓
Physical Exam	✓	✓	✓		✓	✓	✓		✓
Medications	✓	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]	✓[2]
Na, K, Hgb, HCT, PLTS, WBC, Cr, BUN, AST, ALT, T Bili, Alk phos	✓		✓[3]		✓[3]		✓[3]		
Pregnancy, PT, PTT, INR, Hgb, HCT, Cr, cardiac Troponin (T, I or C)		✓							
COVID-19 Serological Tests [9]					✓				
BNP or NT-proBNP	✓								
12 Lead ECG	✓								
Chest X-Ray			✓						
Transthoracic echo (TTE)	✓				✓[4]		✓[4]		✓[4]
Transesophageal or intra cardiac echo (TEE/ICE)		ICE/TEE					TEE[5]		
Right Heart Catheterization (RHC)		✓							
NYHA Functional Class	✓				✓	✓	✓		✓
Patient Global Assessment					✓	✓	✓		✓
KCCQ, EQ-5D	✓				✓	✓	✓		✓
Cost Effectiveness[6]		✓	✓		✓	✓	✓		
6-min walk test (x2) / Borg scale	✓				✓	✓	✓		✓[7]
Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓
Worsening HF events treated as an outpatient[10]			✓	✓	✓	✓	✓	✓	✓
COVID-19 history	✓	✓	✓	✓	✓	✓	✓	✓	✓
I/E Criteria Review	✓	✓							
Complete Case Report Forms (CRFs)	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient Perception of Study Assignment			✓[8]				✓[8]		
Assure Blinding Procedures (Randomized pts)		✓	✓	✓	✓	✓	✓	✓	

1 Temperature and Pulse oximetry only required at Baseline, Study Intervention and Prior to Discharge

2 Only cardiovascular, anticoagulant, and antiplatelet therapy medications need be collected during follow-up. SGLT2 medications will also be collected.

3 Limit to CR, Hgb and HCT

4 Once unblinded, shunted patients will have TEE if no shunt flow seen on prior TTE

5 Follow-up TEE at 6 and 12 months will be performed in only the Roll-in arm patients. All patients including the Roll-in patients will have follow-up TTE at the protocol specified follow-up intervals.

6 US sites only
7 A single 6-min walk test is required during extended follow-up on years 3-5
8 Patient blinding assessment should be done on Randomized Patients and prior to discharge and 12-month follow-up only
9 COVID-19 Serological testing done at the time of unblinding, if required.
10 Assessed for randomized patients only

2 INTRODUCTION

2.1 RATIONALE

Heart failure (HF) is a syndrome characterized by high mortality, frequent hospitalization, reduced quality of life and a complex therapeutic regimen.[1] Over 6 million Americans and more than 26 million people worldwide have HF.[2,3,4] In the coming decades, HF is expected to become an increasingly larger healthcare problem as the population ages. HF is most often an incurable disorder. There are more than one million hospitalizations each year in the US where the primary diagnosis is Acute Decompensated Heart Failure (ADHF) with 80-90% of patients having a history of pre-existing chronic HF. About 90% of ADHF hospitalizations present with clinical manifestations of pulmonary congestion.[5,6,7] When ADHF develops, respiratory symptoms, such as tachypnea and dyspnea predominate. Ultimately, if this process is not reversed, pulmonary edema ensues and there is increased likelihood of death. A persistent rise in left atrial pressure (LAP) during the preceding days is the predominant pathophysiological factor driving the development of pulmonary congestion.[8] Having an implanted passive device that automatically decompresses the left atrium as heart failure acutely worsens, would constitute a real and important advance that could improve symptoms, quality of life, exercise tolerance, and potentially prolong life expectancy for a significant proportion of these patients who often have few or no alternative therapeutic options.

2.2 BACKGROUND

HF is defined as the pathophysiologic state where the heart requires an elevated diastolic filling pressure to be able to pump blood adequately to meet the requirements of the metabolizing tissues or where the ability to eject blood is reduced.[9] The underlying etiologies of HF are most commonly ischemic heart disease, hypertension, diabetes mellitus, idiopathic cardiomyopathy, valvular heart disease, myocarditis, followed by a host of other less common causes. While traditionally associated with reduced left ventricular (LV) systolic function, it is now widely recognized that HF can occur with normal or mildly reduced LV ejection fraction. Left heart failure is often divided into two clinical syndromes: systolic heart failure or heart failure with reduced ejection fraction (HFrEF), and diastolic heart failure or heart failure with preserved ejection fraction (HFpEF), where the left ventricle fails to relax and fill normally (diastolic dysfunction).[10] Patients with HFpEF tend to be older, are more commonly female, hypertensive and diabetic. The prevalence of patients with HFpEF presenting to hospital with ADHF is growing and is now approximately equally split with or in some cases surpassing HFrEF.[11,12,13]

2.2.1 STANDARD OF CARE TREATMENT

The mainstay therapy for HFrEF patients are medications that regulate the neurohormonal milieu or heart rate. These drug classes include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors—*Entresto* (ARNI), beta blockers, mineralocorticoid receptor inhibitors (MRA), and a hyperpolarization-activated cyclic nucleotide channel blocker—*Ivabradine* (HCN). These agents have been demonstrated in randomized trials to reduce

mortality and morbidity (heart failure hospitalization) and in some cases to result in beneficial ventricular remodeling. All have received Class I guideline indications in patients with HFrEF, except for Ivabradine which is class IIa in both the US and European guideline recommendations.[14,15,16] Several devices also have evidence-based, Class I guideline indications for treating specific subsets of HFrEF patients including Cardiac Resynchronization Therapy (CRT), Implantable Cardioverter Defibrillator (ICD), and Left Ventricular Assist Devices (LVAD) for patients with end-stage disease. Nonetheless, symptoms, especially dyspnea on exertion and poor exercise tolerance require management of excess fluid volume with dietary sodium restriction in all, and chronic use of loop diuretics, in most patients. Fluid removal with intravenous loop diuretics is the most common approach to relieving the worsening symptoms of ADHF.

In the HFpEF patient population, no randomized controlled trials of drugs or devices have achieved their primary effectiveness endpoints, with the exception of implantable hemodynamic monitoring guidance of diuretic or venodilator dosing, which has been shown to significantly reduce HF-hospitalization.[17] Even so, due to a combination of lack of confirmatory trials in the literature, and need for constant monitoring and adjustment without reimbursement, this approach has seen slow adoption. Otherwise, guideline-based medical therapy is limited to treating underlying predisposing conditions such as controlling hypertension, ventricular rate control in atrial fibrillation, treating ischemic heart disease and using diuretics for relief of symptoms of volume overload.

Despite current recommendations for evaluation and management, HF morbidity and mortality remain high. HF is the most common reason for acutely hospitalizing patients 65 years or older.[18,19] In the US, HF is the primary cause of more than 308,000 deaths, over a million hospitalizations, at least 6 million office visits, and almost 700,000 emergency room visits, annually. Most patients (77%) presenting to hospital are severely symptomatic with New York Heart Association (NYHA) Functional Class III or IV symptoms.[20] The factors associated with decompensation and hospitalization are most commonly noncompliance with diet and medications followed by failure to seek care or patients being on inappropriate therapy. These factors result in either total body fluid retention, or fluid redistribution to the pulmonary venous vasculature, or both. Patients admitted with ADHF have an in-hospital mortality of 4%, a 90-day mortality of 10%, and per the OPTIMIZE-HF Registry and other studies, a one-year risk- adjusted mortality rate of 30%.[21,22,23] The mortality and hospitalization rates for patients with HFrEF and HFpEF are generally alike.[24]

A particular area of focus in recent years has been hospital readmission. This is not only important for controlling runaway costs but also because there is a supra-additive mortality risk associated with subsequent HF hospitalizations. Readmission rates following a hospitalization for ADHF average 25% at 30-days and are nearly 50% at 6 months, regardless of systolic function.[25,26,27,28] In a large Canadian database review, the median survival (50% mortality) after the first, second, third, and fourth HF- hospitalizations were 2.4, 1.4, 1.0, and 0.6 years, respectively. Most patients were alive 2 years after the first HF hospitalization, but approximately half were dead by 1 year after 3 hospitalizations.[29]

Irrespective of the state of LV systolic function, most patients tend to have a progressive course characterized by worsening HF stage, symptom class, periodic acute symptomatic worsening with the

need for hospitalization, and ultimately death. There remain large unmet medical and societal needs to reduce the incidence of acutely worsening HF in ambulatory patients. The benefits of doing so would likely include reducing HF morbidity and improving patient reported outcomes such as quality-of-life for countless patients while controlling costs and utilization of resources.

2.2.2 INTERATRIAL SHUNTING AND ITS ANTICIPATED CLINICAL BENEFITS

The V-Wave Shunt is a permanent medical implant that creates a small fixed communication between the left and right atria at the location of the fossa ovalis. The aim of shunting is to reduce symptoms and the frequency of ADHF in patients with advanced chronic HF irrespective of LVEF. Interatrial shunting is expected to be a complementary treatment to other established therapies in HF patients that remain moderately to severely symptomatic.

The background observations supporting interatrial shunting as HF treatment are:

- Sustained elevation of left atrial pressure (LAP) is the direct cause of pulmonary congestion with symptoms responsible for 90% of HF hospital admissions. Studies with implantable hemodynamic monitoring have demonstrated that persistent elevation of LAP is the immediate cause of pulmonary congestive symptoms in ADHF irrespective of the underlying etiology of the patient's heart disease, left ventricular systolic function, or precipitant of clinical worsening.[30] This is because LAP is transmitted to the pulmonary veins where it is the predominate force causing transudation of blood plasma fluid into the pulmonary interstitial and alveolar spaces resulting in worsening dyspnea, orthopnea, and finally in acute pulmonary edema requiring hospitalization. When left-sided filling pressures were used to guide diuretic or venodilator therapy in blinded randomized trials, heart failure hospitalization was significantly reduced, and symptoms and quality of life was improved over a mean follow-up of 18 months.[31,32] Similar benefits were seen in HFrEF and HFpEF patients irrespective of lower boundary cutoff EF levels for HFpEF (40% vs 50%). Moreover, control patients that cross-over to device-guided therapy show the same benefits.[31,32]

- There is a resting interatrial pressure gradient, where LAP exceeds right atrial pressure (RAP) in ~98% of HF patients, nearly all the time throughout the day.[33]

- HF patients with coexisting congenital atrial septal defects (ASD) or patent foremen ovale (PFO) have better than expected outcomes, and closure of ASD and PFO may unmask subclinical left ventricular dysfunction, provoking pulmonary edema.[34,35,36]

- Atrial septostomy (creation of an interatrial communication) has been used to reduce intracardiac pressures and improve forward flow in patients with congenital heart disease and for HF.[37]

In brief, the theory of operation for the Study Device is that the greater the left-sided cardiac filling pressure is elevated relative to right-sided pressure, the more blood will be "shunted" from left-to-right, attenuating further elevation in left-sided pressure. Specifically, due to the presence of an interatrial

pressure gradient, a small portion of the blood normally flowing from the left atrium to the left ventricle is diverted to the right atrium instead. This in turn modestly reduces LV end-diastolic filling volume. When the LAP is elevated, the LV is operating on the steeper portion of its diastolic compliance curve.[38] Even a modest reduction in LV end-diastolic volume leads to a substantial fall in LV end-diastolic pressure. There will be a commensurate fall in upstream filling pressures including LAP, pulmonary venous pressure, and pulmonary artery pressure. The anticipated clinical result will be relief or even prevention of pulmonary congestive symptoms. At smaller interatrial gradients with less shunting, the effect on LV volume and filling pressures becomes progressively smaller until it is negligible. As interatrial shunting primarily affects LV filling and not afterload, the beneficial effects on lowering end- diastolic pressure would be anticipated regardless of LV systolic function. That is, interatrial shunting would be expected to be effective in patients with either HFrEF or HFpEF.

The location, the amount of flow, and the hemodynamic consequences, are similar to what occurs with a hemodynamically insignificant congenital ostium secundum atrial septal defect (ASD). Namely, the shunt is located in the fossa ovalis portion of the atrial septum, the orifice is 5 mm in diameter and the pulmonary to systemic blood flow ratio (Qp:Qs) is less than 1.5. In the absence of severe right ventricular dysfunction, the right heart can tolerate small left-to-right atrial shunts because the additional blood volume causes only a minimal rise in RV end-diastolic pressure. This is due to the right heart having a relatively high compliance (ability to enlarge without a significant pressure increase).

A previous version of the V-Wave Shunt was validated in a pre-clinical ovine model of ischemic dilated cardiomyopathy.[39] The Shunt differed from the current Study Device primarily in that it had a tissue valve disposed on its right atrial side to prevent right-to-left shunting but was otherwise dimensionally similar. Heart failure induction with selective left circumflex coronary artery microembolization resulted in the rapid development of left ventricular dysfunction with LVEF falling to 36% with elevation in LAP and echocardiographic evidence of pathological myocardial remodeling within 2 weeks.

Animals were then either treated with Shunts (n=14) or were Sham Controls (n=7). Control group animals continued to progressively deteriorate so that after another 12 weeks, LVEF was markedly reduced to 18%, the septum further thinned, and LAP monotonically elevated to 25 mmHg. Control animals developed severe secondary pulmonary hypertension (PAP_{mean} 37 mmHg), and worsening right atrial pressure averaging 15 mmHg, consistent with right ventricular volume overload. Control animals had a 43% mortality, which was associated with rapidly worsening hemodynamics, particularly pulmonary hypertension, and tachycardia.

Despite comparable left ventricular function at baseline in the Shunt group, there were marked contrasts in the evolution of objective heart failure indices between the control and shunted animals consistent with a device treatment effect. Shunting abolished the course of rapidly deteriorating left and right ventricular function and induced stability that was associated with global improvement of left ventricular systolic function. Specifically, after shunt placement, instead of LAP rising to levels resulting in pulmonary congestion, LAP fell significantly, approaching normal and remained steady for the study duration. Instead of developing severe pulmonary hypertension and RV volume overload, pulmonary artery and right atrial pressure remained minimally elevated. Instead of progressive worsening of LVEF,

shunting improved systolic function with the ejection fraction increasing to 46% and was still trending upward at study conclusion. The interventricular septum ceased to thin, consistent with interruption of the ventricular remodeling seen in controls. At study termination, high fidelity measurements of left ventricular pressure showed that Control group sheep had diminished indices of contractility and reduced diastolic function, while in shunted animals these indices were nearly normal. Although these measurements are load-dependent, the magnitude and breadth of these data suggest that shunting prevented deterioration of left ventricular inotropic and lusitropic states. Finally, shunting was also associated with a statistically significant survival benefit. These marked salutary effects were accomplished with a 5-mm diameter orifice shunt device with an observed shunt ratio Qp:Qs that averaged ~1.2. This equated to a shunt flow of approximately 700 ml/min.

In summary, these data demonstrate mechanistically how a small interatrial shunt device can selectively unload the heart, resulting in sustained reductions of left-atrial pressure and improved left ventricular function while right-sided cardiac pressures and function remained preserved. Shunt-induced reductions in wall stress due to decreased loading and attenuated remodeling may be important mechanisms behind these beneficial effects. These establish a preclinical proof-of-principle that left-to-right interatrial shunting is a promising therapeutic approach for patients with heart failure with reduced systolic function.

2.2.3 CLINICAL FEASIBILITY STUDY

Methods

V-Wave conducted two concurrent open-label human feasibility studies with a prior version of the V-Wave Interatrial Shunt System, which included a tissue valve located on the right atrial side designed to prevent early reversed (right-to-left) shunting, but was otherwise constructed of the same materials and was dimensionally identical to this study device.

A Canadian Special Access Program (CSAP) at a single site and a First-in-Man (FIM) trial (NCT01965015) at 5 sites in Israel and Spain were performed. The two trials had similar major inclusion/exclusion criteria, follow-up study testing and schedules, trial conduct, monitoring and oversight procedures. The patient's baseline demographics and clinical characteristics were substantially similar, allowing the data to be pooled into a single experience of 38 patients.

The study objectives were to evaluate the early safety and performance of the V-Wave Shunt implanted in a population consisting of patients with chronic NYHA functional class III or ambulatory class IV heart failure (HF) patients with either reduced or preserved systolic function. The major eligibility criteria satisfied by all patients in both CSAP and FIM studies included those patients: be receiving guideline-directed medical therapy (GDMT) inclusive of recommended device therapies; have at least 1 hospitalization in the prior 12 months for worsening HF requiring intravenous therapy or a corrected elevated BNP level of at least 300 pg/ml or an NT-proBNP level of at least 1,500 pg/ml. Patients with severe pulmonary hypertension ($PAP_{systolic}$ >70 mmHg) or severe RV dysfunction (TAPSE <12 mm, or RVFAC ≤30) were excluded. To maximize the likelihood that the CSAP and FIM patient data would be

poolable, the baseline records of each screened patient being considered for V-Wave Shunt implantation were reviewed by a site-independent Eligibility Committee, consisting of at least two physicians skilled in the conduct of heart failure device trials, who were familiar with the inclusion/exclusion criteria. An independent Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB) comprising of three cardiologists with expertise in clinical trials and specializing in interventional procedures, echocardiography, and heart failure and with access to statistical resources met approximately quarterly to adjudicated adverse events and monitor trial safety. A peer-reviewed manuscript describing the first 10 patients with reduced ejection fraction and 3-month follow-up was published in The Lancet in March 2016.[40]

The primary safety outcome measure was the incidence of device, procedure or study-related (device-related) Major Adverse Cardiovascular and Neurological Events (MACNE) at 3-months. The definition of MACNE was pre-specified as the hierarchical composite rate of all death, stroke, MI, device embolization, tamponade, and device related re-intervention or surgery during the 3-months after implantation. Secondary safety measures further assessed the frequency of all-cause MACNE, and all- cause Serious Adverse Events (SAEs) and Serious Adverse Device Effects (SADEs). The primary device performance measure was procedural success defined as the ability to deliver and deploy the V-Wave Shunt across the fossa ovalis with a patent shunt at 3-months.

Secondary effectiveness outcome measures included the assessment of NYHA Functional Class, Quality of Life Changes (KCCQ or MLWHF Questionnaire, depending on site), 6-minute walk test (6MWT) and the rate of hospitalization for worsening HF. The eligibility criteria, follow-up schedule, and definitions for heart failure hospitalization were pre-specified to comport with those used in the CardioMEMS Champion Study, a prospective randomized control study of pulmonary artery pressure guided therapy for historical control purposes.[31,32] A heart failure hospitalization required a non-elective in-hospital stay for worsening heart failure that was present at the time of admission and considered as the primary cause of hospitalization and that included at least one calendar date change and required intravenous or mechanical heart failure therapies or the significant augmentation of oral heart failure medications. Serial transthoracic and transesophageal echocardiograms were systematically acquired at specified intervals and analyzed by an independent Echo Core Laboratory. Case report forms were captured in a computerized data management system and data entry was reviewed and locked.

Results

Patient Characteristics: Between October 10, 2013, and March 17, 2016 the CSAP Study enrolled 22 patients and the FIM Study enrolled 16 for a combined total of 38 patients. For purpose of providing clinical perspective, **Table 1** compares baseline patient characteristics for the combined CSAP/FIM study cohorts with the Champion Study.

The SAP/FIM cohorts were elderly, predominantly male, and moderately obese. Except for one class IV patient receiving regularly scheduled milrinone infusions, the 37 (97%) remaining patients were NYHA class III. A substantial majority (79%) had heart failure of ischemic etiology. The use of ACE inhibitors, ARB, beta blockers, and MRA medications and ICD and CRT devices were consistent with pre-specified

management guidelines. Comorbidities including diabetes, renal dysfunction, and atrial fibrillation were frequent. At baseline, 26/38 (68%) patients were taking anticoagulants (20 vitamin K antagonists, 6 novel oral anticoagulants). The most common indication for anticoagulation was atrial fibrillation in 19 (53%) patients. Of the 38 patients enrolled, 30 had HFrEF defined as LVEF<40 and 8 had HFpEF with LVEF≥40. Natriuretic peptide levels and resting left and right atrial and pulmonary pressures were elevated, while exercise capacity and cardiac index were reduced. The combined CSAP/FIM cohort was well-matched with the Champion Study population with the exception that the shunted patients were significantly (p<0.05) older, more frequently male, more frequently had HF of ischemic origin, more had diabetes and renal function was on average reduced —all factors generally associated with a worse prognosis in HF patients.

Table 1. Baseline Patient Demographics

BASELINE	CSAP + (N=38)	CHAMPION TREATMENT CONTROLS (N=550)
Age, y	66±9	62±13†
Male Sex, %	92	73†
Body Mass Index, kg/m^2	30±6	31±7
NYHA class, %	III (97), IV (3)	III (100)
Ischemic Cardiomyopathy, %	79	60†
DM / HTN / AFIB, %	68 / 84 / 53	49† / 78 / 46
ACEi-ARB / BB / MRA / DIUR, %	71 / 89 / 68 / 87	76 / 87 / 42 / 92
ICD / CRT, %	74 / 39	68 / 35
Frequency LVEF ≥ 0.40, %	21.1	21.6
LVEF HFrEF/HFpEF	26±7/50±9	23±7 / 51±9
NT-proBNP, pg/ml	2640±2301	-
eGFR, mL.min^{-1}.1.73 m^{-2}	54±20	61±23†
6-Minute Walk Distance, m	289±112	-
PCWP, mmHg	21±5	18±8
RAP, mmHg	8±4	-
PAP systolic, mmHg	44±12	45±15
Cardiac Index, L.min^{-1}.m^{-2}	2.2±0.4	2.3±0.7

NYHA, New York Heart Association; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; AFIB, atrial fibrillation; ACEi-ARB, angiotensin converting enzyme inhibitor-angiotensin receptor blocker; BB, beta blocker; MRA, mineralocorticoid receptor antagonist; Diur, diuretic; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate; PCWP, pulmonary capillary wedge pressure; RAP, right trial pressure; PAP, pulmonary artery pressure. Continuous measures shown as mean ± SD. † = p<0.05.

Implantation: All 38 subjects were implanted successfully with shunts placed across the fossa ovalis portion of the interatrial septum. There were no device maldeployments or the need for intraprocedural device repositioning or reintervention resulting in a Procedural Success Rate of 100%. The average

procedure time was 72 ± 24 minutes, which included pre-shunt TEE, RHC, transseptal catheterization, shunt implantation, and post implant data collection. The median length of stay was 2 days.

Device Performance: The shunt patency was confirmed in all subjects by TEE at 3 months. By 12 months, 86% (31/36) of shunts had echo/Doppler evidence of left-to-right flow through their Shunts. In the 5 subjects with no observed flow there was no echocardiographic or clinical evidence of thrombus formation in or near the devices, migration of device from the site of deployment, or erosion of the device into adjacent cardiac structures.

Safety: During the first 12-months, there were 30 SAEs (**Table 2**), not including hospitalization for worsening HF, which were assessed separately. Of these 30, three were adjudicated as Major Adverse Cardiovascular or Neurologic Events (MACNE). Two of the MACNE were deaths due to cardiovascular cause and were not device related. The one device related MACNE, cardiac tamponade was a complication of a transseptal catheterization procedure but not of the shunt *per se*. The patient was treated with pericardiocentesis, did not require surgical intervention, and was later discharged with no lasting sequelae. There were no strokes, TIAs, systemic or pulmonary thromboembolic events. There were no device infections. No shunt removals, surgical or percutaneous, were required. The Primary Safety Outcome Measure, Freedom from Device-Related MACNE at 3 months, was 97.4% (95% CI, 92.3% to 100%) and remained unchanged at one year. Six additional SAEs, were adjudicated as SADEs, which included one case of GI bleed due to gastric erosion while on study mandated anticoagulation, four cases of vascular access complications that resolved with local treatment and did not require surgery and one case of acute urinary retention requiring catheterization. All SADEs except 1 presented within 9 days of shunt implantation. The brachial plexopathy resulted from the right heart catheterization procedure performed at the 12-month follow-up visit.

Table 2. Serious Adverse Events at 12-Months

SAE Type	Number SAE	Number SADE
Acute Coronary Syndromes	5	0
Abdominal Pain	1	0
Arrhythmia (VT)	1	0
GI Bleed	2	1
Heart failure, other	1	0
Depression	1	0
Pulmonary (pneumonia, COPD, etc.)	9	0
Vascular access	4	4
Urinary	2	1
Tamponade	1*	1*
Trauma	1	0
Stroke or thromboembolism	0	0
Death	2*	0
total	30	7
MACNE*	**3**	**1**

* Counted as MACNE

Effectiveness Measures: All patients were NYHA Class III/IV at enrollment. At 3-months. 78% improved to Class to I or II; at 6 months 80% remained improved; and at 12 months 60% continued to be class I or II ($p<0.001$ for all comparisons). For Quality of Life, the proportions improved by ≥ 5 points 74%, 59% and 72% at 3, 6, and 12 months, respectively ($p<0.001$ for all comparisons). 6MWT increased by +41 m at 3 months ($p<0.001$), +41 m at 6 months ($p=0.01$), decreasing to +28 m vs. baseline at 12 months ($p=0.03$).

Table 3 summarizes blood, echo, and hemodynamic parameters in the 36 surviving patients at baseline, 3 and 12-months. Shunt flow was 17% of systemic output at 3 months but fell to 10% at one year. In general, NT-proBNP, renal function, LV and RV function and hemodynamics remained stable throughout the first year after shunting.

Table 3. Selected Blood, Echocardiographic and Hemodynamic Parameters in Surviving Patients

	Baseline	3M	12M
n	36	36	35
Blood			
Log_e NT-proBNP (pg/mL)	7.5 ± 0.9	7.4 ± 1.0	7.5 ± 0.9
eGFR (mL/min·1.73m$^{2)}$	54 ± 20	55 ± 23	53 ± 22
Echocardiographic variables			
LVEF (%), HFrEF / HFpEF	26 ± 7 / 50 ± 9	27 ± 9 / 52 ± 10	28 ± 8 / 54 ± 9
LAV (mL), HFrEF / HFpEF	90 ± 28 / 79 ± 25	84 ± 2 / 75 ± 22	84 ± 28 / 80 ± 24
TAPSE (mm)	16 ± 4	17 ± 4	16 ± 4
Qp:Qs	0.99 ± 0.11	1.17 ± 0.12	1.10 ± 0.13
Hemodynamic variables			
PCWP mean (mmHg)	21 ± 5	20 ± 7	19 ± 7
RAP mean (mmHg)	8 ± 4	9 ± 5	9 ± 4
PAP mean (mmHg)	30 ± 8	29 ± 8	30 ± 10
CI ((L/min·m^2), thermodilution	2.2 ± 0.4	2.4 ± 0.4	2.3 ± 0.5
PVR (WU)	2.8 ± 1.6	2.6 ± 1.1	2.8 ± 1.9

Log_e NT-proBNP (pg/mL), natural logarithm of amino terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LAV, left atrial volume; TAPSE, tricuspid annular plane systolic excursion; Qp:Qs, pulmonary to systemic flow ratio; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; PAP, pulmonary artery pressure; CI, Cardiac Index; PVR, pulmonary vascular resistance.

Medication Changes: Baseline drug therapy with standard heart failure medications is summarized in **Table 4**. In addition, 5 patients were receiving PDE-5 inhibitors (4 sildenafil, 1 tadalafil), 1 patient was taking an HCN channel blocker (Ivabradine), and 1 patient was receiving twice weekly infusions of milrinone.

For the 36 patients surviving 6 months, there were 86 changes in the daily dosage of heart failure medications for a frequency of 0.40 changes per patient per month. Medication dosages were increased in 55% of instances and decreased 45% of the time. The most frequently adjusted medication drug classes were loop/thiazide diuretics (38%), followed by ACE/ARBs (21%), beta blockers (17%), mineralocorticoid receptor antagonists (8%), and nitrates/hydralazine (8%). During follow-up, 1 patient was switched from an ACE inhibitor to a newly available combination ARNI (*Entresto*) and 1 additional patient began receiving twice weekly milrinone infusions.

Table 4 also shows that CSAP/FIM patients were on nearly identical doses of ACE/ARB and beta-blockers as Champion Study Control group patients at baseline and 6 months. CSAP/FIM patients were, however, taking almost 20-35% higher doses of loop diuretic and 65% lower doses of MRA agents throughout the study. This is likely due to the CSAP/FIM patients having significantly poorer renal function. **Figure 2** compares the frequency of medication changes by drug class during 6-month follow-up in shunt patients with the CHAMPION Control group. The frequency of adjusting dosages of neurohormonally active medications including ACE/ARBs, beta blockers and mineralocorticoid receptor antagonists were nearly

identical between the two studies. The observed frequency of adjusting diuretics was less than half in patients treated with interatrial shunts.

Table 4. Baseline and 6-Month Medication Dosing: Comparison Between CSAP/FIM and Champion Trials

CSAP and FIM				CHAMPION Control		
	Baseline	(n)	6 Months	Baseline	(n)	6 Months
ACE or ARB (enalapril equivalents, mg)	21±18	(24)	18±14	20±18	(168)	20±20
Beta Blocker (carvedilol equivalents, mg)	30±19	(28)	28±18	30±23	(206)	31±23
MRA (spironolactone equivalents, mg)	15±6	(23)	16±7	32±22	(90)	35±30
Loop Diuretic (furosemide equivalents, mg)	123±135	(27)	131±134	92±63	(201)	110±89

Data: mean±SD; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist. Doses: for ACE or ARB are enalapril equivalents; for Beta Blockers in carvedilol equivalents; for MRA in spironolactone equivalents; for Loop Diuretics in furosemide equivalents. CHAMPION data from Costanzo MR, Stevenson LW, Adamson PB, et al. JACC Heart Failure 2016;4:333-44.

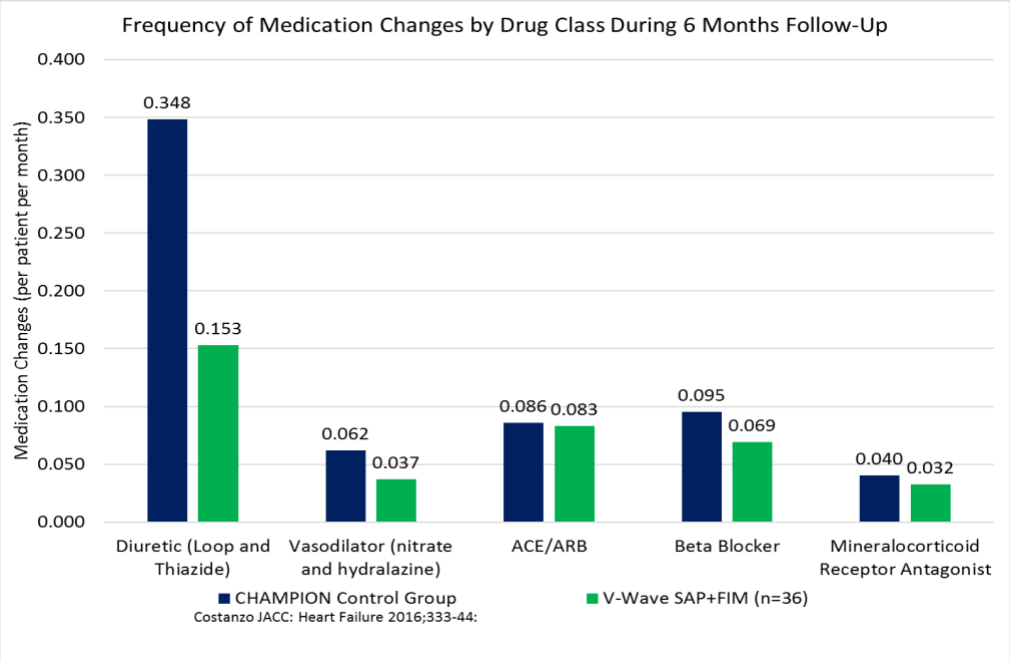


Figure 2. Medication Changes by Drug Class in CSAP+FIM vs. Champion Dataset

Hospitalization and Mortality: During the total follow-up of 12 months, there were 9 HF- hospitalizations. The annualized (Poisson) HF-hospitalization rate was 0.25 per patient per year and the mortality rate was 0.05 deaths per patient per year. For the purposes of developing exploratory effectiveness analyses, **Figure 3** compares these data with similar adjudicated endpoints from Champion at a mean duration of follow-up of 18 months. Shunt patient event rates are shown for the same

duration of follow-up. Shunt patients had annualized HF hospitalization rates or combined rates of death and HF-hospitalization that were significantly lower than CHAMPION Controls. Shunt patients also had consistently lower rates of non-HF-hospitalization, all-cause hospitalization, and death and all-cause hospitalization than either CHAMPION Controls or Treatment group patients.

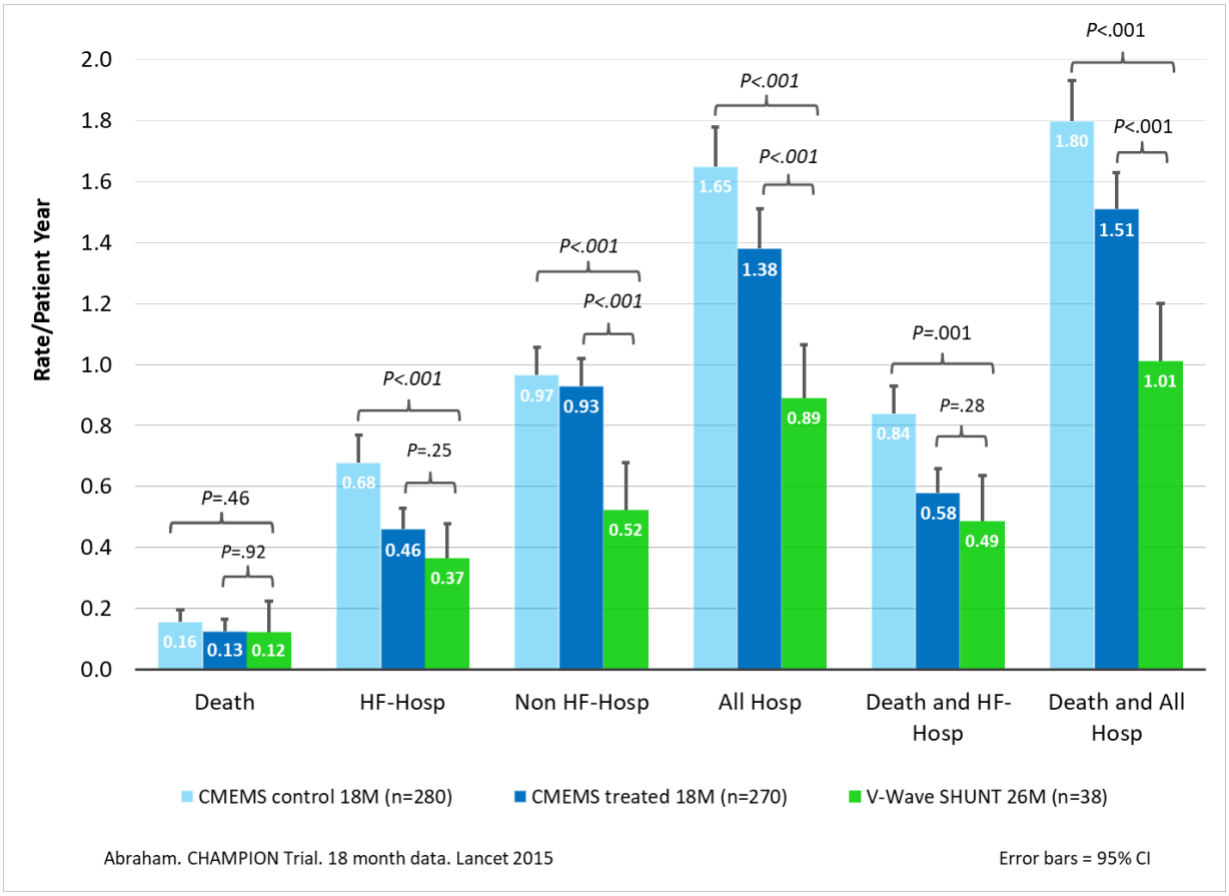


Figure 3. Hospitalization and Mortality of V-Wave Shunt vs. CHAMPION dataset

The overall experience with the V-Wave Interatrial Shunt System to date shows that it can be implanted with a high degree of reliability, safety, and assurance of performance. The data from the feasibility studies shows multiple correlates of benefit over the span of more than one year in the setting of a high-risk population and the very low rates of death and HF-hospitalization in comparison with a well- matched population with advanced HF. These observations provide a reasonable assurance that the V- Wave Interatrial Shunt System is safe, meets satisfactory device performance criteria and likely has a device treatment effect.

There are currently studies underway with another investigational implantable interatrial shunt product manufactured by Corvia Medical Inc. (Tewksbury, MA), called the IASD II, short for interatrial shunt device II. This is also a self-expanding nitinol device that envelops the fossa ovalis leaving an 8-mm orifice for shunting. There is no encapsulation of the device with other biomaterials. The IASD II, has so far only been used in patients with HFpEF with EF ≥40%.

The REDUCE-LAP-HF Study, (NCT01913613) was a 66 patient non-randomized open label clinical trial that evaluated the safety and performance of the IASD II system outside of the US.[41,42] Key inclusion criteria included: LVEF ≥40%, symptomatic NYHA Class II/III/ambulatory class IV or HF hospital admission over past 12-months, PCWP >15 mmHg at rest and greater than CVP, or >25 mmHg during exercise. The primary outcome measure was periprocedural and 6 months Major Adverse Cardiac and Cerebrovascular Events (MACCE) and systemic embolic events (excluding pulmonary thromboembolism). Implantation was successful in 64 of 66 patients. There was no MACCE at 6 months. At 12 months, there were sustained significant improvements in New York Heart Association class (P<0.001), quality of life (Minnesota Living with Heart Failure) score (P<0.001) and 6-minute walk distance compared with baseline (363±93 versus 331±90 m; P=0.01; n=55).

The results of the REDUCE LAP-HF RANDOMIZED TRIAL I (NCT02600234) were recently reported (November 2017).[43] The primary effectiveness endpoint was exercise PCWP at 1 month. The primary safety endpoint was major adverse cardiac, cerebrovascular, and renal events (MACCRE) at 1 month. PCWP during exercise was compared between treatment groups using a mixed effects repeated measures model analysis of covariance that included data from all available stages of exercise. A total of 94 patients were enrolled, of which n=44 met inclusion/exclusion criteria and were randomized to the IASD (n=22) and control (n=22) groups. IASD resulted in a greater reduction in PCWP compared to sham- control (P=0.028 accounting for all stages of exercise). In addition, PCWP during passive leg raise and during 20W of exercise decreased to a greater degree in the patients randomized to IASD compared to sham-control (*P*<0.05 for all comparisons). Peak PCWP decreased by 3.5±6.4 mmHg in the treatment group vs. 0.5±5.0 mmHg in the control group (P=0.14). There were no periprocedural or 1-month MACCRE in the IASD group and 1 event (worsening renal function) in the control group (P=1.0). The authors concluded that in patients with HF and LVEF ≥40%, IASD treatment unloads the left atrium and reduces PCWP during exercise.

Corvia is currently conducting a pivotal multicenter blinded randomized trial called REDUCE LAP-HF TRIAL II (NCT03088033), which began enrolling in June of 2017 and is expected to enroll approximately 380 patients.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Implanting permanent devices in the heart, especially within the left atrium and creating intracardiac shunts, carries with it known risks or complications, some of which may be severe, even at times fatal. Medical and/or surgical interventions may be required to correct clinical complications associated with the V-Wave Interatrial Shunt System and its implantation procedure. These known risks were considered with respect to severity and frequency and addressed by V-Wave according to its risk management procedures as specified under the EN ISO 14971:2012 standard. Specifically, a Failure Mode and Effects Analysis process was conducted beginning with design initiation and revised throughout the development process. Wherever possible, design changes, methods of use, and training, have been

adopted to mitigate the frequency and severity of these identified risks. As with any investigational device, there may be unforeseeable risks, which are not yet known at this time.

The potential risks associated with V-Wave System can be divided into three categories:

- The risks associated with the creation of an interatrial channel in the septum (similar to a small septal defect). These risks are known from ASD and PFO pathologies.
- Risks associated with the implantation of devices within the interatrial septum. These risks are not expected to substantively differ between currently marketed systems (e.g., Gore Helex, Amplatzer Septal Occluder) and the V-Wave Interatrial Shunt System.
- Finally, there are risks associated with the percutaneous implantation procedures (right heart catheterization, transesophageal or intracardiac echocardiography, and transfemoral transseptal cardiac catheterization with implantation of a device in the left atrium). These risks are also not expected to materially differ between marketed system (e.g., ASD closure devices, Left Atrial Appendage devices, Mitral valve treatment devices) and the V-Wave Interatrial Shunt System.

The following list summarizes major anticipated adverse events that may result from the V-Wave Shunt, its implantation, or ancillary investigational protocol specified procedures. This list is not intended to be exhaustive. There may be other device or study procedure risks that are reasonably supported by the literature or expert consensus as foreseeable or anticipated risks.

- Abnormal laboratory results
- Acute decompensated heart failure
- Allergy, anaphylactic reaction, drug reaction, to contrast medium, anesthesia reaction, device components
- Arrhythmia
- Atrial septal defect (iatrogenic)
- Bleeding
- Cardiac arrest
- Cardiac or great vessel perforation
- Cardiac tamponade
- Coagulopathy
- Damage to adjacent cardiac structures
- Death
- Deep venous thrombosis (DVT)
- Device migration, embolization, or erosion
- Device thrombosis
- Dislodgement of other previously implanted devices
- Effusion (e.g., pericardial, pleural, ascites)
- Emboli (air, thrombus, device)
- Emergency cardiac or vascular surgery
- Esophageal irritation, bleeding, perforation, or stricture
- Failure to deliver interatrial shunt to its its its intended site
- Failure to retrieve delivery system components
- Fever or hyperthermia
- Gastrointestinal disturbance (tear or bleeding of esophagus, peritonitis, infarction, ileus, nausea, vomiting, diarrhea)
- Hematuria
- Hemolysis
- Hemoptysis
- Hemorrhage requiring transfusion
- Hypertension
- Hypotension
- Hypoxemia
- Infection (including septicemia and endocarditis)
- Interference with other implanted devices
- Loss of limb
- Myocardial infarction
- Nerve damage
- Pain
- Permanent disability
- Pneumothorax
- Pulmonary thromboembolism
- Radiation induced skin or tissue injury
- Reintervention/closure of shunt due to excessive shunting
- Removal of shunt due to infection
- Renal insufficiency
- Respiratory failure, atelectasis, pneumonia
- Seizure
- Shock (cardiogenic or anaphylactic)
- Skin irritation or inflammation
- Stridor
- Stroke or transient ischemic attack (TIA)
- Syncope
- Thrombosis
- Urinary retention
- Urinary tract infection
- Vascular trauma (dissection, occlusion, hematoma, arteriovenous fistula, pseudoaneurysm, perforation, spasm)
- Worsening right ventricular heart failure and pulmonary hypertension

The following discussion details some of the most severe and direct risks associated with the shunt and its implantation procedure.

2.3.1.1 RISKS ASSOCIATED WITH TRANSSEPTAL CARDIAC CATHETERIZATION

The V-Wave Shunt is placed following transseptal puncture from right femoral venous access using a market approved Brockenbrough needle/dilator/sheath or any other approved transseptal system such as a radiofrequency needle. Transseptal catheterization has been performed successfully in hundreds of thousands of patients for more than 50 years. Procedural safety has improved over time especially with better operator training, the proliferation of case experience, and the routine use of intracardiac or transesophageal echocardiography to assure the absence of left atrial thrombi, to puncture the interatrial septum in the proper location, and to prevent inadvertent puncturing of other cardiac structures. The improving safety can be assessed from studies of atrial fibrillation (AF) ablation and structural heart disease intervention in patients with elevated left atrial pressures. The risk of death generally ranges from 0.1% with AF ablation to 1% with mitral valve repair, and in both cases, the most common causes of death are complications of tamponade or stroke.[44,45,46] Although the literature does not break down if these adverse events were caused by the transseptal puncture or the subsequent intervention, they are likely a mixture of both.

De Ponti et al.,[47] published survey data from 5,520 transseptal catheterizations performed in 33 Italian centers spanning 12 years through 2004. Most of the procedures were for AF ablation. No deaths were reported. Cardiac perforation with tamponade occurred in 2 (0.1%) cases, needle puncture of the right atrium in 4 (0.2%) cases, puncture of the aortic root in 1 (0.05%) case and systemic thromboembolism in 1 (0.05%) case. These complication rates are likely artificially low due to the voluntary and retrospective data collection inherent in the study. The risk of cardiac tamponade increases to 0.4% to 1.3% when transseptal catheterization is followed by large bore sheaths to deliver structural heart therapies in higher risk populations including percutaneous mitral valve repair and left atrial appendage closure where more manipulation in the left atrium and its adjacent structures occurs.[48,49] In a series of left atrial appendage occlusion cases with the Watchman device, cardiac tamponade or other transseptal complications requiring surgical repair was 0.4%. Thus, the risks associated with transseptal device placement are generally known and appears to be acceptable relative to the natural history of the underlying disorders being treated.

2.3.1.2 RISK OF IMPROPER DEVICE PLACEMENT

Device maldeployment or improper device placement is defined as any device that is not seated across the interatrial septum with the intended inlet side in the left atrial chamber and the outlet side in the right atrial chamber. This includes instances of inadvertent deployment, maldeployment, device embolization, and inability to remove an improperly deployed or non-deployed device from the body without surgery. It can occur before or after the device is intended to be released from the Delivery Catheter. Improperly placed devices may impinge or erode into other adjacent cardiac structures or may cause fatigue or wear to the device resulting in strut fracture or device fragmentation.

ASD and PFO occlusion devices are the closest non-shunt predicate devices because they span the interatrial septum. The FDA conducted an extensive literature review of the Gore Helex Septal Occluder and the AGA Amplatzer Septal Occluder devices that was presented at the 24 May 2012 Circulatory Systems Advisory Panel meeting. They concluded that the embolization rates experienced in the clinical trials (~1-3%) were similar to those reported in the literature (~0.3-3.5%) and constitute the majority of adverse events reported to the MAUDE (Manufacturer and User Facility Device Experience) system. These events were not consistently associated with life-threatening sequela; however, they nonetheless require an additional procedure, percutaneous or surgical, for retrieval.

Erosion rate estimates from the literature and MAUDE system were also similar (~0.1-0.2%); however, these estimates are limited given the rarity of event and methodology used to capture data. Most erosions (60%) occur after discharge from the hospital and may occur more than one year after implantation. Although this type of event appears to be quite rare, the associated morbidity is considerable.

Fracture events with the Gore Helix Septal Occluder device were noted in the market entry clinical data (6-7%) and were similar to literature estimates (6-8%). Approximately 2% of post-approval study patients have undergone device explant due to device fracture.

2.3.1.3 RISKS OF THROMBOEMBOLISM AND STROKE

One potential risk of creating an interatrial shunt is paradoxical embolism. Paradoxical embolization refers to thromboembolism originating in the venous vasculature (venous thromboembolism or VTE) and traversing right-to-left through a cardiac shunt into the systemic arterial circulation. VTE in adults is almost exclusively the consequence of *in situ* thrombosis in the deep veins (deep venous thrombosis or DVT) of the lower extremities or pelvis. Heart failure is a well-recognized risk factor for DVT and VTE, especially in patients with reduced left ventricular systolic function.[50] About 3% of deaths in heart failure patients are due to VTE, usually associated with pulmonary emboli.[51]

There is evidence that the risk of paradoxical embolism is directly related to the orifice size of naturally occurring atrial level shunts such as ASD and PFO.[52] In patients with clinically significant ASD referred for closure, the incidence of paradoxical embolus has been reported to be up to 14%.[53,54]

It has been asserted that for VTE to enter the systemic circulation, the prevailing LA to RA pressure gradient seen in heart failure must be temporarily eliminated or reversed so that blood will flow retrograde across the shunt. In patients with existing ASD or PFO, bidirectional shunting can be best demonstrated when a subject performs a Valsalva maneuver, which causes the RA and LA pressures to equalize after several seconds and for the gradient to transiently reverse immediately upon secession of straining.[55] Intermittent bidirectional flow may also be observed at rest when the interatrial pressure gradient is low, or intermittently during the cardiac cycle when LA contraction is delayed compared to RA contraction (interatrial conduction delay). Bidirectional shunting can also be seen transiently during inspiration, when venous return to the RA is increased, during coughing, forced expiration, with abdominal compression, or in the presence of severe tricuspid valve regurgitation.

Any risk of stroke from paradoxical embolization must be weighed against the background rate of stroke in HF patients who have a 2- to 3-fold increased risk of stroke due to many risk factors, including LV apical dyskinesia, a high incidence of atrial fibrillation (typically 35-45%), hypercoagulable states, endothelial dysfunction, atherosclerosis, hypertension and diabetes.[56] Abdul-Rahim et al.,[57] reported the rates of stroke in the long term follow-up cohorts of the CORONA and GISSI-HF studies totaling 9,585 patients, 3,531 (37%) with any history of atrial fibrillation (AF) and 6,054 without AF. In patients with AF, the 1-, 2-, and 3-year cumulative incidence rates of stroke were 1.7%, 2.8%, and 4.2%, respectively. In patients without AF, the 1-, 2-, and 3-year rates of stroke were lower at 1.2%, 2.2%, and 3.1%, respectively. In a review of 402 patients with cardioembolic strokes, Arboix and Alio[58] reported that only 2(0.5%) patients were diagnosed as having paradoxical emboli. The overwhelming majority of cardioembolic strokes were associated directly with atrial arrhythmias or LV dysfunction. Cardioembolic stroke constitutes a minority of all strokes: about 15% of all strokes in patients 65 years old or younger, increasing to 36% of all strokes in patients 85 years or older. Atherothrombotic strokes, lacunar infarctions, and strokes of unknown causes make up the rest. These data suggest that although paradoxical embolic stroke may be associated with atrial shunting, it is likely to be very uncommon in relationship to the underlying rate of stroke in patients with advanced HF, especially in the setting of a predominately left-to-right shunt.

Another potential concern is thromboemboli originating from the surfaces of the shunt device itself. Krumsdorf et al.,[59] reviewed 1,000 consecutive ASD and PFO device closure cases with transesophageal echocardiography after 4 weeks and 6 months. The incidence of thrombus formation was highly device-dependent ranging from very low with ASD devices (0-0.8% at 4 weeks and 0-0.3% at 6 months) to generally higher early rates with PFO devices (5.7-7.1% at 4 weeks, 0-3.3% at 6 months). Risk factors for device thrombosis include atrial fibrillation, persistent atrial septal aneurysm, and coagulation disorders. The treatment for device thrombosis is anticoagulation; however, there is a risk of stroke when the thrombus is on the LA side, and surgical treatment might be considered for large, mobile thrombi.

2.3.1.4 RISK OF CREATING TOO LARGE A LEFT-TO-RIGHT SHUNT

There is wide consensus that atrial septal defects (ASDs) of more than 10 mm in diameter are associated with clinically significant left-to-right shunting where the pulmonary to systemic blood flow ratio (Qp:Qs) is greater than 1.5, or there is dilation of the right heart chambers.[60,61,62,63] ASDs that are between 5-10

mm in diameter, with smaller shunt ratios, generally have excellent outcomes and are not indicated for device or surgical closure. They are recommended to be followed every few years and ASDs with a diameter of 5 mm or less, Qp:Qs <1.5 and no RV dilation do not adversely impact the natural history of the patient and require no intervention.

Creation of iatrogenic ASD or iASD has become more common with the proliferation of percutaneous interventions using the transseptal approach including: electrophysiological ablation procedures, atrial appendage occlusion, percutaneous mitral valvuloplasty, and mitral valve repair with the MitraClip.[64,65,66] When these ASDs did not exceed a diameter of 5 mm (measured on 3-D echo) and had a Qp:Qs that did not exceed 1.4, these patients had no differences in clinical outcomes or pulmonary pressures compared to those without iASDs when followed for more than an average of 6 years.[67,68] Persistent iASDs with shunt diameters of up to 6 mm in patients undergoing pulmonary vein isolation has demonstrated similar results with no worsening of symptoms or complications due to hemodynamically relevant interatrial shunting.[64,69]

There are cautionary reports suggesting that patients with residual iASDs larger than 8mm in diameter may be at risk to develop right-sided heart failure and may have a higher mortality rate than those with iASDs ≤8mm, thus requiring percutaneous ASD closure.[70,71] In summary, these observations, from a variety of experiences support that small ASDs or iASDs, in the range of 5-8 mm in diameter, appear to be well tolerated and may decompress the left atrium, reducing symptoms from LV dysfunction.
Conversely, larger shunts are associated with poorer outcomes due to right heart volume overload.

2.3.1.5 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS

The V-Wave Shunt may interfere with catheter-based or surgical procedures which require access to the left atrium. These include but are not limited to mitral valve repair or replacement, left atrial appendage occlusion, electrophysiological studies and ablation of structures in or near the left atrium, such as pulmonary vein isolation.

Shunted patients will be receiving antiplatelet or anticoagulant therapy. These may require interruption if certain surgical procedures are needed.

The Shunt may cause an artifact on MR imaging within a range of a centimeter surrounding the Shunt's location.

2.3.2 POTENTIAL BENEFITS

The potential benefits to patients implanted with the V-Wave Shunt include:

- Serial evaluation, close monitoring, and medical optimization by cardiologist and skilled heart failure team
- Reduction in the severity and frequency of heart failure symptoms such as dyspnea
- Improvement in quality of life
- Improvement in exercise capacity

- Reduction in the number of hospitalizations for worsening heart failure
- Reduction in the number of Emergency Room visits for worsening heart failure
- Reduction in the number of urgent clinic visits of worsening heart failure
- Prolongation of life

The potential benefits to patients not implanted with the Shunt (Controls) include:

- Serial evaluation, close monitoring, and medical optimization by cardiologist and skilled heart failure team
- Opportunity to receive the Shunt after unblinding (maximum of 24 months)

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

2.3.3.1 STEPS TO MITIGATE RISK

Special considerations have been taken in designing the V-Wave System for the purpose of achieving its safe and reliable performance. The risk management procedures and related documentation and activities were performed according to the EN ISO 14971:2012 standard. The program was designed to identify the sources of risk during the design, development, and production processes. Specifically, a Failure Mode and Effects Analysis table was created and periodically assessed and revised. Preventive and/or control actions were implemented into device development and manufacturing to eliminate or reduce potential failure modes wherever and whenever possible.

For example, the Shunt, its Delivery System, and the Instructions for Use have been designed to reduce the likelihood of cardiac perforation, and tamponade during the device implantation procedure. The potential risk of creating too large a shunt, resulting in right heart volume overload, pulmonary hypertension, right ventricular failure and increased mortality has been in part mitigated by fixing the shunt orifice size at 5.1 mm diameter, which is expected to limit shunt flow, with a resulting Qp:Qs of approximately 1.2. This is expected to reduce the chances of right heart deterioration.

The protocol, by way of inclusion/exclusion provisions, study design, and follow-up procedures is intended to minimize patient risks. Certain clinical, imaging, and laboratory inclusion/exclusion criteria at baseline screening and at final screening performed at the time of the Study Intervention Procedure are intended to maximize the patient population anticipated to benefit from shunting while minimizing the risk of device and procedure related complications. For example, the exclusion of patients with poor RV function and severe pulmonary hypertension is intended to reduce the potential of even modest volume left-to-right interatrial shunting to exaggerate these conditions. All potential patients considered for entry into the trial who pass initial non-invasive screening will be reviewed by a Central Eligibility Committee to ensure that appropriate patients are being enrolled. Patients are evaluated for clinical, hemodynamic, heart rhythm, and respiratory stability just prior to randomization/enrollment to further assure their safety. Similarly, the peri- and post-procedural medication regimen is designed to minimize thromboembolic complications.

Site selection with only highly experienced HF services and two physician expert investigators is required. These include a HF cardiologist (*HF-Investigator*) and an implanting cardiologist (*Implanter- Investigator*). Only implanters with advanced experience in transseptal catheterization, structural heart

disease therapeutic procedures such as MitraClip mitral valve repair, and left atrial appendage occlusion, or AF ablation will participate in the trial.

The Company will develop a site training program. All site investigation personnel will be thoroughly trained on the protocol and study procedures. Investigators will be trained in the selection of patients for potential participation in this study, ensuring that all patients meet all the inclusion criteria and none of the exclusion criteria. The *Implanter-Investigator* will by trained in the proper use of the Study Device, first on a bench-top model and then proctored during the first cases per the protocol requirements. The Sponsor will share its experience training implanters in "bailout" procedures that may be considered to retrieve a maldeployed or embolized shunt, or to close a Shunt that is not clinically tolerated. A trained and experienced company representative will be present to support all device implantation procedures.

Mandatory safety data events reporting, and regular clinical monitoring will ensure the timely awareness of untoward outcomes and compliance with protocol requirements that affect risk including patient eligibility criteria, study medications, follow-up schedule, and use of the Study Device according to the Instructions-for-Use (IFU). Unanticipated adverse events will be evaluated and reported as required per the protocol and local regulations. A Sponsor-independent Clinical Event Committee (CEC) will adjudicate all SAEs for device or procedure-relatedness. A Sponsor-independent Data Safety Monitoring Board (DSMB) will provide trial oversight to assure patient safety.

2.3.3.2 TABLE OF ANTICIPATED DEVICE AND PROCEDURE-RELATED MAJOR RISK FREQUENCIES VS. BACKGROUND RISK RATES

Table 5 lists the anticipated device and procedure-related major risks as well as expected event frequencies with respect to background rates.

Table 5. Anticipated Device and Procedure-Related Risks

Major Risk	Anticipated 30-day Device-Related Frequency	Background Rate/yr in Control group
Death	≤2%	15-20%
Stroke and systemic thromboembolism	≤1%	~2%
Tamponade/cardiac perforation requiring surgical repair	≤0.5%	-
Shunt embolization requiring surgery	≤0.5%	-
Need to remove or close shunt (infection, over-shunting)	≤1%	-
Vascular complication (requiring surgical repair)	≤2%	-

The major risks listed are the components of the Primary Safety Endpoint (see Section 3.1.1). The anticipated rates are based on prior CSAP/FIM experience with the prior V-Wave Shunt and publicly available Watchman and MitraClip summary information presented at FDA Circulatory Systems Devices Panel Meetings of March 20, 2013 and October 8, 2014, respectively.[72,73] Other major risks including arrhythmias, myocardial infarction, and major bleeding, are not expected to be materially different between shunted and control patients based on the anticipated high background rates of ischemic heart

disease, LV dysfunction, atrial fibrillation and widespread use of anticoagulation/antiplatelet agents in the target population.

Finally, the anticipated risks for the V-Wave Shunt are not expected to be substantively different than those observed in comparable marketed devices used to treat structural heart disease that are placed in the left atrium including mitral valve clips, appendage occluders and ASD/PFO occlusion devices. Moreover, based on our preclinical and preliminary clinical experience and those of the Corvia IASDII shunt, as detailed above, these risks will likely be outweighed by the potential benefits of interatrial shunting as a therapeutic option for patients with advanced HF that are currently poorly responsive to optimal medical therapy, that have a guarded prognosis, and are subject to disease progression with accompanying deterioration of their general health status.

3 OBJECTIVES AND OUTCOME MEASURES

The objective of the RELIEVE-HF study is to provide reasonable assurance of safety and effectiveness of the V-Wave Interatrial Shunt System by improving meaningful clinical outcomes in patients with NYHA functional class II, class III or ambulatory class IV heart failure, irrespective of left ventricular ejection fraction, who at baseline are treated with guideline-directed drug and device therapies.

RELIEVE-HF, COVID-19, and Heart Failure Events

Globally, the COVID-19 pandemic has decreased the rate of heart failure (HF) hospitalizations by about 50%[74] and has had an uncertain effect on quality of life. This reduction in HF hospitalizations may be associated with an increase in worsening HF events treated as an outpatient.[75] Worsening HF events treated as an outpatient are clinically meaningful, associated with a poor outcome, and responsive to effective HF therapies in both HFrEF and HFpEF.[76 77 78 79 80]

3.1 PRIMARY ENDPOINTS

Detailed definitions of endpoints and statistical approaches will be defined in the separate Statistical Analysis Plan (SAP).

3.1.1 PRIMARY SAFETY ENDPOINT

The Primary Safety Endpoint is the percentage of Treatment Group patients experiencing any device-related Major Adverse Cardiovascular or Neurological Events (MACNE) during the first 30-days after randomization, compared to a pre-specified performance goal. MACNE is defined as all-cause death, stroke, systemic embolism, need for open cardiac surgery or major endovascular surgical repair. Specifically, percutaneous drainage of a pericardial effusion, percutaneous catheter snaring and removal of an embolized but otherwise uncomplicated Study Device and non-surgical treatment of access site complications are excluded from the definition of MACNE.

3.1.2 PRIMARY EFFECTIVENESS ENDPOINT

The Primary Effectiveness Endpoint is a hierarchical composite ranking of all-cause death, cardiac transplantation or left ventricular assist device (LVAD) implantation, recurrent HF hospitalizations (including Emergency Room HF Visits with duration ≥6 hours), recurrent worsening HF events treated as an outpatient (including ER HF visits with duration < 6 hours), and change in KCCQ overall score, comparing Treatment and Control groups. The analysis is based on the method of Finkelstein and Schoenfeld.[81]

3.2 SECONDARY ENDPOINTS

3.2.1 HIERARCHICALLY TESTED SECONDARY EFFECTIVENESS ENDPOINTS

The following secondary endpoints will be tested hierarchically. The order of hierarchical endpoints testing will be specified in the Statistical Analysis Plan.

- KCCQ changes from Baseline to 12 months
- Heart failure hospitalizations adjusted for all-cause mortality
- Time to all-cause death, LVAD/Transplant, or heart failure hospitalization
- Time to all-cause death or first heart failure hospitalization
- Cumulative heart failure hospitalizations
- Time to first heart failure hospitalization
- Modified Primary Effectiveness Endpoint including all-cause death, LVAD/Transplant, HF Hospitalizations, and worsening HF events treated as an outpatient but without KCCQ
- 6MWT changes from Baseline to 12 months

3.3 ADDITIONAL MEASUREMENTS

Details of analyses, including time points where not specified, will be defined in the separate Statistical Analysis Plan.

3.3.1 EFFECTIVENESS

- NYHA Class
- Patient Global Assessment
- Combined all-cause death and all-cause hospitalizations
- All-cause death
- Time to all-cause death (KM analysis)
- Time to cardiovascular death (KM analysis)
- Time to all-cause death, transplant or LVAD (KM analysis)
- Time to cardiovascular death, transplant or LVAD (KM analysis)
- Days alive free from heart failure hospitalization

- Outpatient Clinic HF Visit and / or Outpatient Intensification of Heart Failure Therapy
- Emergency room HF visits
- HF Clinical Composite Assessment (improved, unchanged, or worsened) as described by Packer comprised of all-cause mortality, HF hospitalization, and changes in NYHA functional class ranking and Patient Global Assessment
- Comparison of transthoracic echocardiographic parameters as listed in Echocardiography Core Laboratory Manual
- Incidence of loss of shunt flow as measured on TTE and/or TEE
- Changes in 6MWT
- Changes in KCCQ
- Death: All-cause; Cardiovascular cause (with breakdown by cause, e.g. sudden death, myocardial infarction, pump failure, stroke); Non-Cardiovascular cause; Undetermined cause; and relationship to device, study intervention or other cardiovascular procedure
- Hospitalization: All-cause; HF hospitalization, Non-HF hospitalization (with breakdown for cause including if associated with secondary worsening of HF)
- Change in renal function
- Medication utilization including type, dose, frequency, and changes
- Cost and cost-effectiveness data
- Technical success
- Device success
- Procedural success
- For Roll-in patients, transesophageal echocardiography at 6 and 12 months to assess shunt patency and other parameters as listed in the Echocardiography Core Laboratory Manual

3.3.2 SAFETY DATA COLLECTION

- Major Adverse Cardiovascular and Neurological Events (MACNE) and Bleeding Academic Research Consortium (BARC) types 3 and 5 bleeding at 30 days
- Percentage of Treatment Group patients with device related MACNE at 12 months
- Incidence of all Serious Adverse Events by type at study duration
- Incidence of cerebrovascular events at study duration with sub-classification of CNS infarction, CNS hemorrhage, and TIA and their relationship to device or study procedures (per NeuroARC)
- Incidence of MI events at study duration after implantation
- Incidence of systemic embolization events at study duration after implantation
- Incidence of pulmonary embolism events at study duration after implantation
- Incidence of shunt implant embolization at study duration
- Device-related MACNE annually through 5 years
- MACNE in Shunt treated patients receiving LVADs annually through 5 years post-study device implantation

3.4 EFFECTIVENESS QUALIFYING ENDPOINT AND ELIGIBILITY EVENT DEFINITIONS

3.4.1 HOSPITALIZATION (ALL-CAUSE)

Defined as an admission to an acute care facility, inpatient unit, observation unit or emergency room, or some combination thereof, for at least 24 hours. Excludes hospitalizations planned for pre-existing conditions (elective admissions), unless there is worsening in the baseline clinical condition prior to the planned admission. Overnight stays at nursing home facilities, physical rehabilitation, or extended care facilities, including hospice, do not meet the definition of hospitalization. Hospitalizations will be adjudicated by the Clinical Events Committee as Heart Failure Hospitalization, Other Cardiovascular Hospitalization, or Non-Cardiovascular Hospitalization.

3.4.2 HEART FAILURE HOSPITALIZATION

Meets the definition of Hospitalization above and the primary reason for admission is acute decompensated heart failure (ADHF) meeting the following criteria:

1) Patient has one or more symptoms of ADHF such as worsening or new onset of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, reduced exercise capacity and/or lower extremity/abdominal swelling;

AND

2) Patient has one or more signs or laboratory evidence of ADHF such as: rapid weight gain, pulmonary edema or rales, elevated jugular venous pressure, radiological signs of pulmonary congestion or increased pulmonary venous pressure, increasing peripheral edema or ascites, S3 gallop, hepatojugular reflux, and/or elevated BNP or NT pro-BNP above most recent baseline, right heart catheterization within 24 hours of admission showing elevated PCWP or low cardiac index;

AND

3) Admission results in the initiation of intravenous heart failure therapies such as diuretics, vasodilators, inotropes, or mechanical or surgical intervention (e.g., ultrafiltration, intra-aortic balloon pump, mechanical assistance) or the intensification of these therapies or at least doubling of the oral diuretic dose with the clear intent of promoting increased diuresis for the treatment of ADHF.

AND

4) No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

Admissions for heart transplantation, implantation of a right or left ventricular assist device or other intervention procedure for worsening heart failure (e.g. MitraClip implantation), as adjudicated by the independent CEC, will be counted as a HF Hospitalization. This does not include elective hospitalizations exclusively for diagnostic evaluation of candidacy for these procedures.

It is recognized that some patients may have multiple simultaneous disease processes. Nevertheless, for the endpoint event of heart failure requiring hospitalization, the diagnosis of HF would need to be the primary disease process accounting for the above signs and symptoms. All hospitalizations where the primary reason for admission is other than ADHF, if accompanied by worsening HF or subsequently complicated by ADHF, do not meet the criteria for HF Hospitalization. This includes the admission for the study intervention procedure. For example, patients admitted where the primary reason for admission is pneumonia, which are adjudicated to have secondary worsening of HF, would not be counted as HF Hospitalization.

Heart Failure Clinic ADHF Visit (as defined in Section 3.4.6) and Outpatient Intensification of Heart Failure Therapy (as defined in Section 3.4.7), do not meet the definition of HF Hospitalization. However, these events will be collected and used in sensitivity analyses.

3.4.3 OTHER CARDIOVASCULAR HOSPITALIZATION

Meets the definition of Hospitalization in 3.4.1 for conditions such as coronary artery disease, acute coronary syndromes, hypertension, cardiac arrhythmias, pericardial effusion, atherosclerosis, peripheral vascular disease, pulmonary embolisms, stroke and aortic dissection.

3.4.4 NON-CARDIOVASCULAR HOSPITALIZATION

Meets the definition of Hospitalization in 3.4.1 and does not meet the definition of HF Hospitalization or Other Cardiovascular Hospitalizations.

3.4.5 EMERGENCY ROOM HEART FAILURE VISIT

Admission to an emergency room for less than 24 hours, where the primary reason for admission is ADHF otherwise meeting the same criteria 1-4 defined for HF Hospitalization (Section 3.4.2) when the patient is not transferred to an inpatient unit or observation unit, but is discharged home.

3.4.6 **WORSENING HF EVENTS TREATED AS AN OUTPATIENT (INCLUDING ER HF VISITS WITH DURATION < 6 HOURS)**

Standardized definition from Heart Failure Collaboratory Academic Research Consortium (HFC-ARC).[82] Broadly characterized as unscheduled outpatient medical contact associated with changes in heart failure therapy and requires:

- Documented new or worsening symptoms due to heart failure
- Objective evidence of new or worsening heart failure
- Treatment specifically for worsening heart failure

- Significant augmentation in oral diuretic therapy (including at least a doubling of loop diuretic dose, initiation of loop diuretic therapy, initiation of combination diuretic therapy)
- Initiation of intravenous diuretic (even a single dose)
- Initiation of an intravenous vasoactive agent (catecholamine, phosphodieaterase-3 inhibitor, other vasopressor, vasodilator)
- Mechanical fluid removal (ultrafiltration, hemofiltration, initiation of dialysis for what is felt to be a primary cardiac rather than renal cause)

- Documented response to treatment

.

3.4.7 OUTPATIENT INTENSIFICATION OF HEART FAILURE THERAPY

Requires that the patient has worsening symptoms, signs or laboratory evidence of worsening heart failure and the dose of diuretics was increased and sustained for a month, or intravenous treatment given for HF, or a new drug was added for the treatment of worsening HF. This event category excludes patients meeting the definition of Outpatient Clinic Heart Failure Visit (Section 3.4.6).

3.4.8 HEART FAILURE ENDPOINT QUALIFYING EVENTS

Only Heart Failure Hospitalization and Emergency Room Heart Failure Visits lasting at least 6 hours and worsening HF events treated as an outpatient (including ER HF visits lasting < 6 hours) that meet these definitions as adjudicated by the CEC as Endpoint Qualifying Events for inclusion in the Primary Effectiveness Endpoint analysis.

3.4.9 TECHNICAL SUCCESS

Technical success will be measured at exit from Cath lab and is defined as alive, with successful access, delivery and retrieval of the transcatheter V-Wave delivery system, with deployment and correct positioning of the single intended device and no need for additional emergency surgery or re-intervention related to either the device or the access procedure.

3.4.10 DEVICE SUCCESS

Device success will be measured at 30 days and all post-procedural intervals and is defined as alive and stroke free, with original intended device in place and no additional surgical or interventional procedures related to access or the device and intended performance of the device with no device migration, embolization, detachment, fracture, hemolysis or endocarditis, and expected hemodynamic performance including patent device with Qp:QS <1.5, and no detected para-device complications including device leak, erosion, systemic or pulmonary thromboembolization.

3.4.11 PROCEDURAL SUCCESS

Procedural success will be measured at 30 days and is defined as device success and no device or procedure related SAEs including life threatening bleeding (>4 units of packed red blood cells), acute kidney injury (stage 2 or 3, including renal replacement therapy), major vascular complications or tamponade requiring intervention, myocardial infarction or coronary ischemia requiring PCI or CABG, severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatment (e.g. ultrafiltration or hemodynamic assist devices including intra-aortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for ≥ 48 hours).

3.5 OTHER ENDPOINT DEFINITIONS

3.5.1 NEUROLOGICAL EVENTS

Neurological events will be classified according to Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative (NeuroARC).[83] Events will be classified as CNS injury (Type 1) including ischemic stroke, with or without hemorrhagic conversion, along with other Type 1 subtypes, and neurological dysfunction without CNS injury (Type 3) including TIA.

Clinical assessment will include a neurological consultation, assessment of the National Institutes of Health Stroke Scale, and assessment of neurological deficits and cognitive function according to institutional standards. Patients experiencing a neurological event will have an MRI or a head CT (if MRI is contraindicated) per standard of care and will undergo transesophageal echocardiography (TEE) to evaluate cardiac origin, device patency and involvement in their neurological event.

3.6 HEALTHCARE ECOMOMIC ANALYSES

The RELIEVE-HF trial will include a prospective health economic evaluation in order to provide rigorous, prospective data with respect to the cost-effectiveness of the interatrial shunt procedure compared with standard medical therapy. Resource utilization and cost data will be assessed only for U.S. patients in the trial from the time of randomization through a minimum of 1 and a maximum of 2 years of follow- up (at which point some patients assigned to the control group may cross over to the shunt procedure). These data will include hospital billing data (UB-04 summary bills and itemized hospital bills) for all U.S. patients, which will be used, along with supplementary material from the case report forms, to determine the initial treatment costs. Follow-up costs will be assessed from the perspective of the U.S. healthcare system based on resource utilization data including follow-up hospitalizations, office visits, medications, etc. At the completion of the trial, these data will be used in conjunction with quality of life and utility data collected from the trial to develop a long-term Markov model in order to project patient- level survival, quality-adjusted life expectancy, and costs beyond the time frame of the trial in order to

estimate the incremental cost-effectiveness ratio for the interatrial shunt procedure compared with standard medical therapy for the trial population.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The RELIEVE-HF trial hypothesis is that the V-Wave Shunt System is a safe and effective method for improving clinically meaningful outcome measures in a population of patients with advanced, highly symptomatic HF, irrespective of left ventricular systolic function, who are at high risk for morbidity and mortality events. This is accomplished by achieving both the Primary Safety Endpoint, demonstrating an acceptably low level of device-related Major Cardiovascular and Neurological Events, and the Primary Effectiveness Endpoint, establishing superiority of interatrial shunting for a hierarchical composite ranking of death, cardiac transplantation or left ventricular assist device (LVAD) implantation, recurrent HF-hospitalizations (including Emergency Room HF Visits ≥6 hours), recurrent worsening HF events treated as an outpatient (including ER HF visits < 6 hours), and change in KCCQ overall score.

RELIEVE-HF is a pivotal study (Schema Figure 1), comprising a prospective, multi-center, multinational, randomized, controlled, clinical assessor blinded and patient-blinded trial design. The study is anticipated to include up to 120 centers in the United States and other countries with most sites located in the US. If the recommendation from the interim analysis results in an increase in the original maximum total sample size of 600 subjects, then approval may be sought from the FDA for increase up to 150 sites with the majority of sites located in the US.

All patients will be screened for eligibility in a 3-stage process. After Preliminary Screening by the site, de-identified patient information including Echocardiographic Core Lab data will be reviewed by an independent *Eligibility Committee*, to confirm that inclusion/exclusion criteria are met and to minimize site selection bias. Screening assessments should be completed with the patient in stable condition as an outpatient. Consenting a patient predischarge or at discharge is acceptable. Final eligibility for study enrollment is then determined by the *Implanter-Investigator* in the Cardiac Catheterization Laboratory after a right heart catheterization and transesophageal echocardiographic (TEE) or intracardiac echocardiographic (ICE) imaging is performed to assess whether final hemodynamic and anatomic exclusion criteria are absent.

RELIEVE-HF is a 2-arm trial with roll-in patients. Sites will first familiarize themselves with the V-Wave system by implanting the shunt in up to 2 Roll-in patients and follow them in an open-label (unblinded) manner. Implantation performance during Roll-in will be assessed during the implant by a Sponsor provided qualified *Proctor*. The Roll-in arm will be closed once 100 patients have been enrolled. Roll-in patients will otherwise be followed and analyzed identically as Randomized patients, but their study data will be presented separately. Roll-in patients will additionally undergo TEE imaging at 6 and 12 months to assess Shunt patency.

Once a site has successfully completed proctoring, they will begin the Randomized Access (blinded) phase of the study. Initiation of sites and patient randomization will be staged and controlled so that early safety data can be evaluated before opening all centers and fully enrolling the trial.

During the Randomized Access phase, approximately 400 patients will be randomized 1:1 into a Shunt Treatment arm or a Control arm, with a possible increase to approximately 600 total patients based on interim analysis results. Randomization will be stratified by site and left ventricular ejection fraction (HFrEF, LVEF≤40% or HFpEF, LVEF>40%) as determined by the Echocardiography Core Laboratory on the baseline transthoracic echocardiogram. Treatment arm patients will undergo transseptal catheterization and Shunt implantation. Control patients will not have transseptal catheterization or shunt placement but will undergo all other study procedures. All patients are blinded to study assignment in the Cath Lab (see Section 6.3.2 Blinding Procedures). After randomization, all patients and study personnel involved in endpoint collections will remain blinded until a maximum of 24 months or until the last enrolled patient reaches the 12-month follow-up, whichever occurs sooner. All patients will have the same in- clinic and telephone follow-up schedule as described in the Schedule of Activities (SoA, Section 1.3) and be treated with Guideline-Directed Medical Therapy. Patients who receive the shunt require adjunct antiplatelet or anticoagulant pharmacological treatment. Many HF patients are already taking these medications, but for those who are not, the study will supply antiplatelet medications for Treatment patients and placebo for Control patients to maintain blinding.

The Randomized Access phase incorporates an adaptive design that allows sample size adjustment upward to a maximum of 600 randomized patients if a one-time interim analysis, performed by the independent *Unblinded Statistician,* results in updates to the original planning assumptions for the components of the composite primary effectiveness endpoint requiring a sample size change to maintain the original design statistical power.

Upon reaching 24 months of follow-up or at study unblinding, whichever occurs first, individual patients enter an Open Access phase where Control arm patients may cross over and receive a shunt if they consent, still meet eligibility criteria, and the cross-over phase of the study is active.

RELIEVE-HF uses standard trial methodologies to minimize patient risk and bias in interpreting the trial results. Risks are minimized by the selection of a defined patient population similar to that used in early feasibility studies and by the use of strictly enforced inclusion/exclusion criteria, including requiring data from invasive diagnostic procedures to help avoid patients at high risk for device-related complications, specifically those with severe pulmonary hypertension, significant RV failure, unstable hemodynamics, arrhythmias, or unsuitable anatomy. Patients are closely followed at regular intervals and observed for the detection and reporting of Serious Adverse Events (SAEs) and Serious Adverse Device Effects (SADEs). Standard sponsor-independent trial governance procedures including event endpoint adjudication by a Clinical Events Committee and trial oversight by the Data Safety Monitoring Board will also help assure patient safety.

Enrolling and randomizing patients immediately after diagnostic catheterization and invasive echocardiographic procedures (TEE or ICE) in the Cath Lab is also a means to prevent inadvertent

selection bias at implant and to capture events that may occur between randomization and device implantation or control procedures. Randomization and blinding of patient, observers, and data analysis are the standard methods that will be used to reduce bias. The additional use of an Eligibility Committee, Echo Core Lab, and CEC is expected to reduce inter-site heterogeneity in applying inclusion/exclusion criteria and adverse event reporting. Finally, the sponsor will not have access to any aggregate endpoint data that is identified by treatment assignment in the Randomized Access cohort patients until the completion of the study. However, some patient data may need to be unblinded to Sponsor to allow investigation of study safety and device performance concerns.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The multicenter, randomized, blinded, controlled design was selected to minimize institution, observational, and reporting bias. Although great care will be taken to assure patient and observer blinding, it cannot be guaranteed. The adequacy of blinding and the patients' perception as to whether they were treated with the shunt or remained in the control arm will be assessed in patients with a blinding questionnaire at the time of hospital discharge from the Study Intervention Procedure and at the 12-month follow-up visit. A blinding manual will provide guidance for sites and blinding logs will be maintained for all site research personnel that are involved in performing study procedures that will be used to assess study endpoints.

The study will enroll patients irrespective of LV systolic function. Randomization will be stratified for patients by ejection fraction, with HFrEF (LVEF≤0.40) and HFpEF (LVEF>0.40). From prior studies of implantable hemodynamic monitoring that have enrolled similar patients, including COMPASS-HF, CHAMPION, and LAPTOP-HF, it is anticipated that approximately 20-25% of patients meeting the enrollment criteria will qualify as HFpEF. [31,84,85] Just as with implantable hemodynamic monitoring, the main treatment goal of interatrial shunting is to prevent the highest excursions of LAP. The use of combined HFrEF and HFpEF populations for evaluation of the shunt is justified, since the major clinical outcomes associated with the resulting episodes of acute decompensated heart failure from each are identical. These include mortality, HF hospitalization, and exercise capacity, all of which are likely to be either caused by, or correlated with, sustained elevations in LAP, irrespective of LVEF.[8] The safety and effectiveness of the shunt according to pre-specified LVEF subgroups will be assessed by interaction testing.

4.3 END OF STUDY DEFINITION

It is anticipated that the study will require approximately 9 years to complete. This includes the initial period for Roll-in patients, randomization and follow-up through unblinding and determination of the primary endpoints and then annual follow-up for 5 years after implantation for Roll-In, Treatment and Control arm patients that receive a shunt at the end of the blinded phase.

A participant is considered to have completed the study if they complete all phases of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

After each scheduled review of the accumulating safety data, the DSMB will provide the Executive Committee and the Sponsor with a written recommendation whether to continue the study as planned, suspend enrollment, or terminate enrollment in the clinical investigation early for safety reasons. All DSMB recommendations will be reviewed by the Sponsor in consultation with the Executive Committee, with the Sponsor making the final determination about accepting, modifying, or rejecting the recommendations. If a decision is made to terminate the study early, the Sponsor will notify sites and develop a modified protocol for follow-up of implanted patients, which will be submitted to the appropriate regulatory authorities and Ethics Committees/IRBs. The Sponsor reserves the right to terminate the clinical investigation at any time and for any reason.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1) Ischemic or non-ischemic cardiomyopathy with either reduced or preserved LV ejection fraction and documented heart failure for at least 6 months from Baseline Visit.

2) NYHA Class II, Class III or ambulatory Class IV HF (historical assessment documented at the Baseline Screening visit).

3) Receiving guideline directed medical therapy (GDMT) for heart failure which refers to those HF drugs carrying a Class I indication:

   a) Patients with reduced LVEF (≤40%): An inhibitor of the renin-angiotensin system (RAS inhibitor), including an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI) and a beta-blocker (BB), for at least 3 months prior to the Baseline Visit.

   b) Patients with reduced LVEF (≤40%): Other medications recommended for selected populations, e.g., a mineralocorticoid receptor antagonist (MRA) or nitrates/hydralazine, should be used in appropriate patients, according to the published guidelines.

   c) All patients: Patient has been on stable HF medications as determined by the investigator, for at least 1 month, with the exception of diuretic therapy. Stable is defined as no more than a 100% increase or 50% decrease in dose within these periods.

   d) All patients: Drug intolerance, contraindications, or lack of indications must be attested to by the investigator. Patients should be on appropriate doses of diuretics as required for volume control.

4) Receiving Class I recommended cardiac rhythm management device therapy. Specifically: if indicated by class I guidelines, cardiac resynchronization therapy (CRT), an implanted cardioverter-defibrillator (ICD) or a pacemaker should be implanted at least 3 months prior to Baseline Visit.

These criteria may be waived if a patient is clinically contraindicated for these therapies or refuses them and must be attested to by the investigator.

5) NYHA Class II must meet both 5a **AND** 5b. NYHA Class III, and ambulatory Class IV, must meet 5a **OR** 5b.

a) One (1) prior Heart Failure Hospitalization with duration >24 hours or Emergency Room Heart Failure Visit with duration ≥6 hours, or Heart Failure Clinic ADHF Visit with duration ≥6 hours, within 12 months from Baseline Visit.

i) If a CRT device was previously implanted, the heart failure hospitalization must be ≥ 1 month after CRT implantation.

ii) If a mitral valve repair device (e.g. MitraClip) was previously implanted, the heart failure hospitalization must be ≥ 1 month after mitral valve repair implantation.

b) Alternatively, if patients have not had a HF hospitalization or ER HF Visit within the prior 12 months, they must have a corrected elevated Brain Natriuretic Peptide (BNP) level of at least 300 pg/ml or an N-terminal pro-BNP (NT-proBNP) level of at least 1,500 pg/ml, according to local measurement, within 3 months of the Baseline Visit during a clinically stable period and at least 1 month after implantation of a CRT or mitral valve repair devices. (Note: "corrected" refers to a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m^2 in BMI above a reference BMI of 20 kg/m^2). If patient is on ARNI, NT-proBNP should be used exclusively.

6) Able to perform the 6-minute walk test with a distance ≥100 meters and ≤450 meters. The test will be performed twice separated by a minimum of 60 minutes between tests. The second test may be performed up to 7 days after the first test, if needed. The higher reading shall be used as the baseline value.

7) Provide written informed consent for study participation and be willing and able to comply with the required tests, treatment instructions and follow-up visits.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

5.2.1 PRELIMINARY EXCLUSION CRITERIA (PEC)

1) Age <18 years old.

2) BMI >45 or <18 kg/m^2.

3) Females of childbearing age who are not on contraceptives or surgically sterile, pregnant or lactating mothers.

4) Resting systolic blood pressure <90 or >160 mmHg after repeated measurements.

5) Baseline echocardiographic evidence of unresolved, non-organized or mobile intracardiac thrombus.

6) Severe pulmonary hypertension defined as PA systolic pressure >70 mmHg by echo/Doppler (or PVR >4.0 Wood Units by PA catheter measurement that cannot be reduced to ≤4 Wood Units by vasodilator therapy).

7) RV dysfunction defined as TAPSE <12mm or RVFAC ≤25% as assessed on Baseline TTE.

8) Left Ventricular End-Diastolic Diameter (LVEDD) >8cm as assessed on Baseline TTE.

9) Atrial septal defect (congenital or iatrogenic), patent foramen ovale, or anomalous pulmonary venous return, with more than trace shunting on color Doppler or intravenous saline contrast (bubble study) or prior surgical or interventional correction of congenital heart disease involving the atrial septum (excluding closure by suture only but including placement of a PFO or ASD closure device).

10) Untreated moderately severe or severe aortic or mitral stenosis.

11) Untreated severe or greater regurgitant valve lesions, which are anticipated to require surgical or percutaneous intervention within 12 months.

12) Mitral valve repair device (e.g. MitraClip) implanted within 3 months prior to Baseline Visit.

13) Untreated coronary stenosis which requires surgical or percutaneous intervention.

14) Acute MI, acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), rhythm management system revision, (not including generator change), lead extraction, or cardiac or other major surgery within 3 months of Baseline Visit. Rhythm management system generator change within 1 month of Baseline Visit.

15) Known active valvular vegetations, atrial myxoma, hypertrophic cardiomyopathy with significant resting or provoked subaortic gradient, acute myocarditis, tamponade, or large pericardial effusion, constrictive pericarditis, infiltrative cardiomyopathy (including cardiac sarcoidosis, amyloidosis, and hemochromatosis), or congenital heart disease, as cause of HF.

16) Stroke, transient ischemic attack (TIA), systemic or pulmonary thromboembolism, or deep vein thrombosis (DVT) within 6 months of Baseline Visit. Any prior stroke with permanent neurologic deficit. Any IVC filter.

17) Transseptal procedure for another indication (e.g. AF ablation, left atrial appendage occlusion, mitral valve repair/replacement) anticipated within 6 months.

18) Bradycardia with heart rate <45 bpm (unless treated with a permanent pacemaker) or uncontrolled tachyarrhythmias. This includes defibrillation shocks reported by the patient within 30 days of Baseline Visit.

19) Intractable HF with:

a) Resting symptoms despite maximal medical therapy (ACC/AHA HF Stage D).

b) Treatment with IV vasoactive medications (e.g., IV inotropes, IV vasodilators) within the last 30 days.

c) Cardiac Index <1.5 L/min/m^2.

d) Treated with a ventricular assist device (VAD).

e) Listed for cardiac transplantation.

20) Prior cardiac transplantation.

21) Patients with HFrEF (LVEF ≤40%) who are intolerant to a RAS inhibitor including all of ACEI, ARB or ARNI, and intolerant to beta-blocker medical therapy.

22) Not eligible for emergency cardiothoracic or vascular surgery in the event of cardiac perforation or other serious complication during study intervention procedure.

23) Life expectancy <1 year due to non-cardiovascular illness.

24) Coagulopathy or is taking anticoagulation therapy which cannot be interrupted for the study intervention procedure or has contraindications for all of the study mandated post implantation anticoagulation / antiplatelet regimens, or known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically.

25) Estimated glomerular filtration rate (eGFR) <25 ml/min/1.73 m^2 by the MDRD method, or not responsive to diuretics, or is receiving dialysis.

26) Hepatic impairment with a documented liver function test result (transaminases, total bilirubin, or alkaline phosphatase) ≥ 3 times upper limit of normal.

27) Severe chronic pulmonary disease requiring daytime home oxygen or chronic oral steroid therapy (Note: nighttime oxygen therapy and inhaled steroid therapy are acceptable).

28) Active infection requiring parenteral or oral antibiotics.

29) Known allergy to nickel.

30) Any condition that may interfere with compliance of all protocol procedures, such as active drug addiction, active alcohol abuse, or psychiatric hospital admission for psychosis within the prior year.

31) Currently participating in a clinical trial of any investigational drug or device that has not reached its primary endpoint, or any study that may interfere with the procedures or endpoints of this trial. Participation in an observational study or registry with market approved drugs or devices would not exclude a patient from participation in this trial.

32) Patient is otherwise not appropriate for the study as determined by the investigator or the Eligibility Committee, for which the reasons must be documented.

33) Patient belongs to a vulnerable population per investigator's judgment or patient has any kind of disorder that compromises his/her ability to give written informed consent and/or to comply with study procedures.

5.2.2 FINAL EXCLUSION CRITERIA (FEC) ASSESSED DURING CARDIAC CATHETERIZATION, AT STUDY INTERVENTION VISIT, JUST PRIOR TO RANDOMIZATION

The FEC serves two important purposes: 1) to exclude patients with anatomy or physiology less suitable for interatrial shunt implantation; and 2) to exclude clinically and hemodynamically unstable patients.

1) Change in clinical status between baseline screening and Study Intervention visit such that the patient is not stable to undergo the Intervention Procedure.

2) Females with a positive pregnancy test on laboratory testing for FEC.

3) Unable to undergo TEE or ICE.

4) Unable to tolerate or cooperate with general anesthesia or conscious sedation.

5) Anatomical anomaly on TEE or ICE that precludes implantation of Shunt across fossa ovalis (FO) of the interatrial septum including:

   a) FO Thickness >6mm in and adjacent to the location intended for shunt placement.

   b) Minimal FO Length <10mm.

   c) ASD or PFO with more than a trace amount of shunting.

   d) Intracardiac thrombus felt to be acute and not present on prior exams.

   e) Atrial Septal Aneurysm defined as ≥ 10 mm of phasic septal excursion either into either atrium or a sum total excursion of ≥ 15 mm during the cardiorespiratory cycle, with a base of ≥ 15 mm.

6) Inadequate vascular access for implantation of Shunt. Femoral venous or inferior vena cava (IVC) access for transseptal catheterization are not patent as demonstrated by failure to pass Swan-Ganz or ICE catheter from the right or left femoral vein to the right atrium.

7) Hemodynamic, heart rhythm, or respiratory instability at time of cardiac catheterization including:

   a) Mean PCWP <7 mmHg, not correctable by IV volume infusion (maximum 1,000 ml normal saline or equivalent).

b) Mean PCWP >35 mmHg, not correctable by medical therapy (e.g. IV Furosemide, IV or sublingual nitroglycerin).

c) Right Atrial Pressure (RAP) ≥ Left Atrial Pressure (LAP or PCWP) when LAP (PCWP) ≥7 mmHg.

d) Cardiac Index (CI) <1.5 liters/min/m^2 after correction of volume depletion with IV fluids (maximum 1,000 ml normal saline or equivalent).

e) Severe pulmonary hypertension defined as PASP >70 mmHg associated with PVR >4.0 Wood Units, that cannot be reduced to PVR ≤4 Wood Units by acute vasodilator therapy.

f) Resting systolic Blood Pressure <90 or >160 mmHg, not corrected with IV fluid administration or vasodilators, respectively.

g) Need for IV infusions of vasopressor or inotropic medication. Transient hypotension or bradycardia during anesthesia or catheterization, manifest as a vagal or similar acute episode or dehydration, responding promptly to IV fluid boluses or IV push vasopressors or chronotropic agents is not an exclusion criterion.

h) Malignant arrhythmias such as ventricular fibrillation, ventricular tachycardia, atrial fibrillation/flutter with rapid ventricular response associated with hypotension and requiring cardioversion.

i) Acute respiratory distress or hypoxemia.

8) Patient is otherwise not appropriate for study as determined by the Investigator.

Note: Patients excluded for any of the FEC criteria related to clinical or hemodynamic stability may be considered for repeat screening at a later date once the Investigator has determined the cause of the instability and patient has been shown to return to baseline stable status (see Section 5.3).

5.3 SCREEN FAILURES

Screen failures are defined as patients who sign informed consent to participate in the clinical trial but do not meet all inclusion/exclusion criteria. All AEs that occur after patient consent and before study enrollment will be reported and assessed for their relationship to study procedures.

All potential study patients will be tracked at each site with a *Site Screening Log*. The log documents each patient's study eligibility based on the 3-part screening process described in Section 4.1. The reasons for non-eligibility will be documented. The log also informs the level of screening effort at each site and that consecutively eligible patients are enrolled.

Patients that fail screening may be re-screened after 30 days if the Investigators and the Sponsor agree (documented in writing). Rescreened participants should be assigned the same participant number as for the initial screening.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

In summary, the trial is expected to enroll approximately 100 patients in the Roll-in arm and approximately 400 patients in the Randomized arms. The total number of randomized patients may be further increased to approximately 600 patients after a single interim analysis. Each site may enroll up to 15% of the total enrollment. The primary analysis will be performed when the last enrolled patient has been followed for a minimum of 12 months from randomization. The duration of follow-up evaluated by the primary effectiveness endpoint will range from a minimum of 12 to a maximum of 24 months. All implanted patients (Roll-Ins, Randomized to Treatment and Control patients that cross-over and receive the shunt) will be followed for a total of 5 years from the time of the Study Device implantation.

The target population includes adult male and female patients irrespective of age, race, and ethnicity. It is recognized that female patients have been traditionally underrepresented in HF trials for a variety of reasons. Similarly, minority populations have been under-represented in prior HF trials. To enhance enrollment of underrepresented groups this study plans to:

- Where appropriate, target investigational sites where recruitment of needed populations can be more easily facilitated (hospitals with women's clinics, urban facilities).
- Have tailored communication strategies for study recruitment including social media outreach.
- Have physician investigators involved in recruiting patients.
- Have flexibility in follow-up visit schedules including provision for transportation or elder care services during appointments.
- Perform periodic evaluation of Site Screening Logs to understand reasons for screen failures.

The study is anticipated to include up to 120 centers in the United States and other countries with most sites located in the US. The anticipated accrual rate is approximately 0.6 patients per site per month. Sources for participant patients are expected to include inpatients, outpatient Heart Failure Clinics, and local community outreach programs. Patients will be approached by investigational site personnel only. Social media, patient advocacy groups or advertising may be used to attract potential patients to make inquiries at local sites or be approached by individual sites.

6 STUDY INTERVENTION

6.1 STUDY DEVICE

6.1.1 V-WAVE INTERATRIAL SHUNT SYSTEM INTENDED USE AND INDICATIONS FOR USE

The V-Wave Shunt System consists of the V-Wave Shunt and the V-Wave Delivery System. The V-Wave Shunt is a permanent implant, which is designed to enable shunting of blood from the left to the right

atrium and by that, improve symptoms in NYHA Class III and ambulatory Class IV heart failure patients with reduced or preserved left ventricular systolic function.

6.1.2 V-WAVE INTERATRIAL SHUNT SYSTEM

The V-Wave™ Ventura™ Interatrial Shunt System consists of the (1) V-Wave™ Ventura™ Interatrial Shunt Model VIS-01-5.0-14F, (2) the V-Wave™ Ventura™ Delivery System Model VDS-01-0.0-14F85, and (3) the V-Wave™ Ventura™ Introducer Sheath Model VDI-01-15F85.

The Ventura Delivery System is introduced into the body through a Ventura Delivery Sheath placed in the left atrium following a standard femoral venous access transseptal cardiac catheterization procedure.

The Ventura Shunt is a permanent implant, which is designed to shunt blood from the left to right atrium thereby, improving symptoms in patients with advanced chronic heart failure. It is constructed on an hourglass-shaped, self-expanding Nitinol frame, with ePTFE encapsulation to block tissue ingrowth. The Shunt is implanted across the fossa ovalis of the interatrial septum. Once implanted, it protrudes into the left and right atria, with a total length of ~12mm. The external diameter at the right and left atrial ends are ~11 mm and ~14 mm, respectively. The implant is designed for single-use and is sterilized using ethylene oxide.

The Ventura Delivery System includes a Delivery Catheter and Loading Tools. The Loading Tools are used to compress the shunt for attachment to the distal end of the Delivery Catheter and for loading the Shunt/Catheter into the Delivery Sheath. The Delivery Sheaths include the V-Wave Ventura Introducer Sheath, or the optional commercially available Cook Medical (Bloomington, IN) 14 Fr Mullins Introducer Sheath (Part Number RCFW-14.0-38-85-RB). The Delivery Catheter includes a handle to control the release of the Shunt, a flushing port and a safety clip to prevent unintended release of the Shunt. Detailed instructions for loading and implanting the Shunt with its dedicated Delivery System are included in the IFU.

6.1.3 SUMMARY OF NECESSARY TRAINING, EXPERIENCE AND FACILITIES NEEDED TO USE THE INVESTIGATIONAL DEVICE

Sites will be selected that have experienced HF services and at least two physician expert investigators who are experienced in participating in randomized trials. Each site will include at least one cardiologist with expertise in the diagnosis and medical management of patients with severe HF (*HF-Investigators*) and at least one implanting physician (*Implanter-Investigators*). Implanting physicians may be interventional cardiologists highly experienced in ultrasound-guided transseptal catheterization and structural heart disease therapeutic procedures such as MitraClip mitral valve repair or left atrial appendage occlusion; or they may be electrophysiologists with similar transseptal experience who are skilled at AF ablation by pulmonary vein isolation. On-site cardiac surgery must be available. One of these physician investigators will be designated the Primary Investigator for each site.

All Investigators and trial personnel are required to attend Sponsor training sessions. Training of trial personnel will include the clinical investigation plan and its requirements, investigational device usage, case report form (CRF) completion and trial personnel responsibilities. All Investigators must be trained to the clinical investigation plan and trial procedures prior to consenting and enrolling patients. Investigators will be specifically trained in the selection of patients for participation. The (*Implanter-Investigator*) will be trained in the proper use of the V-Wave Interatrial Shunt System, first on a bench-top model and then proctored during the first Roll-in cases per the protocol requirements.

6.1.4 PROCTORING

The RELIEVE-HF Study involves the use of new device implantation techniques and post implantation patient management. As such, resources must be available to sites for proctoring device implantation and sharing experience. The Sponsor will assign each site an experienced proctor for each V-Wave Interatrial Shunt implantation during Roll-in cases. The proctor may be an employee of the Sponsor or another investigator. A proctor will be present at implantations for each new implanting physician to assure adequate training and compliance with the protocol and the *Implant Guidelines* comprising *Best Practices* and *Tips and Tricks* documents contained within the *Manual of Operations* (MOP) until both the Sponsor and implanting physician feel it is no longer necessary. The proctor is encouraged to observe and advise but not to participate in the procedure in a hands-on fashion. Sites are encouraged to consult their proctor or other knowledgeable implanter with questions or concerns prior to, during, or after device implantations. Satisfactory completion of proctoring is certified by the proctor. This typically requires 1-2 implantation procedures, but no more than 3 cases. If a proctor has not certified an Implanter after 3 cases, a plan to either drop the site or Implanter, or add additional proctoring cases must be agreed to in written communications between the Investigators and the Sponsor.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

The Sponsor must maintain device accountability, documenting all shipments and returns of investigational devices. Each device is traceable using the lot or serial numbers that is affixed to the device label.

Investigational product will be shipped only after site activation and shipping authorization is complete. The Sponsor will only ship the V-Wave Shunt and Delivery System to the site's *Primary-Investigator* (or designee). Storage locations for the devices at investigational sites will be locked with access restricted to investigators and authorized study personnel only. Alternatively, depending on individual site logistics, a Sponsor representative may hand-deliver devices to the sites as needed for case performance.

The Principal Investigator or an authorized designee must maintain records on the *Device Inventory Log* of the date of receipt, the identification of each investigational device (batch number, serial number or unique code), identification of participant receiving the device, the date of use, expiration date and final

disposition. The *Implanter-Investigator* will also maintain adequate records on case report forms (CRFs), including date implanted, patient identification number and implanting Investigator.

Upon study enrollment completion, the *Primary-Investigators* at each site will be notified. All unused V-Wave products must be returned to the Sponsor when enrollment is complete according to the returned goods process. All V-Wave products or any remaining components that are associated with a device malfunction must be returned to the Sponsor.

The *Inventory Accountability Report* generated by the Sponsor must document the disposition of all investigational devices including those that have been returned to the Sponsor.

Use of any investigational device outside of the clinical investigation plan (e.g. compassionate use) is strictly forbidden and may constitute grounds for removal of the Investigator/Site from the trial.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All potentially eligible patients at approximately 120 sites worldwide will be approached for participation in the study. Baseline data from consented patients will be reviewed by the Eligibility Committee to ensure that inclusion/exclusion criteria are met. These measures will help minimize patient selection bias and assure that a breadth of patient demographic characteristics will be included in the study. In addition, these practices optimize the chances that trial inclusion/exclusion criteria are strictly adhered to and create a cadre of multiple heart failure specialists and implanter investigators who can critically evaluate their experience with interatrial shunting in general and the V-Wave System in particular.

6.3.1 RANDOMIZATION

Once a site has successfully completed Roll-in cases, the Sponsor will notify the site to begin the Randomized Access phase of the study. Patients who are eligible based on meeting Inclusion Criteria and Preliminary Exclusion Criteria during outpatient screening and after approval by the Eligibility Committee, will undergo cardiac catheterization and TEE or ICE for evaluation of the FEC. Randomization will occur if the right heart catheterization and the TEE or ICE demonstrate that the patient has no Final Exclusion Criteria as determined by the *Implanter-Investigator*. If necessary, randomization and the index procedure may be delayed for up to 24 hours for patient safety, but the reasons must be documented. In this situation, the patient may remain hospitalized until randomized.

Patient randomization will be via an automated interactive system available on the electronic data capture (EDC) system, which will require entry of the site's ID, and the patient's participant number. The system will have knowledge of the site and the patient's LVEF as determined by the Echo Core Lab for stratification purposes. After data are verified, a randomization assignment will be given. The randomization assignment will be kept by the *Implanter-Investigator* or unblinded designate and kept separate from other study documents until the patient has been unblinded. Randomization will be 1:1 to the Shunt or the Control group. Unblinded cross-over of Control patients to receive a Shunt is allowed

when the patient completes the Randomized Access period (at 24 months or when the last patient enrolled reaches 12 months of follow-up), and the cross-over phase of the study is active.

6.3.2 BLINDING PROCEDURES

RELIEVE-HF will be a double-blinded study with the patient and the physicians and research staff managing the patients after the Randomization/Study Intervention Procedure, including all those involved in conducting post-randomization evaluations or treatment decisions will be blinded to study assignment. Personnel at the site who will be unblinded include the implanting physician, research staff present during the implant procedure and the study pharmacist (responsible for maintaining and dispensing the study provided antiplatelet or placebo medications).

At the time of randomization in the Cath Lab, any staff members present who are designated as blinded personnel will be instructed to leave the area. The *Implanter-Investigator* will be the responsible local authority throughout the trial for maintaining the blind and managing the blinding procedures of the *HF-Investigator* and blinded research staff. The *Study Pharmacist*, will also be unblinded and be responsible for administering the medications or placebos in the study. Selected members of the echocardiography department will similarly have to be unblinded.

Patient blinding begins in the Cath Lab with general anesthesia or conscious sedation. Patients will be provided earphones to wear with music playing to preclude hearing procedural discussions. A blindfold or other shielding may be used to prevent the patient from viewing the imaging screens during the procedure.

Patients randomized to the Control arm will not undergo transseptal catheterization and Shunt placement. The *Implanter-Investigator* will perform a mock transseptal catheterization and device placement from a script provided in the manual of operations. After approximately 15 minutes have passed, the echo probes and right heart catheter will be removed, and the skin incisions closed. Treatment and Control patients may transition from general anesthesia to conscious sedation during the study intervention procedure as soon the indication for general anesthesia no longer exists.

At the completion of the intervention procedure, the *Implanter-Investigator* will read a script to the patient, informing them that they qualified for the study, that they were treated according to their randomization assignment, and they will remain unaware of whether they received the Study Device or were a Control, until the end of the Randomized Access phase of the study. All Site personnel who have knowledge of the patient study assignment will be instructed to maintain blinding of study assignment to patient, treating clinicians and blinded research staff. Randomization assignment should not be recorded in the patient medical record. Hospital notes should state that the patient is enrolled in the RELIEVE-HF Trial only, that it is a blinded trial, and that the patient may or may not have an interatrial shunt device implanted. However, it is understood that each hospital may use different procedures for maintaining the study blind.

The managing *HF-Investigator* and blinded research staff that have patient contact after the intervention procedure will be blinded to the patient's randomization assignment. They will remain

blinded until the completion of each patient's Randomized Access phase of the study. This is to ensure that all patients have equal interactions with study personnel and procedures and be maintained on GDMT throughout the study.

Hospital discharge from the Study Intervention Procedure occurs after a minimum of an overnight stay. The patient should be seen prior to discharge by the unblinded Implanter-Investigator or his/her designate to assess for the presence of procedure-related adverse events. The patient should also be seen by the blinded HF team, and to assure that the patient is stable for discharge with appropriate medications and follow-up appointments. In certain instances, appropriated blinded antiplatelet medications will need to be provided by the unblinded pharmacist.

Blinded research staff will perform in-clinic follow-up visits at 1, 3, 6, 12, 18, and 24 months and telephone contact visits at 2 weeks and 9, 15, and 21 months. Only a blinded staff member should perform or administer study evaluations including:

- 6MWT
- KCCQ, EQ-5D
- NYHA classification
- Physical Exam (including those related to assessments for potential LVAD use or heart transplant)

The unblinded staff members are responsible from preventing patient and blinded staff members from observing imaging screens during imaging studies or image review sessions. With all blinding procedures, it is crucial that the local teams work out and practice procedures in advance of randomizing the first patient, including formal assignment of personnel roles, so that patients and blinded staff are not inadvertently unblinded.

To determine the effectiveness of blinding procedures, patients will be asked to complete a *Blinding Questionnaire* shortly after their study intervention procedure and at the 12-month follow-up to determine if they had knowledge or belief of their randomized group assignment. Staff will be designated as Blinded or Unblinded on the Delegation of Authority Log. All Blinded Staff who become unblinded to an individual patient will be recorded on a *Blinding Log* and must be replaced with another blinded staff member for subsequent blinded interactions with that patient.

Hospital notes, office notes, letters to referring physicians, procedure notes, billing information, and other related patient information should refer to the assigned treatment as "RELIEVE-HF study procedure where the patient may or may not have received an interatrial shunt device" or other non-revealing language, or other methods may be used to maintain the study blind.

All request for unblinding before the scheduled date of unblinding must be submitted in writing by a treating physician to the study sponsor. The request will be evaluated by the Chief Medical Officer or designee to determine if unblinding is justified to ensure patient safety.

Individual patient study assignment will be known to Sponsor's Field Engineers supporting the study intervention procedures, the Monitors and the in-house personnel required to evaluate possible device-

related safety events and report them to FDA and other required authorities. To further minimize the potential for bias, Field Clinical Engineers and/or Field Monitors shall not have communication with any patient once enrolled in the study. Any questions or comments received from patients should be referred to site personnel. In addition, Field Clinical Engineers and/or Field Monitors shall have no contact with site personnel while they are conducting study-related activities involving Randomized patients (e.g. when a patient is performing a 6MWT).

Sponsor personnel and the trial Executive and Steering Committees will be blinded to all Randomized Access Phase combined and individual assignment group outcome measures, until the time of primary endpoint unblinding and database lock is complete. This does not include baseline demographics for the combined randomized cohort or recommendations from the DSMB regarding the interim analysis.

To further minimize bias, the CEC will be blinded to patient, site, and operator when performing SAE and endpoint adjudications. CEC may subsequently become unblinded for specific adjudications where knowledge of procedures performed is required. The echocardiographic core laboratory cannot be blinded to individual patient study assignment. The Independent Statistician(s) will generate blinded tables for review as requested by the DSMB to evaluate safety and for the planned interim analysis.

6.3.3 ASSESSMENT OF BLINDING AND PERCEPTION BIAS

Patients' perception as to whether they received the control or test device may affect the outcomes of the study. As described throughout the protocol, comprehensive efforts will be undertaken to maintain patient blinding. Nonetheless, for a variety of reasons patients may develop a belief as to the Randomization Group they were assigned, even if the blind is maintained.

To assess blinding and any potential perception bias on the endpoints of the study, information will be collected in a brief patient blinding and perception assessment questionnaire administered by the research coordinator post-procedure in the hospital prior to discharge (≥ 4 hours to ≤7 days after the procedure) and at 1 year. Subjects will be asked for their perception of what treatment they believe they might have received, and the basis of this perception (see MOP for the questionnaire). Analysis of the primary and secondary effectiveness endpoints will be performed in subgroups according to the results of this survey.

6.3.4 ECHOCARDIOGRAPHY CORE LABORATORY

Echocardiographic imaging, whether transthoracic (TTE), transesophageal (TEE) or intracardiac (ICE) will provide essential data to evaluate cardiac structure and function before and after interatrial shunting (as well as changes over time in the control group) and to examine the function of the shunt itself. To enhance the accuracy of study results, an independent core laboratory will be assigned to evaluate all echo imaging studies performed during the study. The Echocardiography Core Laboratory will:

- Develop an *Echo Core-Lab Manual* to be included in the MOP.
- Certify each site prior to first enrollment.

- Provide echo-based Inclusion/Exclusion parameters to sites and *Eligibility Committee*.
- Analyze all echocardiographic data per the Echo Core-Lab Manual.
- Provide quality assurance.
- Provide information technology services, image management - digitization, transfer, storage, and summary data management.
- Consult with and provide services to the study Executive Committee, as necessary.

6.4 STUDY INTERVENTION COMPLIANCE

The V-Wave Interatrial Shunt is a passive device that shunts blood between the atria in relation to the pressure gradient across the device. To use the device requires no action by the patient other than to take their daily prescribed adjunct anticoagulant/antiplatelet therapy described in Section 6.5. Medication compliance will be clinically assessed at each study visit through questioning by research staff. Non-compliance with study medications will be noted in the CRF and standard clinical means including patient education, administration of medications by a caregiver, pill counts, etc., will be instituted by the site on an as needed basis. See MOP for further details.

6.5 CONCOMITANT THERAPY

All patients should continue to receive medical therapy for heart failure. Prior to enrollment the central eligibility committee will confirm that all patients eligible for enrollment are on GDMT. After randomization and during the follow-up phase of the study the types and doses of HF medications should not be changed, unless required for clinical or symptomatic changes or side effects. Any changes in dose or medication type will be documented in the Case Report Form.

All HF treatment decisions in randomized patients during the blinded phase of the study must be made by blinded investigators.

Patients with HFrEF should be:

a) Maintained on tolerated doses of an inhibitor of the renin-angiotensin system either an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI)) and a beta-blocker (BB). Doses should be adjusted per published guidelines and clinical conditions. Such changes will be documented in the Case Report Form.

b) Other medications recommended for selected populations, e.g., a mineralocorticoid receptor antagonist (MRA) or nitrates/hydralazine, should be used in appropriate patients, according to the published guidelines.

c) Diuretics should be used to relieve symptoms due to volume overload.

d) Receive any cardiovascular devices (e.g. pacemaker, cardiac resynchronization therapy, implantable defibrillator) for which they develop a class I indication.

e) Drug intolerance, new contraindications, or other reason for changes in drug dose should be attested to by the investigator in the CRFs.

GDMT for patients with HFpEF generally includes:

a) Systolic and diastolic blood pressure should be controlled in accordance with current clinical practice guidelines.

b) Patients with atrial fibrillation should have adequate rate control

Diuretics should be used to relieve symptoms due to volume overload in both HFrEF and HFpEF patients. All medications including doses and dose changes will be recorded in the *Medication Log* at the time of baseline and follow-up visits.

Additionally, for all patients:

Due to the creation of an artificial interatrial shunt, there is the possibility of right-to-left (paradoxical) embolization of thromboemboli, fat, and air emboli. These events are anticipated to be rare. They may however be more likely if or when the normally present left-to-right interatrial pressure gradient is reversed. The most likely situations for this to occur are straining with stool, strong coughing and purposefully Valsalva maneuvers in the presence of occult right-sided emboli. Therefore, consideration should be given to prudent general medical measures to prevent constipation, use of antitussives during upper respiratory illness, prevention of deep venous thrombosis, prevention of air injection in intravenous lines, and careful observation after falls or fractures.

If patients are considered for mitral valve repair device implantation (e.g. MitraClip), it is recommended that:

- The Echocardiography Core Lab confirms that the patient meets the echocardiographic eligibility criteria of the COAPT study[86].
- Implantation of the mitral valve repair device be delayed until after 6 months after the Study Intervention Visit to allow adequate healing of a possible Shunt.

6.5.1 REQUIRED ANTIPLATELET/ANTICOAGULATION AND OTHER MEDICATIONS

A. Implantation. During the Implant of the Shunt, patients should be anticoagulated with unfractionated heparin per institutional standard of care to target the ACT ≥250. If ACT is ≥200 the implanter may choose to give an additional bolus of 2500 units and start the procedure and monitor ACT targeting ACT≥250. In cases where a patient is allergic to or otherwise has contraindication(s) to unfractionated heparin, use of bivalirudin is acceptable, with dosing according to the manufacturer's instructions.

B. Chronic Therapy. All patients who receive a shunt must be treated with a 6-month course of either 1) aspirin (≥75 mg daily) and a P2Y12 inhibitor (clopidogrel, ticagrelor or prasugrel at clinically indicated doses), or 2) warfarin or a direct acting oral anticoagulant (dabigatran, apixaban, rivaroxaban or edoxaban or other approved agent at clinically indicated doses). Patients who are already receiving one

of these regimens for a clinical indication unrelated to the shunt implant (e.g. prior stent or atrial fibrillation) should remain on their medications as clinically indicated. Patients who are not on either of these regimens will be treated with dual antiplatelet therapy. Control patients should remain on any clinically indicated antiplatelet/anticoagulant agents.

To maintain patient and study site personnel blinding all patients (regardless of treatment assignment) who are not on an antiplatelet/anticoagulant for a clinical indication will be provided study medications. Clopidogrel 75mg and Placebo clopidogrel 75mg will be provided to the site for maintenance and management by a site pharmacist. Aspirin 75-100 mg will be provided to patients by sites.

The clopidogrel provided by sponsor to all participating sites, including US and International sites, will be commercially available clopidogrel sourced in the US. (A matching placebo manufactured under GMP in the US (Sharp Clinical Services, Inc.) will be provided.) Both clopidogrel and placebo will be properly labeled to maintain the study blind.

Specific study required medications for all patients are shown in **Table 6**. **Table**

6. Study Required Medications

Medication	Patients	Peri-Procedure	Post-Procedure
Oral anticoagulant	Those taking Warfarin, Warfarin analogue or NOAC	Holding dose per institutional standard of care	Continue oral anticoagulant at dose indicated by pre-existing condition.
Dual Agent Antiplatelet Therapy (DAPT)	All others	Loading/holding of P2Y12 inhibitor*/ aspirin per institutional standard of care with transseptal procedure	**Treatment Arm:** Continue P2Y12 inhibitor* already in use for 6 months or longer if clinically indicated, otherwise, clopidogrel 75 mg daily for 6 months. All Treatment Arm patients should be on aspirin 75-100 mg daily indefinitely. **Control Arm:** Continue P2Y12 inhibitor* already in use for 6 months or longer if clinically indicated, otherwise, placebo for clopidogrel for 6 months. All Control Arm patients should be on aspirin 75-100 mg daily for duration of blinding.

*P2Y12 inhibitors include clopidogrel, ticagrelor and prasugrel.

Treatment Arm patients who have an unsuccessful implant and who are not on anticoagulation or dual antiplatelet therapy for a prior indication should receive aspirin and placebo for clopidogrel.

If during the course of therapy patient develops a contraindication to their anticoagulation/antiplatelet regimen, manage per local standards and consult with Sponsor's Medical Director regarding alternative regimens.

For patients screened for eligibility outside of the United States, there may be limitations on the use of certain medication regimens that are country or region specific as required by local regulatory authorities or ethics committees. This may be based on availability of medications, indications, or perceived risks, etc., and may result in the need to exclude certain patients from the study. These patients shall be excluded under Exclusion Criteria #24. "Coagulopathy or is taking anticoagulation therapy which cannot be interrupted for the study intervention procedure, or has contraindications for all of the study mandated post implantation anticoagulation / antiplatelet regimens or known hypersensitivity, or contraindication to procedural medications which cannot be adequately managed medically." Such patient exclusions are anticipated to affect only a very small portion of the study population. The Sponsor will work with the affected sites and the Eligibility Committee to assure that all patients that should be excluded for such reasons are correctly excluded from enrollment in the study.

C. Endocarditis prophylaxis. All patients should receive infective endocarditis prophylaxis as per institutional standards for a permanently implanted device for coverage of the Study Intervention Procedure. Endocarditis prophylaxis is specifically indicated before dental procedures with manipulation of gingival tissue, periapical region of teeth or perforation of oral mucosa or other procedures with high risk of bacterial seeding for a duration of six months after randomization in all Treatment and Control patients. Choice of drug and dosage are per institutional standards.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Each enrolled patient should agree at the time of consent to remain in the study until completion of the 5-year follow-up period. However, a patient's participation in any clinical trial is voluntary and the patient has the right to withdraw at any time without penalty or loss of benefit. Withdrawal is defined as termination of participation of a patient from a clinical trial. Reasonable efforts should be made to retain the patient in the clinical trial until completion of the clinical trial. Reasons for withdrawal include, but are not limited to the following:

- Withdrawal of informed consent by patient or family request (if patient unable to communicate their preference). No reason for withdrawal need be given.
- If any adverse event whether anticipated or not, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would, in the opinion of the Investigator, endanger the patient if study treatment were to continue.

- Disease progression which requires discontinuation of the study intervention (e.g. heart transplant). Patients treated with a VAD should continue to be followed in the trial (see Section 8.1.19) but will be censored from all study endpoints from date of VAD hospitalization.
- Non-compliance with the clinical investigation procedures or study protocol deemed by the Investigator to be sufficient to impact patient outcomes
- Lost to follow-up (as defined in Section 7.2)
- Patient death

The reason for participant discontinuation or withdrawal from the study will be recorded on the appropriate Case Report Form (CRF). Patients who sign the informed consent form but are not randomized may be replaced. Patients who sign the informed consent form, and are randomized (regardless of treatment assignment), and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

Patients who do not want to continue clinical follow up visits will be asked if they will continue to permit: 1) telephone follow up 2) medical record follow up 3) vital status follow up. Patients will also be asked to participate in an Early Termination Follow-Up Visit (see Section 8.1.19).

Withdrawn patients will be followed according to the standard of care existing at their care facilities.

7.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for three contiguous study scheduled contacts (in-clinic or telephonic) and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant as below:
    - 2 documented telephone calls
    - a certified letter to the participant's last known mailing address with return receipt documented (or local equivalent methods).
- After the above steps are taken, the patient will be considered withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 STUDY ASSESSMENTS: EFFECTIVENESS AND SAFETY

8.1.1 SCREENING / BASELINE VISIT

Once informed consent has been obtained and documented with a signed and dated Informed Consent Form, screening procedures may begin. In hospitalized patients who are approaching discharge, informed consent can be obtained predischarge or at discharge, but screening assessments must be completed with the patient in a stable state and as an outpatient.

The following activities are performed as part of the screening process:

- **Obtain Patient Informed Consent.** A copy of the informed consent must be retained in the patient medical record and study file.
- **Demographics and Medical History:** Includes age, sex, etiological factors for HF, all HF hospitalizations and Emergency Department visits during the prior 12 months, relevant co-morbidities, previous cardio-pulmonary procedures/surgeries.
- **Vital Signs and Physical Examination**: includes height, weight, blood pressure, temperature, pulse oximetry, heart rate and rhythm, and cardiovascular focused physical examination for assessing heart failure and performing study intervention procedure.
- **Medications**: collect all medications that the patient is currently taking.
- **Laboratory Tests:** to include Na, K, HGB, HCT, PLTS, WBC, Cr, BUN, AST, ALT, T Bili, BNP, or NT-pro BNP. BNP or NT-pro BNP obtained up to 90 days prior to the Baseline Visit may be used.
- **12-Lead ECG**
- **Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE)** with color Doppler, tissue Doppler, and optional 3D assessment of atrial septum. Elements per Core Laboratory Manual. Saline contrast (bubble study) may be performed at sonographer's discretion.
- **NYHA Functional Class**
- **KCCQ and EQ-5D Quality of Life assessments**
- **6MWT:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Inclusion/ Preliminary Exclusion Criteria (PEC) Review**
-
- **COVID-19 historyComplete CRFs**

Patients who do not meet all the inclusion criteria or who meet any of the exclusion criteria will be considered screening failures; however, patients may be re-screened after 30 days if the *HF-Investigator* and the Sponsor agree that he/she has a reasonable likelihood to subsequently become eligible (see Section 5.3). A *Screening/Baseline CRF* will be completed for all screened patients and submitted to the

Sponsor. The *Screening/Baseline CRF* and the *Screening Log* will indicate the inclusion/exclusion criteria that were not met.

NOTE: Patients in need of dental or periodontal repair should preferably receive it prior to study participation.

8.1.2 FINAL SCREENING / STUDY INTERVENTION VISIT (+ 60 DAYS FROM START OF BASELINE ASSESSMENT TO FEC)

Once the investigator has reviewed the baseline screening information and has determined that the patient meets the Inclusion and without Exclusion criteria, the baseline assessment information from baseline screening will be submitted to the *Eligibility Committee* The baseline TTE will be read by the Echo Core Lab and the pertinent results passed on to the *Eligibility Committee*. The *Eligibility Committee* will review the records to assure eligibility for the final screening phase. If clarifications are required, the site will be contacted by the Sponsor for the required information. Once approved by the Eligibility Committee, the Sponsor will notify the site and the Final Screening/Study Intervention Visit should be scheduled. Total time from start of baseline assessment to FEC shall not exceed 60 days. Otherwise, the patient will have to be rescreened

CAUTION: To assure the patient's wellbeing during the *Final Screening/Study Intervention Visit,* it is critical that the Investigator has determined and is satisfied that the patient is clinically stable prior to that visit. If not, the patient should be medically stabilized prior to scheduling the Final Screening/Intervention Visit. This can reduce the risk of study-related complications or the need to cancel procedures. This includes a physical examination with a careful assessment of volume status with consideration of diuresis prior to the procedure, or consultation with an anesthesiologist if patient has orthopnea or sleep disordered breathing. This stability requirement is limited to the patient's clinical status. A full reassessment of the Preliminary Exclusion Criteria performed at the Baseline Visit <u>is not required</u>. Chronic oral anticoagulation should be discontinued prior to the Study Intervention Visit per the site's standard of care.

Note: If after Eligibility Committee approval but before cardiac catheterization and randomization a major change is required in HF study medications (either increase in dose by >100%, reduction in dose by >50%, or introduction of a new study medication (RAS inhibitor, beta-blocker or MRA), or the patient receives a new ICD or CRT device, the patient should be screen failed and subsequently rescreened. .

8.1.2.1 FINAL ELIGIBILITY DETERMINATION

Final eligibility is determined in the Cardiac Catheterization Laboratory from the right heart catheterization and ICE or TEE measurements. The Implanting Physician will determine if the patient meets the Final Exclusion Criteria (FEC). After confirmation that the patient does not have any FEC, the randomization will proceed. **The patient will be considered enrolled in the study when the patient is randomized after confirmation by the *Implanting-Investigator* to have none of the FEC**.

Patients will be evaluated when presenting for the Study Intervention Visit. The following assessments will be performed prior to the Intervention Procedure, During and Post Procedure:

- **Vital Signs and Physical Examination**: includes weight, temperature, blood pressure, pulse oximetry, heart rate and rhythm, and focused cardiovascular physical examination pertinent to heart failure and study intervention procedure.
- **Medications**: Record all cardiovascular, anticoagulants, antiplatelet, SGLT2 medications, and all medications taken during last 72 hours.
- **Blood tests:** PT, PTT, INR (coagulation parameters per institutional standards), Hgb, HCT, Cr, cardiac Troponin (Troponin T, I, C – per institutional standard), and Pregnancy-urine or blood (if applicable).
- **Intracardiac or Transesophageal echocardiogram/Doppler examination (ICE/TEE):**

Elements per Core Laboratory Manual.

- **Right Heart Catheterization (RHC):** Per RHC manual conducted at the beginning of the procedure in both Treatment and Control patients and performed from femoral venous access.
- **Assessment of AEs** that occurred during implantation and all hospitalizations and Emergency Department visits since the Baseline visit.
- **COVID-19 history**
- **Cost Effectiveness**
- **Complete CRFs**

During the Randomized Access phase, once the patient is placed on the cardiac catheterization table, strict blinding procedures must be followed and maintained until the patient has reached the designated time for unblinding. Please see Section 6.3.2 detailing blinding procedures.

TEE or ICE must be used for confirming the FECs and guiding the implantation procedure. If TEE is used, general anesthesia administered by a dedicated anesthesiologist or equivalent is required. ICE can be performed under conscious sedation as required for patient comfort when patient cooperation is expected.

The RHC procedure must be performed from femoral venous access to minimize potential for unblinding. TEE/ICE and fluoroscopy/cine fluoroscopic images and hemodynamic pressure and thermodilution cardiac output waveforms should be recorded to document all pertinent findings during the FEC procedure. These will be used in training implanters and determining causality of potentially associated adverse events or adverse device effects.

Participants who meet one or more FEC will be considered a screen failure and will not be randomized. These patients may remain in the hospital overnight for observation at the investigator's discretion. They will be followed for 30 days to determine if there are procedure-related adverse events and visit should be documented on the Unscheduled Clinic Visit CRF. They may be considered for rescreening after 30 days if the Investigator and Sponsor agree (see Section 5.3). A *Final Exclusion Criteria CRF* will be

completed for all screened patients and submitted to the Sponsor. The *Final Exclusion Criteria CRF* and the *Screening Log* will indicate the inclusion/exclusion criteria that were not met.

If the FEC evaluation is not completed due to an AE during the Intervention Procedure, and the *Implanter-Investigator* wishes to repeat the FEC evaluation, the case should be rereviewed by the Eligibility Committee before reattempting the Intervention Procedure.

8.1.2.2 PATIENT ENROLLMENT IN THE STUDY AND RANDOMIZATION

After patient blinding procedures have been instituted and Final Eligibility Criteria are confirmed by the *Implanter-Investigator* (see Section 5.2.2), the patient is then randomized (see Section 6.3.1). With randomization, the patient is enrolled in the study.

8.1.2.3 STUDY INTERVENTION PROCEDURE

Patients randomized to the Shunt arm will undergo transseptal catheterization and Shunt placement as described below.

The V-Wave Shunt will be inspected and prepared for implantation according to the *Instructions for Use.*

A Sponsor representative will be available during the implantation procedure to support the study staff with device set-up and implantation processes and any training needs they may have.

In brief, the implantation procedure of the Shunt includes:

- TEE or ICE measurements and fluoroscopically guided transseptal puncture near the mid fossa ovalis with left atrial access.
- System set-up in accordance with the IFU
- Placement of Delivery Introducer Sheath
- Delivery and deployment of the Shunt in the target site in accordance with IFU
- TEE or ICE confirmation of successful Shunt placement and function
- Vascular access site care - introducer sheath removal immediately after completion of the intervention procedure. Other care per institutional standards

CAUTION: Introducer sheath must be removed immediately after completion of the intervention procedure. Failure to do so may increase the risk of potential paradoxical embolus and/or pulmonary embolism.

Treatment patients may transition from general anesthesia to conscious sedation during the study intervention procedure as soon the indication for general anesthesia no longer exists.

Implant data including procedure times, fluoroscopy time, radiation dose and contrast dose will be collected and reported on the *Intervention Procedure CRF*. Investigational products that are opened during a procedure and not used shall be recorded on a CRF. **TEE/ICE and fluoroscopy/cine fluoroscopic images and hemodynamic pressure and thermodilution cardiac output waveforms should be recorded**

to document all pertinent findings during the Study Intervention Procedure. These will be used for training implanters and determining causality of potentially associated adverse events or adverse device effects. TEE or ICE imaging must be uploaded to Echo Core Lab and Cine fluoroscopy images and right heart catheterization waveforms and summary data must be made available to study Sponsor at the end of the procedure.

All AEs during intervention procedure including date and time are to be documented.

Every effort should be made to maintain patient and medical staff blinding. Entries into the patient's clinical chart and disclosure to the patient should not reference the result of the randomization or whether a shunt was implanted. They should only reference that the patient was enrolled in a blinded study of interatrial shunting.

8.1.2.4 UNSUCCESSFUL IMPLANT

Implantation failure is defined when a patient enrolled in either the Roll-in or randomized to the Treatment arm does not have a successful device implantation. **At the *Implanter-Investigator's* discretion, several attempts to implant the device may be made during a single Study Intervention Procedure. Patients that fail implantation during this single procedure may not undergo a second Study Intervention Procedure attempt.**

If the implantation failure is due to a suspected device malfunction, the occurrence will be documented in the CRF. Devices, Delivery Systems and Tools that malfunction during the procedure will be returned to the sponsor for analysis.

Roll-in arm patients that have an unsuccessful procedure should have a 30-day telephonic follow-up to evaluate any adverse events and the visit should be documented on the Unscheduled Clinic Visit CRF. They should remain in the study until any events have been resolved.

In all cases, randomized patients will remain blinded to study assignment and be followed for the study duration and analyzed on an Intention to Treat basis starting from the time of Enrollment immediately after Randomization.

Treatment Arm patients that have an unsuccessful implant and who are not on anticoagulation or dual antiplatelet therapy for a prior indication should receive aspirin and placebo for clopidogrel (see Section 6.5.1). This should be arranged by the unblinded Implanter Investigator consulting with the unblinded pharmacist.

8.1.2.5 CONTROL PROCEDURE

Patients randomized to the Control arm will not undergo transseptal catheterization and Shunt placement. For patients undergoing ICE with moderate sedation, the *Implanter-Investigator* will perform a mock transseptal catheterization and device placement from a script provided in the MOP. After approximately 15 minutes have passed, the echo probe and any remaining catheters will be removed, and hemostasis obtained at vascular access sites.

Control patients may transition from general anesthesia to conscious sedation during the study intervention procedure as soon the indication for general anesthesia no longer exists.

Implant data including procedure times, fluoroscopy time, and contrast dose will be collected and reported on an Index Procedure CRF. CRFs will be sent to the Sponsor.

All AEs during hospitalization including date and time are to be documented.

Every effort should be made to maintain patient and medical staff blinding. Entries into the patient's clinical chart and disclosure to the patient should not reference the result of the randomization or whether a shunt was implanted. They should only reference that the patient was enrolled in a blinded study of interatrial shunting.

8.1.3 POST PROCEDURE & DISCHARGE EVALUATION

Following the intervention procedure, the Implanter-Investigator will read the **Blinding script** to the patient (see 6.3.2). All patients (Roll-In, Randomized to Treatment and Randomized to Control) shall be admitted to the hospital for an overnight stay and not discharged until the *Implanter-Investigator* deems the patient clinically stable. If not, appropriate clinical work-up should be performed.

Patients will be evaluated at hospital discharge and the following assessments will be performed:

- **Blinding procedures per Blinding MOP**: ensure patient remains blinded to study assignment.
- **Vital Signs and Physical Examination**: includes weight, temperature, blood pressure, pulse oximetry, heart rate and rhythm and cardiovascular focused physical examination pertinent to assessing heart failure and study intervention procedure complications including vascular access sites, pulses and extremities.
- **Medication**: Record all discharge medications including anticoagulation, antiplatelet therapy per protocol.
- **Blood test:** HGB, HCT, Cr
- **Chest X-Ray:** Attention should be paid to complications of procedure (e.g. pneumothorax). No reference should be made in the patient's clinical chart on whether a Shunt is present or not. Patient blinding should be maintained.
- **Assessment of AEs** that occurred in the hospital.
- **Patient Perception of Study Assignment:** Applied only to randomized patients.
- **COVID-19 history**

- **Cost Effectiveness**
- **Complete CRF**

Note: The unblinded Implanter-Investigator should specifically review the Chest X-Ray prior to discharge to confirm there are no procedure-related complications and to facilitate maintenance of patient and research staff blinding.

8.1.4 2-WEEK TELEPHONIC FOLLOW UP (± 7 DAYS)

All HF treatment decisions in randomized patients during the blinded phase of the study must be made by blinded investigators.

Patients will be evaluated at 2-week (14 days ±7 days) post implantation. This telephone call and the following assessments must be conducted by blinded staff:

- **Blinding procedures per Blinding MOP**
- **Medications:** Record all cardiovascular, anticoagulation and antiplatelet medications as per protocol, and SGLT2 medications.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Assessment of Worsening HF events treated as an outpatient**: randomized patients only
- **COVID-19 history**
- **Complete CRFs**

8.1.5 ONE (1) MONTH IN-CLINIC FOLLOW UP (± 7 DAYS)

All HF treatment decisions in randomized patients during the blinded phase of the study must be made by blinded investigators.

Patients will be evaluated at 1-month (30 days ±7 days) post implantation. This visit and the following assessments must be conducted by blinded clinicians:

- **Blinding procedures per Blinding MOP**
- **Vital Signs and Physical Examination**: includes weight, blood pressure, heart rate and rhythm and cardiovascular focused physical examination pertinent to assessing heart failure status and study intervention procedure complications.
- **Medications:** Record all cardiovascular, anticoagulation and antiplatelet medications as per protocol, and SGLT2 medications.
- **Blood test:** HGB, HCT, Cr
- **Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE):** Elements per Core Laboratory Manual. No reference should be made in the patient's clinical chart on whether the Shunt is present or not. Patient blinding should be maintained.
- **NYHA Functional Class**

- **KCCQ and EQ-5D Quality of Life assessments**
- **Patient Global Assessment**
- **6MWT:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Assessment of Worsening HF events treated as an outpatient**: randomized patients only
- **COVID-19 history**
- **Cost Effectiveness**
- **Complete CRFs**

8.1.6 THREE (3) MONTHS IN-CLINIC FOLLOW UP (± 14 DAYS)

All HF treatment decisions in randomized patients during the blinded phase of the study must be made by blinded investigators.

Patients will be evaluated at 3 months (90 days ±14 days) post implantation. This visit and the following assessments must be conducted by blinded clinicians:

- **Blinding procedures per Blinding MOP**
- **Vital Signs and Physical Examination**: includes weight, blood pressure, heart rate and rhythm, and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications**: Record all cardiovascular, anticoagulation and antiplatelet medications as per protocol, and SGLT2 medications.
- **NYHA Functional Class**
- **KCCQ and EQ-5D Quality of Life assessments**
- **Patient Global Assessment**
- **6MWT:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Assessment of Worsening HF events treated as an outpatient**: randomized patients only
- **COVID-19 history**
- **Cost Effectiveness**
- **Complete CRFs**

8.1.7 SIX (6) MONTHS IN-CLINIC FOLLOW UP (± 30 DAYS)

All HF treatment decisions in randomized patients during the blinded phase of the study must be made by blinded investigators.

Patients will be evaluated at 6 months (180 days ±30 days) post implantation. This visit and the following assessments must be conducted by blinded clinicians:

- **Blinding procedures per Blinding MOP**
- **Vital Signs and Physical Examination**: includes weight, blood pressure, heart rate and rhythm, and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications**: Record all cardiovascular, anticoagulation and antiplatelet medications as per protocol, and SGLT2 medications.
- **Blood test:** HGB, HCT, Cr
- ***All Patients* - Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE):** Elements per Core Laboratory Manual. No reference should be made in the patient's clinical chart as to whether the Shunt is present or not. Patient blinding should be maintained.
- ***For Roll-In Patients Only* - Transesophageal 2-dimensional echocardiogram/Doppler examination (TEE):** Elements per Core Laboratory Manual.
- **NYHA Functional Class**
- **KCCQ and EQ-5D Quality of Life assessments**
- **Patient Global Assessment**
- **6MWT:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Assessment of Worsening HF events treated as an outpatient**: randomized patients only
- **COVID-19 history**
- **Cost Effectiveness**
- **Complete CRFs**

8.1.8 NINE (9) MONTHS TELEPHONIC FOLLOW UP (± 30 DAYS)

All HF treatment decisions in randomized patients during the blinded phase of the study must be made by blinded investigators.

Patients will be evaluated at 9 months (270 days ±30 days) post implantation by blinded research staff with telephonic contact, and the following assessments will be performed:

- **Blinding procedures per Blinding MOP**
- **Medications:** Record all cardiovascular, anticoagulation and antiplatelet medications as per protocol, and SGLT2 medications.

- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Assessment of Worsening HF events treated as an outpatient**: randomized patients only
- **COVID-19 history**
- **Complete CRFs**

8.1.9 TWELVE (12) MONTHS IN-CLINIC FOLLOW UP (± 30 DAYS)

All HF treatment decisions in randomized patients during the blinded phase of the study must be made by blinded investigators.

Patients will be evaluated at 12 months (365 days ±30 days) post implantation. This visit and the following assessments must be conducted by blinded clinicians:

- **Blinding procedures per Blinding MOP**
- **Vital Signs and Physical Examination**: includes weight, blood pressure, heart rate and rhythm, and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications:** Record all cardiovascular, anticoagulation and antiplatelet medications as per protocol, and SGLT2 medications.
- **Blood test:** HGB, HCT, Cr
- ***All Patients* - Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE):** Elements per Core Laboratory Manual. No reference should be made on the patient's clinical chart as to the presence or absence of the Shunt. Patient blinding should be maintained.
- ***For Roll-In Patients Only* - Transesophageal 2-dimensional echocardiogram/Doppler examination (TEE):** Elements per Core Laboratory Manual.
- **NYHA Functional Class**
- **KCCQ and EQ-5D Quality of Life assessments**
- **Patient Global Assessment**
- **6MWT:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Patient Perception of Study Assignment:** Applied only to randomized patients.
- **Assessment of Worsening HF events treated as an outpatient**: randomized patients only
- **COVID-19 history**
- **Cost Effectiveness**
- **Complete CRFs**

8.1.10 FIFTEEN (15) MONTHS TELEPHONIC FOLLOW UP (± 30 DAYS)

All HF treatment decisions in randomized patients during the blinded phase of the study must be made by blinded investigators.

Patients will be evaluated at 15 months (455 days ±30 days) post implantation by blinded research staff with telephonic contact, and the following assessments will be performed:

- **Blinding procedures per Blinding MOP**
- **Medications:** Record all cardiovascular, anticoagulation and antiplatelet medications as per protocol, and SGLT2 medications.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Assessment of Worsening HF events treated as an outpatient**: randomized patients only
- **COVID-19 history**
- **Complete CRFs**

8.1.11 EIGHTEEN (18) MONTHS IN-CLINIC FOLLOW UP (± 30 DAYS)

All HF treatment decisions in randomized patients during the blinded phase of the study must be made by blinded investigators.

Patients will be evaluated at 18 months (545 days ±30 days) post implantation. This visit and the following assessments must be conducted by blinded clinicians:

- **Blinding procedures per Blinding MOP**
- **Vital Signs, and Physical Examination:** includes weight, blood pressure, heart rate and rhythm, and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications:** Record all cardiovascular, anticoagulation and antiplatelet medications as per protocol, and SGLT2 medications.
- **NYHA Functional Class**
- **KCCQ and EQ-5D Quality of Life assessments**
- **Patient Global Assessment**
- **6MWT:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Assessment of Worsening HF events treated as an outpatient**: randomized patients only
- **COVID-19 history**
- **Cost Effectiveness**
- **Complete CRFs**

8.1.12 TWENTY-ONE (21) MONTHS TELEPHONIC FOLLOW UP (± 30 DAYS)

All HF treatment decisions in randomized patients during the blinded phase of the study must be made by blinded investigators.

Patients will be evaluated at 21 months (635 days ±30 days) post implantation by blinded research staff with telephonic contact, and the following assessments will be performed:

- **Blinding procedures per Blinding MOP**
- **Medications:** Record all cardiovascular, anticoagulation and antiplatelet medications as per protocol, and SGLT2 medications.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Assessment of Worsening HF events treated as an outpatient**: randomized patients only
- **COVID-19 history**
- **Complete CRFs**

8.1.13 TWENTY-FOUR (24) MONTHS IN-CLINIC FOLLOW UP (± 30 DAYS)

All HF treatment decisions in randomized patients during the blinded phase of the study must be made by blinded investigators.

Patients will be evaluated at 24 months (730 days ±30 days) post implantation. This visit and the following assessments must be conducted by blinded clinicians:

- **Blinding procedures per Blinding MOP**
- **Vital Signs and Physical Examination**: includes weight, blood pressure, heart rate and rhythm and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications:** Record all cardiovascular, anticoagulation and antiplatelet medications as per protocol, and SGLT2 medications.
- **Blood test:** HGB, HCT, Cr.
- **Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE).** Elements per Core Laboratory Manual. No reference should be made on the patient's clinical chart as to the presence or absence of the Shunt. If no flow seen through Shunt, patient to be referred for TEE evaluation.
- **NYHA Functional Class**
- **KCCQ and EQ-5D Quality of Life assessments**
- **Patient Global Assessment**
- **6MWT:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits.**
- **Cost Effectiveness**

- **Assessment of Worsening HF events treated as an outpatient**: randomized patients only
- **COVID-19 history**
- **Complete CRFs**
- **Unblind patient following completion of all data collection.**

For patients finishing the blinded phase prior to the 24 months visit, a blood test collecting HGB, HCT and Cr should be performed.

8.1.14 COVID-19 SEROLOGICAL TESTS

COVID-19 serological testing should be conducted at the at the time of unblinding follow up visit, unless the patient has a documented positive COVID-19 test (antigen or PCR) or has been vaccinated for COVID-19.

8.1.15 UNBLINDING TELEPHONIC VISIT

The primary endpoint analyses of the study will be conducted after the last patient enrolled completes the 12-month follow-up, which is defined as the study unblinding date. Patients who have not yet reached their 24 Month visit will be unblinded at the study unblinding date. Sponsor will inform sites of this unblinding date in advance.

Where possible, patients due for 18- and 24-month in-clinic follow-up visit should be scheduled during the one month before the unblinding date, which will serve as their unblinding visit. All other patients that have not reached 24 months follow-up will have a telephonic unblinding visit within one month of the unblinding date. The elements of the unblinding visit include:

- **Assure blinding procedures**
- **Medications:** Record all cardiovascular, anticoagulation and antiplatelet medications as per protocol, and SGLT2 medications.
- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Complete CRFs**
- **Unblind patient following completion of all data collection.**

For patients randomized to the Control group who are not interested in crossing over, study participation will end following telephonic close-out unblinding visit. Patients who are interested in receiving a shunt will be invited to return to the clinic to be re-consented and to be evaluated for study eligibility.

8.1.16 FOLLOW-UP SCHEDULE FOR CONTROL PATIENTS THAT CROSS-OVER AND RECEIVE A SHUNT IMPLANT

A patient will only be eligible for cross-over if they remain in the study through the time of per protocol unblinding. Cross-over patients who receive the Shunt will be followed for 12 months according to the follow-up schedule described above for the first 12 months post randomization (see Sections 8.1.3 - 8.1.9) and then yearly thereafter until they reach 5 years post implantation. If after cross-over, their study participation ends before the protocol guidelines, an early termination visit should be attempted (see Section 8.1.19).

8.1.17 UNSCHEDULED CLINIC VISITS

Unscheduled clinic visits are defined as any clinic visit relating to the protocol that is not a required protocol visit. **If an unscheduled clinic visit occurs, patient blinding should be maintained.** If patient has an unscheduled clinic visit, the clinical information should be captured on the *Unscheduled Clinic Visit CRF*. Unscheduled visits will be classified by type according to the reason for the visit according to the following categories:

- Worsening HF status according to the definitions of Intensification of Heart Failure Therapy described in Section 3.4.7:
  - signs or laboratory evidence of worsening heart failure
  - if the dose of diuretics was increased and if sustained for a month or more
  - if intravenous treatment given for HF
  - if a new HF drug class was added for the treatment of worsening HF
- Worsening clinical status not related to HF
- Stable clinical status for medication change/titration
- Patient education
- Elective follow-up of previous visit or recent hospital discharge
- Other, (specify)

8.1.18 POST-UNBLINDING ANNUAL IN-CLINIC FOLLOW-UP YEARS 2, 3, 4, AND 5 YEARS (± 60 DAYS) IN IMPLANTED PATIENTS

All patients who receive an implant (Roll-Ins, randomized to Shunt Treatment or Control patients that cross-over and receive an implant) will be evaluated in-clinic at years 2 (if unblinded prior to this time point), 3, 4 and 5 (±60 days) post implantation, and the following assessments will be performed:

- **Vital Signs and Physical Examination**: includes weight, blood pressure, heart rate and rhythm and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications:** Record all cardiovascular, anticoagulation and antiplatelet medications and SGLT2 medications.

- **Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE).** Elements per Core Laboratory Manual. If no flow seen through Shunt, patient to be referred for TEE evaluation.
- **NYHA Functional Class**
- **KCCQ and EQ-5D Quality of Life assessments**
- **Patient Global Assessment**
- **6MWT:** The test should be performed only once. Obtain Borg score.
- **Assessment of AEs that occurred during the last one year (since last contact) including Hospitalization and Emergency Room visits.** Current health status and obtain information about any treatment for heart failure including hospitalizations or emergency room visits, procedures or surgeries
- **Assessment of Worsening HF events treated as an outpatient**: randomized patients only
- **COVID-19 history**
- **Complete CRFs**

Unblinding of study patients will occur if they receive an LVAD. Patients that receive an LVAD and have the study device will be followed for 5 years from shunt implant to collect study device related MACNE. Control patients that receive an LVAD will be withdrawn from the study.

8.1.19 EARLY TERMINATION IN-CLINIC VISIT

An early termination visit should be attempted in all patients that exit the clinical trial before the per protocol completion of their participation in the study. This could happen, for example, if a patient moves to a different region where there are no investigational sites that could continue their study follow-up. This visit and the following assessments must be conducted by blinded clinicians:

- **Blinding procedures per Blinding MOP**
- **Vital Signs and Physical Examination**: includes weight, blood pressure, heart rate and rhythm, and cardiovascular focused physical examination pertinent to assessing HF status.
- **Medications:** Record all cardiovascular, anticoagulation and antiplatelet medications as per protocol, and SGLT2 medications.
- **Blood test:** HGB, HCT, Cr
- **Transthoracic 2-dimensional echocardiogram/Doppler examination (TTE):** Elements per Core Laboratory Manual. No reference should be made on the patient's clinical chart as to the presence or absence of the Shunt. Patient blinding should be maintained.
- **For Roll-In Patients Only - Transesophageal 2-dimensional echocardiogram/Doppler examination (TEE):** Elements per Core Laboratory Manual.
- **NYHA Functional Class**
- **KCCQ and EQ-5D Quality of Life assessments**
- **Patient Global Assessment**
- **6MWT:** The test should be performed twice separated by a minimum of 60 minutes. The second test may be performed up to 7 days after the first test, if needed. Obtain Borg score.

- **Assessment of AEs that occurred since last visit including Hospitalization and Emergency Room visits**
- **Patient Perception of Study Assignment:** Applied only to randomized patients that have not completed their 12-month follow-up.
- **Cost Effectiveness**
- **Complete CRFs**
- **Unblind patient following completion of all data collection.**

8.1.20 HOSPITALIZATIONS

All events that result in ER visits, outpatient short stays or hospitalizations shall be reported on a Hospitalization CRF. Additionally, an Adverse Event CRF must be completed. The following information will be documented: primary diagnosis requiring hospitalization (e.g. ADHF, pneumonia, AMI, etc.), length of stay, days in ICU/CCU (if applicable) and all therapies for HF treatment including specifying parenteral therapies. Deidentified source records related to a patient's hospitalization must be obtained and submitted to the sponsor for review by the CEC. For prolonged hospitalizations, an investigator summary note should accompany the event. Source documentation includes:

- Emergency department notes
- Physician consultation notes
- Medication records and logs
- Admission notes (required for all hospitalizations)
- Laboratory results and summary details
- Discharge summary (required for all hospitalizations)
- Operative reports
- Clinician progress notes
- X-ray reports
- Diagnostic test reports
- Death summary written by Investigator including: date and time of death, place death occurred, if death was witnessed, heart rhythm at time of death (if known), cause of death, classification of death (HF related, cardiovascular, non-cardiovascular), time interval to death from initiating event, autopsy report (if available), relationship to device or study procedures and any other comments regarding the death.

8.2 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

Adverse events will be reported to the Sponsor by the Investigator. The Investigator will classify events by diagnosis or by specific signs, symptoms, or abnormal laboratory values, if no medical diagnosis is available. Definitions and safety reporting requirements will follow 21CFR Part 812, ISO 14155:2011 and EU and National legislation and guidance such as MEDDEV 2.7/3 documents (hereafter "Applicable Requirements"). The Sponsor is responsible for determining which adverse events are required to be reported to regulatory authorities in accordance with Applicable Requirements and company SOP.

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons whether or not related to the investigational medical device.

Note 1: This includes events related to the investigational device or the comparator.
Note 2: This includes events related to the procedures involved (any procedure in the clinical investigation plan).
Note 3: For users or other persons this is restricted to events related to the investigational medical device.

Serious Adverse Event (SAE): Adverse event that:

a) Led to death,
b) Led to a serious deterioration in the health of the subject, that either resulted in:
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function, or
    3) in-patient or prolonged hospitalization, or
    4) medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect

Note 1: SAE definition specific for BfArm is any undesired event occurring in a clinical investigation or a performance evaluation study requiring an authorization, which has led, or could have led, or could lead directly or indirectly to the death or severe health impairment of volunteers, users, or other persons regardless of whether the event was caused by the medical device.
Note 2: Planned hospitalization for pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

Adverse Device Effect (ADE): Adverse event related to the use of an investigational medical device.

Note 1: This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
Note 2: This includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Device Effect (SADE): Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Adverse Device Effect (UADE): Any serious effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or

application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

Unanticipated Serious Adverse Effect (USADE): Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

8.2.2 DEFINITION OF DEVICE DEFICIENCY

Device Deficiency (DD): A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. *Note: Device deficiencies include malfunctions, use errors, and inadequate labeling.*

Malfunction: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or protocol.

Use Error: Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

Notes: Use error includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence:

a) if either suitable action had not been taken,

b) if intervention had not been made, or

c) if circumstances had been less fortunate, shall be reported as appropriate to EU Competent Authorities.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the study investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other procedures or medications.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other procedures or medications.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "potentially related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

For the purposes of endpoints and outcome measures that involve device relatedness assessments, only AEs classified as definitely or probably related by the Clinical Event Committee ("CEC") will be included for analysis. AEs categorized as potentially, unlikely, or not related will be tabulated and reported separately.

8.2.3.3 ADJUDICATION OF ADVERSE EVENTS

The CEC will be ultimately responsible for providing an independent review and adjudication of protocol defined clinical events, such as serious adverse events.

8.2.4 LIST OF ANTICIPATED ADVERSE EVENTS AND ANTICIPATED ADVERSE DEVICE EFFECTS

Risk analysis was used as a basis for identifying anticipated adverse device effects characterized by their nature, incidence, severity, and outcome. An anticipated adverse event is an event that has been reported in the literature. A list of adverse events which may result from these percutaneous procedures, as well as those clinical adverse events identified as unique to the study device can be found in Section 2.3 Risk/Benefit Assessment as well as in the Investigators Brochure.

8.2.5 HANDLING OF ADVERSE EVENTS

Investigator will report “to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports” (ISO 14155:2011 § 9.8 b and 21 CFR 812.150 and MEDDEV 2.7/3). Device malfunctions and use errors should also be reported without unjustified delay.

Reporting all Serious Adverse Events (SAEs and SADEs), including all device deficiencies that could have led to a SAE should be done by completing the CRF (AE/SAE and Device Deficiency forms) without unjustified delay and not later than 48 hours of event knowledge. Investigator should return the entire delivery system, and if available, the implant involved in potential deficiency to V-Wave for analysis.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while in the study must be documented appropriately regardless of relationship, seriousness, intensity, outcome, or casualty. All AEs will be followed to adequate resolution.

In case of a patient death, the Study Investigator will determine the mode and cause of death and its relationship to the investigational device. In addition, the Study Investigators will make reasonable efforts to obtain an autopsy and provide an autopsy report to the Sponsor. In all cases of death, the Investigator will provide a signed narrative description of the events surrounding the death including the cause of death and relationship to the study device.

The Investigator will monitor the occurrence of adverse events or device deficiencies for each patient during the course of the trial. All adverse events (AEs) reported by the patient, observed by the Investigator, or documented in medical records will be recorded on the adverse event CRF, whether believed by the Investigator to be related or unrelated to the study device. Information about all adverse events, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Report Form and followed as appropriate. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Principal Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.2.6 SERIOUS ADVERSE EVENT REPORTING

The following section describes the roles and responsibilities for serious adverse event reporting to regulatory authorities, IRBs and ECs.

8.2.6.1 REPORTING ADVERSE EVENTS

V-Wave is responsible for the classification and reporting of adverse events and ongoing safety evaluation of the clinical investigation in line with the Applicable Requirements. V-Wave will assure that all Serious Adverse Events and Device Deficiencies are reported to regulatory agencies, including the Competent Authorities in accordance with all Applicable Requirements.

8.2.6.2 REPORTING ADVERSE EVENTS TO THE ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD (EC/IRB)

It is the responsibility of each investigator to report all Serious Adverse Events and/or Serious Adverse Device Effects to the Ethics Committee/Institutional Review Board, according to Applicable Requirements, including Ethics Committee requirements. A copy of the Ethics Committee/IRB report should be shared with V-Wave.

8.2.6.3 REPORTING USADE(S) /UADE(S) TO IRB/FDA

The definitions for Unanticipated Serious Adverse Device Effect (USADE) and Unanticipated Adverse Device Effect (UADE) from the Investigational Device Exemption (IDE) regulations is provided in Section8.2.1.

- An investigator is required to submit a report of USADE/UADE to the sponsor and to the reviewing Ethics Committee/Institutional Review Board as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect or earlier as required by Applicable Requirements.
- Sponsors must immediately conduct an evaluation of USADE/UADE and must report the results of such evaluation to the FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the USADE/UADE.

8.2.6.4 REPORTING SAE(S) TO COMPETENT AUTHORITIES AND REGULATORS

V-Wave must report SAEs to the relevant Competent Authorities/Regulators in accordance with the Applicable Regulations and reporting timelines (**Table 7**).

Table 7. Comprehensive SAE Timelines per Applicable Country Requirement (following awareness by the sponsor)

Country	SAE Reporting Timeline(s)
Belgium/Poland	All SAEs, and DDs with SAE potential: immediately, but no later than 2 calendric days (CD) if requires immediate action for other study patients; 7 CD if other.
Germany	SAEs related to the investigational device/intervention procedure, and DDs with SAE potential: immediately, but no later than 2 CD if requires immediate action for other study patients; 7 CD if other Other SAEs: quarterly
Switzerland	SAEs related to the investigational device/intervention procedure, and DDs with SAE potential: immediately, but no later than 2 CD if requires immediate action for other study patients; 7 CD if other.
Netherlands	All SAEs which have led to alteration or withdrawal of the medical device to be researched; all SAEs which indicate an inevitable risk of death, serious injuries or serious illness, and requiring prompt remedial action for other patients: 2 working days and no later than 4 Calendar Days. Other SAEs: quarterly Includes DDs with SAE potential.
Spain	All SAEs, and DDs with SAE potential: 7 CD if fatal/life-threatening;15 CDs if other
Israel	Domestic UADEs/USADEs: 7 CD if fatal/life-threatening; 15 CDs if other
US	World-wide UADEs/USADEs: 10 working days
Canada	Domestic SAEs related to investigational device, and DDs: if led to death or a serious deterioration in the state of health of a patient, user or other person within 10 CD. if the incident has NOT led to the death or a serious deterioration in the state of health of a patient, user or other person, BUT could do so were it to recur - within 30 days.
Australia	Domestic USADEs: 7CD if fatal/life threatening; 15CDs if other

Country	SAE Reporting Timeline(s)
New Zealand	Domestic Death/Serious Injury: 10 CDs

8.2.6.5 REPORTING DD(S) TO COMPETENT AUTHORITIES AND REGULATORS

All device deficiencies related to the identify, quality, durability, reliability, safety or performance of an investigational medical device shall be documented throughout the clinical investigation and appropriately managed by the sponsor.

V-Wave must report to the Competent Authorities / Regulators DD(s) that might have led to a SAE if:

- Suitable action has not been taken,
- Intervention had not been made, or
- Circumstances had been less fortunate

The same timelines shown in **Table 7** for reporting SAE(s) apply here.

9 STATISTICAL CONSIDERATIONS

The following sections summarize statistical considerations for the RELIEVE-HF study. Additional details will be provided in the Statistical Analysis Plan (SAP) for the study.

9.1 STATISTICAL HYPOTHESES

9.1.1 SAFETY

The safety endpoint will be compared to a pre-specified Performance Goal (PG) of 11%. The expected rate (R) of observed Device/Procedure-related MACNE is 5% of patients at 30 days.

The hypothesis for safety is:

$$H_0: R \geq PG$$
$$H_1: R < PG$$

Where, PG = 11%. The hypothesis will be tested with an exact binomial test, with a one-sided significance level of 0.025.

9.1.2 EFFECTIVENESS

The hypothesis for effectiveness is:

$$H_0: T_{Shunt} \leq 0$$
$$H_1: T_{Shunt} > 0$$

Where, T_{Shunt} = sum of ranks in the Shunt group and the hypothesis is evaluated using the method of Finkelstein and Schoenfeld with a one-sided significance level of 0.025.

9.2 SAMPLE SIZE DETERMINATION

9.2.1 FOR SAFETY

Assuming an alpha level of 0.025 (one-sided), a sample size of 200 evaluable Treatment group patients from the Randomized cohort would achieve a power of 87% to detect a difference between the expected safety endpoint rate of 5% and a Performance Goal of 11%. Primary safety endpoint analysis will be conducted in all patients implanted with the device using an intention to treat analysis including patients randomized to the Therapy arm regardless of whether the implantation procedure was successful.

9.2.2 FOR EFFECTIVENESS

Primary effectiveness endpoint analysis will be performed on a combined HFrEF and HFpEF population. The homogeneity of the treatment effect will be examined in an analysis of the interaction between treatment effect and the HFrEF/HFpEF subpopulations. It is estimated that 20%-25% of the total study population will be HFpEF patients. Based on 10,000 simulated trials, a study of 400 patients (200 per arm) would achieve an expected power of 90% to detect a sum of ranks greater than zero in the treatment group, with a one-sided alpha of 0.025. Details about specific assumptions used for each of the composite endpoint components in the HFrEF and HFpEF subpopulations will be provided in the SAP.

9.3 POPULATIONS FOR ANALYSES

The following populations are defined for study analyses:

Safety Population: Subjects who met the initial inclusion and exclusion criteria, signed an Informed Consent form, and underwent any invasive procedure associated with evaluation of the final exclusion criteria.

Intention-to-Treat (ITT): Subjects who were randomized to the Shunt Implant or Control study arms.

Per Protocol (PP): Randomized subjects who met all initial and final inclusion/exclusion criteria, had no major protocol deviations which may have impacted study outcomes, and had sufficient data to be considered evaluable for the primary safety and effectiveness endpoints.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

1. Descriptive statistics will be used to summarize all subject Baseline and outcome data collected during the study. Continuous variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized in frequency distributions.
2. Statistical analyses will be performed by validated software (e.g., SAS, IBM/SPSS, or Cytel Software)
3. Statistical tests appropriate to the endpoint being examined will be used and identified. The non-parametric Finkelstein-Schoenfeld test will be used for the evaluation of the primary effectiveness endpoint. Parametric tests (e.g., Student's t-tests) will be utilized for other endpoints, if the distributional properties of the data are suitable. If parametric tests are not indicated, the associated non-parametric tests (e.g., Mann-Whitney tests, Fisher's Exact Tests) will be used.
4. A one-sided p-value of 0.025 or less for tested primary and secondary endpoints will be considered evidence of statistical significance. Reported p-values for all other tests will be considered nominal and unadjusted for multiple testing, without conclusions regarding statistical significance levels.
5. Copies of databases used to prepare clinical report summaries will be archived to enable any statistical analyses performed to be replicated.
6. A full data listing will be prepared, including an electronic version in a standard computer-accessible format (e.g., SAS) at the completion of the study. Listings of data represented on the case report forms (eCRF) will be provided for all key baseline, demographic, and outcome variables to facilitate further investigation of tabulated values and to allow for clinical review of safety variables.

9.4.2 ANALYSIS OF THE PRIMARY SAFETY ENDPOINT(S)

The Primary Safety Endpoint is the percentage of Treatment Group patients experiencing any device-related Major Adverse Cardiovascular and Neurological Events (MACNE) during the first 30-days after randomization. The proportion of subjects with MACNE events will be tested against a Performance Goal of 11% with an exact binomial test, with a one-sided significance level of 0.025. The Intention-to- Treat population randomized to the Shunt implant is the primary analysis population for this safety analysis.

9.4.3 ANALYSIS OF THE PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint will be evaluated with a sum of ranks (T_{Shunt}) test statistic in the Shunt group using the method of Finkelstein and Schoenfeld. All subjects have a scheduled minimum follow-up period of 12 months, and all data collected through 24 months of follow-up will be included in the final analyses. The ITT population is the primary analysis population for the primary effectiveness endpoint, with supportive analyses in the PP population.

The ranks are based on a hierarchical evaluation of the components of the composite primary effectiveness endpoint across the total evaluable study population (Shunt and Control groups) in the following order:

1. Death (all-cause)
2. Heart transplant or LVAD implant

3. HF hospitalizations (including ER visits ≥ 6 hours)
4. Worsening HF events treated as an outpatient (including ER visits < 6 hours)
5. KCCQ Overall Score, measured as absolute point change from baseline)

The rank of a subject relative to other subjects is based on consideration of the following factors: level of an observed event in above hierarchical list, the time of the event(s) after randomization, the number of events, the observed time in study, and KCCQ overall score. Details of the hierarchical ranking procedure will be provided in the SAP. For clarification, heart transplant and LVAD implant are considered terminal endpoints from an effectiveness analysis standpoint and will be censored for HF hospitalizations and KCCQ after the date of admission that results in heart transplant or LVAD placement.

The sum of ranks (T_{Shunt}) under the null hypothesis of no difference between study groups has an expected mean value of zero and a variance equal to:

$V = [N (N – m) / N (N -1)] (\sum U_i^2)$

Where,

N = total sample size
m = number of shunt patients U_i = rank of patient (i)
$\sum U_i^2$ represents a summation across all shunt and control patients

The hypothesis will be tested by comparing the test statistic ($T_{Shunt} / V^{½}$) to the normal distribution, with a one-sided significance level of 0.025. Multiple imputation methods will be used to address any missing data for the primary effectiveness endpoint.

9.4.4 ANALYSIS OF HIERARCHICALLY TESTED SECONDARY EFFECTIVENESS ENDPOINTS

The difference between study groups will be hierarchically tested for the following secondary effectiveness endpoints in the order shown below, if the primary effectiveness endpoint is met. The same significance level (one-sided, alpha = 0.025) used for the primary effectiveness endpoint will be applied at each step in the hierarchical testing. The PP population is the primary analysis population for these secondary endpoints.

Where indicated, the analyses of secondary endpoints will be covariate adjusted. The final list of pre-specified baseline covariates will be described in the SAP, but will include:

- Randomized treatment
- Stratification factor of HFrEF and HFpEF
- Ischemic vs. non ischemic cardiomyopathy
- Sex
- Age
- eGFR

The secondary endpoints are as follows. The order of hierarchical assessment will be defined in the Statistical Analysis Plan.

1. KCCQ changes from Baseline to 12 months

   Analysis: Ancova adjusting for the baseline value

2. Heart failure hospitalizations adjusted for all-cause mortality at study duration

   Analysis: Joint frailty method model

3. Time to death, LVAD/Transplant, or heart failure hospitalization

   Analysis: Cox regression with pre-specified covariates

The above analysis without covariate adjustment will be performed as a supportive analysis

4. Time to death or first heart failure hospitalization

   Analysis: Cox regression with pre-specified covariates

The above analysis without covariate adjustment will be performed as a supportive analysis

5. Cumulative heart failure hospitalizations at study duration

Analysis: Non-parametric Kolmogorov-Smirnov comparison of cumulative curves

6. Time to first heart failure hospitalization

Analysis: Cox regression with pre-specified covariates

7. Modified Primary Effectiveness Endpoint including mortality, LVAD/Transplant, HF Hospitalizations, and Worsening Heart Failure events treated as an outpatient, but without KCCQ

Analysis: Finkelstein-Schoenfeld analysis of primary effectiveness endpoint without KCCQ

8. 6MWT changes from Baseline to 12 months

Analysis: Ancova adjusting for the baseline value. Note that if a subject cannot walk during follow-up because of a cardiac limitation, his/her follow-up 6MWT will be set to 0.

9.4.5 ANALYSIS OF THE ADDITIONAL SAFETY DATA

The following additional safety data will be evaluated. There are no tests of hypotheses associated with these analyses.

- Comparison of Major Adverse Cardiovascular and Neurological Events (MACNE) and Bleeding Academic Research Consortium (BARC) types 3 and 5 bleeding at 30 days

This endpoint will be evaluated by estimating the rates of MACNE and BARC events at 30 days, together with the associated exact, 95% confidence intervals.

- Percentage of Treatment Group patients with device related MACNE at 12 months.

This endpoint will be evaluated by estimating the MACNE rate at 12 months, together with its exact, 95% confidence intervals and a Kaplan-Meier analysis of the time-to-events.

9.4.6 PLANNED INTERIM ANALYSES

A single, midpoint interim analysis with adaptive sample size re-estimation is planned at the point when approximately 50% of the original planned study population (200 randomized subjects) have completed approximately 6 months of follow-up, but no later than 3 months prior to completion of enrollment of the original 400 subjects. This interim analysis would consider only data collected for the composite primary effectiveness endpoint and be based on validation of the original planning assumptions for the components of the endpoint. The interim analysis would be performed by an independent third party, who would communicate results only to the study DSMB. The interim analysis plan is summarized below, with final details of plan and a full description of the adaptive design to be found in the SAP.

The interim analysis will be limited to data collected in an identified study cohort (e.g., the first 200 evaluable subjects). Using the analysis method specified for evaluation of the primary effectiveness endpoint (Finkelstein-Schoenfeld), the unconditional power to meet the endpoint at the conclusion of the study will be re-estimated.

Increases in study sample size will occur only if updated estimates for the composite endpoint components require an increase to maintain the original design goal of 90% power. The increase, if any, would be limited to an additional 600 subjects: from a total of 400 to 1000 evaluable subjects.

Based on the interim analysis results, the DSMB would be expected to make one of the following recommendations to the Sponsor, who will make the final decision regarding actions to be taken in response to the recommendation:

- Continue the study as originally planned,
- Increase the study sample size, or,
- Terminate the study early for futility.

The first DSMB recommendation option (Continue the study as originally planned) would be made if it is determined that no increase in sample size is required or that an increase of 200 subjects would not meaningfully change the estimated power achieved. The DSMB will also have an ongoing responsibility to monitor the study for patient safety, and so, may consider safety issues in making recommendations at the time of the interim analysis, or independently, make recommendations concerning safety issues at any time during the conduct of the study.

The interim results leading to any potential increase in the required study sample size would be known to only the independent party performing the interim analysis and DSMB members, with the Sponsor and other study participants blinded to this information.

If the study continues after the interim analysis as originally planned, with no sample size increase, then the Finkelstein-Schoenfeld analysis on the total study population would be performed at the completion of the study. If a sample size increase occurs, then the results from the first cohort of subjects used in the interim analysis would be combined with the results from subsequent subjects using the method of *Cui et al*.[87] (i.e., pre-specified weights assigned to the two stages). There are no prespecified analyses for the DMSB to perform, however the DSMB does have a broad charter in review of data with potential for additional analyses.

9.4.7 SUB-GROUP ANALYSES

The consistency of the primary safety endpoint and primary effectiveness endpoint will be examined in subgroups defined by sex, LVEF stratification factor of HFrEF and HFpEF, and clinical sites. A complete listing and methodology for sub-group analyses will be included in the Statistical Analysis Plan.

Sex: The primary safety endpoint of MACNE rates at 30 days will be compared by sex using a Fisher's Exact test. The primary effectiveness endpoint will be compared using Z-test based on the Finkelstein-Schoenfeld estimates of the test statistic and its variance in the sex subgroups.

LVEF Stratification: The primary safety endpoint of MACNE rates at 30 days will be compared between HFrEF and HFpEF subjects using a Fisher's Exact test. The primary effectiveness endpoint will be compared using Z-test based on the Finkelstein-Schoenfeld estimates of the test statistic and its variance in the HFrEF and HFpEF subgroups.

Sites: The primary safety endpoint of MACNE rates at 30 days will be compared between study sites (poolability) using a Mantel-Haenszel analysis to examine the homogeneity of the odds ratios at sites. The consistency of the primary effectiveness endpoint across sites will be examined by summarizing the distribution of the within-site Finkelstein estimates of the test statistic and its variance.

Additional sub-group analyses will be specified in the SAP.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

A listing by subject of key demographic and study outcome data (MACNE and SAE events, components of the primary effectiveness endpoint) will be prepared.

9.4.9 ADDITIONAL ANALYSES

The following additional analyses will be summarized using descriptive measures appropriate to the endpoint (e.g., rates, mean and standard deviations, frequency distributions, time-to-events). There are no tests of hypotheses associated with these endpoints. Any reported p-values associated with statistical tests comparing results between study groups are considered nominal, unadjusted for multiple testing, and without assignment of statistical significance levels. The PP population is the primary population for examining these additional endpoints.

Effectiveness

- NYHA Class

- Patient Global Assessment
- Combined all-cause death and all-cause hospitalizations
- All-cause death
- Time to all-cause death (KM analysis)
- Time to cardiovascular death (KM analysis)
- Time to all-cause death, transplant or LVAD (KM analysis)
- Time to cardiovascular death, transplant or LVAD (KM analysis)
- Days alive free from heart failure hospitalization
- Outpatient intensification of heart failure therapy
- Emergency room HF visits
- HF Clinical Composite Assessment (improved, unchanged, or worsened) as described by Packer comprised of all-cause mortality, HF hospitalization, and changes in NYHA functional class ranking and Patient Global Assessment
- Comparison of transthoracic echocardiographic parameters as listed in Echocardiography Core Laboratory Manual
- Incidence of loss of shunt flow as measured on TTE and/or TEE
- Changes in 6MWT
- Changes in KCCQ
- Death: All-cause; Cardiovascular cause (with breakdown by cause, e.g. sudden death, myocardial infarction, pump failure, stroke); Non-Cardiovascular cause; Undetermined cause; and relationship to device, study intervention or other cardiovascular procedure
- Hospitalization: All-cause; HF hospitalization, Non-HF hospitalization (with breakdown for cause including if associated with secondary worsening of HF)
- Change in renal function
- Medication utilization including type, dose, frequency, and changes
- Cost and cost-effectiveness data
- Technical success defined as successful delivery and deployment of the device and retrieval of the delivery catheter
- For Roll-in patients, transesophageal or intracardiac echocardiography at 6 and 12 months to assess device patency and other parameters as listed in the Echocardiography Core Laboratory Manual

<u>Safety</u>

- Incidence of all Serious Adverse Events at study duration
- Incidence of cerebrovascular events at study duration with sub-classification of CNS infarction, CNS hemorrhage, and TIA and their relationship to device or study procedures (per NeuroARC)
- Incidence of MI events at study duration after implantation
- Incidence of systemic embolization events at study duration after implantation
- Incidence of pulmonary embolization events at study duration after implantation
- Implant embolization at study duration
- Device-related MACNE annually through 5 years
- Device-related MACNE in Shunt treated patients receiving LVADs followed for 5 years post study device implantation.

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 INFORMED CONSENT PROCESS

10.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention or administering study intervention.

10.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided to the prospective patients in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document, including the date of consent, and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The investigator or an authorized member of the research team who has witnessed the prospective patient's signature must also sign and date the informed consent, prior to enrollment of the prospective patient. A copy of the completed informed consent form must be provided to the patient. Local EC regulations regarding obtaining informed consent must be followed. The patient's medical record should have a notation regarding the signing of the informed consent.

If records are consistent with Inclusion/Exclusion criteria, patients will then be approached to undergo the informed consent process and only then the Baseline Visit.

Informed consent will be completed by research personnel trained on the study background and requirements prior to performing any study specific testing. Patients will be introduced to the scope, purpose, rights, and duties of the study. Study background information, study requirements, potential

risks and benefits will be explained to the patient. After receiving complete information about the study, both orally and in writing, the patient will have to confirm their consent in writing.

Patients who provide a written informed consent will be assigned a study identification number, which will consist of a code indicating the site identification and a sequential number.

In hospitalized patients who are approaching discharge, informed consent can be obtained predischarge or at discharge, but all screening assessments must be completed with the patient in a stable state and as an outpatient.

After written informed consent is obtained, patients will undergo additional evaluation and testing that is required to determine their study eligibility.

Clinical study specific procedures or alterations of patient care must not be performed until the prospective patient has provided a signed informed consent. The informed consent will be in the prospective patient's native language and will contain non-technical language to describe the investigational procedures. The informed consent should also include a clause that ensures important new information will be provided to the patient throughout the clinical investigation.

The Primary-Investigator is ultimately responsible for the achievement of written consent from the prospective patient before they are included in the trial. All patients must provide informed consent in accordance with the local EC requirements, using EC-approved informed consent forms. **Figure 4** below outlines the screening process and illustrates the point where informed consent should be obtained. The final eligibility for the clinical trial will be confirmed based during the study intervention visit using right heart catheterization and intracardiac or transesophageal imaging.

10.1.3 INFORMED CONSENT PROCESS WHEN PATIENT IS UNABLE TO GIVE IT

It is anticipated that the patients enrolled in this trial will not be requiring emergency treatments as part of the clinical investigation. Therefore, there will be sufficient time to obtain proper written informed consent without emergency measures being taken.

It is possible that prospective patients may be unable to provide written consent due to limitations in their ability to read or write. In this case, informed consent shall be obtained through a supervised oral process of a prospective patient. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective patient and, whenever possible, the patient shall sign and personally date the informed consent form. The witness must also sign and personally date the informed consent form attesting that the information was accurately explained, and that informed consent was freely given.

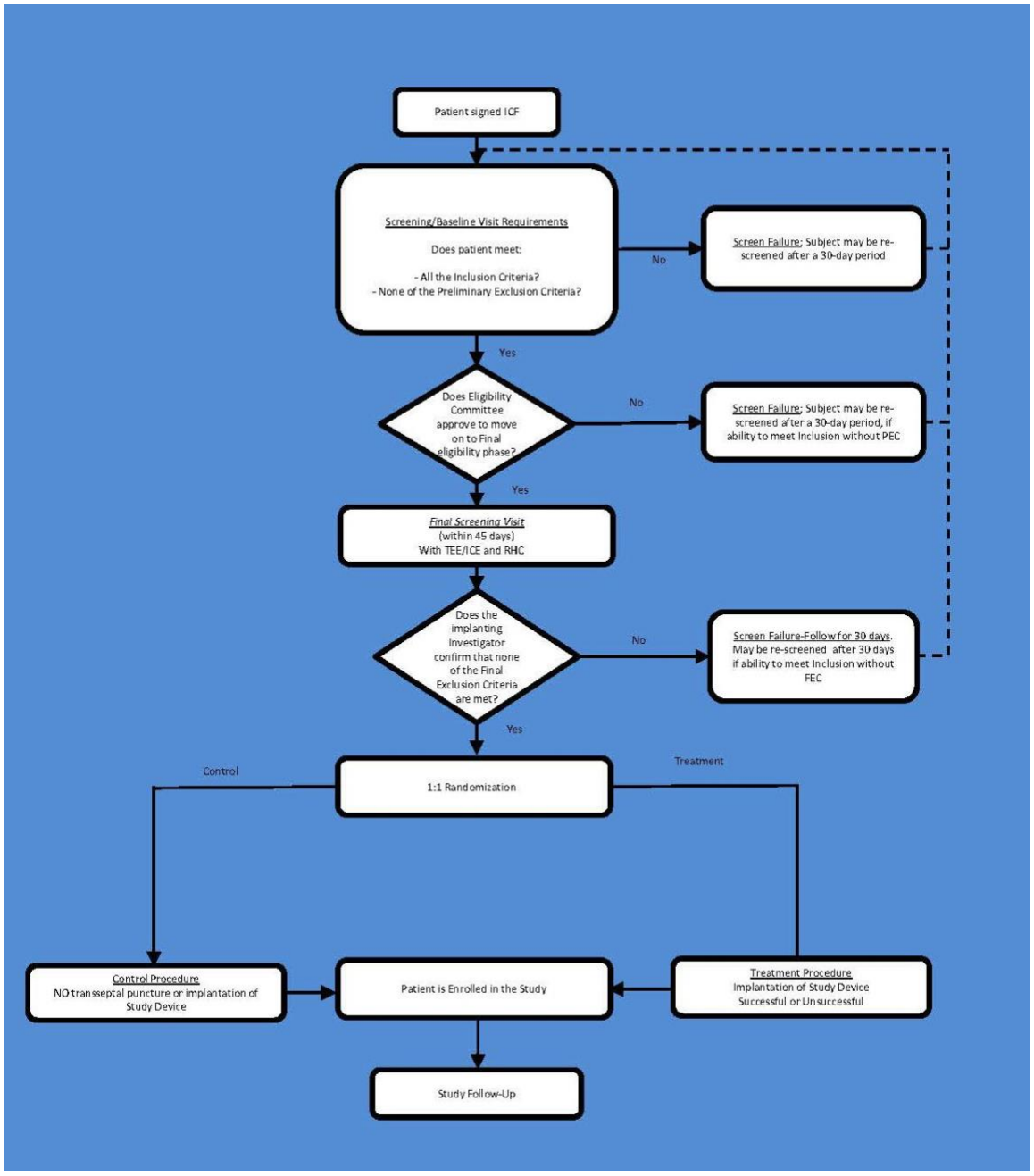


Figure 4. Screening and enrollment process

10.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and regulatory authorities. If the study is prematurely terminated or suspended by the sponsor, the PI will be responsible for promptly notifying the study participants and IRB/ECs. Sponsor will provide the reason(s) for the termination or suspension.

10.2.1 CRITERIA AND ARRANGEMENTS FOR SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION OR OF THE CLINICAL INVESTIGATION IN ONE OR MORE SITES

In case one or more sites are incapable of continuing to follow the patients in accordance with GCP (e.g. failure to comply with the study protocol), the site may be temporarily suspended or terminated by the Sponsor. Arrangements will then be made to reassign patients to a nearby site, conditional to consent by the affected patients.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA) and other regulatory agencies.

Specifically, placing a prosthetic device that creates an interatrial communication may have a risk of thrombotic events including stroke and systemic embolization. For that reason, formal suspension criteria have been developed to be applied to the Roll-in cohort. A plan to rapidly and thoroughly evaluate strokes associated with device occlusion was defined using the NeuroARC evaluation protocol. If two or more strokes adjudicated to be probable or definitely device-related and associated with a device occlusion in the first 45 Roll-in patients during the first 6 months after implantation, randomization will be put on hold, pending regulatory review.

10.2.2 CRITERIA FOR ACCESS TO AND BREAKING THE BLINDING CODE IN THE CASE OF SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

The trial is a double-blind study and every effort should be made to maintain the blinding so as not to compromise the integrity of the trial. In the unlikely event that it becomes medically necessary to unblind the patient, the site will request written permission to unblind from the Sponsor, with explanation of the

circumstances requiring unblinding. If the Sponsor agrees to unblind, the site as the treatment facility will provide the information to the patient and/or treating physician. The site will also notify the sponsor that unblinding has occurred.

10.2.3 REQUIREMENTS FOR SUBJECT FOLLOW-UP

All patients will continue to receive standard of care follow-up in the event of suspension or premature termination of the clinical investigation.

10.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or Sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital), pharmacy records and billing records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, sponsor requirements and local regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Data Coordinating Center (DCC). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by DCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Study Sponsor.

10.3.1 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored by the Study Sponsor. After the study is completed, the de-identified, archived data will be transmitted to and stored by the Sponsor, which may be used by other researchers including those outsides of the study. Permission to transmit data to the Sponsor will be included in the informed consent.

10.4 KEY ROLES AND STUDY GOVERNANCE

The names and contact information of the Executive Committee Investigators is provided in **Table 8**. Medical Monitor details will be contained in the Manual of Operation (MOP).

Table 8: Executive Committee Investigators' name and contact information

Stefan D. Anker MD, PhD, FESC	**Josep Rodés-Cabau, MD, FHSA**
University Medical Center Gottingen, Germany	Université Laval (CRIUCPQ-ULaval)
Robert-Koch-Straße 40 37075 Göttingen Briefpostadresse 37099 Göttingen, Germany	2725, Chemin Sainte-Foy, U-2755 Québec (Québec) G1V 4G5, Canada
s.anker@cachexia.de	Josep.Rodes@criucpq.ulaval.ca
JoAnn Lindenfeld, MD	**Gregg W. Stone, MD**
Vanderbilt University	Colombia University Medical Center
1215 21st Ave S Nashville, TN 37212	161 Ft. Washington Ave. Herbert Irving Pavilion, 6th Floor. New York NY 10032
joann.lindenfeld@vanderbilt.edu	*gstone@crf.org*

10.5 STUDY LEADERSHIP COMMITTEE

The RELIEVE HF study uses four committees to oversee safety and proper conduct of the trial. Charters of committees (DSMB and CEC) will be included in trial master file (TMF). In addition, a list of study team roles of those involved in the conduct, management, or oversight of the trial is included in the manual of operation binder (MOP).

10.5.1 EXECUTIVE COMMITTEE

The Executive Committee is comprised of the Trial Chairmen (Sponsor CEO and CMO), Principal Investigators, Medical Monitor, and a representative of the Sponsor (Biostatistician and Echocardiographic Core Laboratory Director). This committee will oversee general aspects of the trial. This oversight includes review of the final clinical investigation plan, ongoing monitoring of the general data collection, as well as review and consideration of implementation of operational issues that may arise and warrant a clinical investigation plan amendment or other corrective action. This committee will review recommendations from the DSMB and determine policy regarding publication. The Executive Committee will also approve policy regarding presentations and/or publications. It is recommended that the Committee will meet at least twice yearly. Meeting minutes from this committee will be filed with the sponsor.

10.5.2 ELIGIBILITY COMMITTEE

The Eligibility Committee is comprised of at least 2 members (cardiologists). Eligibility Committee members will not evaluate patient candidates from their own site. The Eligibility Committee will review each patient baseline clinical information prior to final eligibility check and randomization. Baseline clinical information will include at a minimum medical history, Guideline Directed Medical Therapy

(GDMT), previous HF hospitalization in the prior year, blood tests results, echocardiography report and other relevant clinical data for purposes of determining enrollment eligibility.

Crossover patients will be reviewed and approved by the Sponsor.

10.5.3 CLINICAL EVENT COMMITTEE

The Clinical Event Committee (CEC) will be comprised of cardiologists who are not participants in the trial and who have no conflict of interest with the trial or the trial sponsor. The CEC will retain a consultant neurologist to assist with these adjudications. All members of the CEC will be blinded to the primary results of the trial.

The CEC will be responsible for the adjudication of the clinical trial events. At the onset of the trial, the CEC will establish explicit rules outlining the process for adjudication and the algorithms followed, in order to classify a clinical event. The CEC will also review and rule on all deaths that occur throughout the blinded phase of the trial. In addition, the CEC will review and adjudicate all clinical endpoints events during the blinded phase of the trial. Definitions are provided in Section 3.4. The CEC will employ a 2- step adjudication process: first, blinded to randomization, and then if an endpoint event is positively adjudicated, the CEC will be unblinded to determine the likelihood of the event being related to the study device.

Once the specific criteria for clinical endpoints are established by the CEC, the independent DCC will be responsible for preparing all clinical endpoint event dossiers and for the conduct of the CEC meetings.

10.5.4 DATA SAFETY MONITORING BOARD (DSMB)

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB). The Data Safety Monitoring Board (DSMB) is comprised of at least three members with the appropriate expertise (heart failure, interventional cardiology and biostatistics), who are not directly involved in the conduct of the trial, independent from the study conduct and free of conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the study sponsor.

All adverse events will be reported to the DSMB and reviewed on an on-going basis throughout the subject enrollment and follow-up period as specified in the DSMB charter, to ensure the safety of subjects enrolled in this trial. The DSMB may request additional information as needed. Based on safety data, the DSMB may recommend that the Executive Committee modify or discontinue the trial. All final decisions, regarding trial modifications, however, rest with the Study Executive Committee and the Sponsor.

10.6 CLINICAL MONITORING

The sponsor will manage the monitoring and data collection of this study per ISO 14155:2011, E6: ICH GCP Guideline, and 21 CFR 812. Study monitoring representatives with adequate medical experience and training to perform the assigned tasks to ensure that the study is performed as defined and to ensure that the required data is accumulated, will monitor this study. An Executive Committee has been assembled and assigned the tasks of maintaining the quality of study conduct.

Prior to initiating the study, the Sponsor will ensure that the appropriate personnel at each site are adequately trained in study procedures and in the proper use of the study device, and that the study protocol, patient informed consent form, Investigator and site agreements, and the case report forms are in place.

Review of study required documentation including signed agreements, protocol, required institutional approvals, Ethics Committee/Institutional Review Board Approval will be conducted. The investigator guarantees direct access to source documents by the sponsor and regulatory bodies. Source data verification is performed in accordance with data protection regulations and guidelines and all information reviewed will be kept confidential.

Participant data will be documented in the CRF. CRFs will be periodically monitored and 100% of primary safety and effectiveness endpoints, hierarchically tested secondary effectiveness endpoints and SAEs will be verified. Risk-based monitoring will be applied for all other elements of the study. The investigator is responsible for completing the CRFs in a timely manner and the monitor is responsible for reviewing them and clarifying and resolving any data queries.

All deviations from the protocol that occur during the study will be captured and the impact of each deviation on the validity and integrity of the data collected will be evaluated.

Data in the study will be collected on all participants until study termination. Data collection will be terminated if the patient withdraws their consent.

Investigational device and medication accountability records will be reviewed including devices and medications received, receipt dates, quantity, lot numbers, identification of patient and date of implantation of the device, storage, and signature of study personnel responsible for accountability.

10.6.1 MONITORING PLAN

Sponsor and/or designee will monitor the trial over its duration according to the pre-specified monitoring plan. The trial monitor will visit each site at appropriate intervals to review investigational data for accuracy and completeness and ensure compliance with the clinical investigation plan. The trial monitor may inspect all documents and required records that are maintained by the Investigator/Site, including medical records (office, clinic, or hospital) for the subjects in this trial. Source documentation must be available to substantiate proper informed consent procedures, adherence to clinical investigation plan procedures, adequate reporting and follow-up of adverse events, accuracy of data

collected on case report forms, and device information. A monitoring visit sign-in log will be maintained at the site. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator/Site will provide the trial monitor with a suitable working environment for review of study-related documents.

10.6.1.1 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator and the associated institution will permit direct access to source data/documents for study-related monitoring, audits, IRB review and regulatory inspections.

Patients providing informed consent agree to allow the Sponsor or designee access and copying rights to pertinent information in their medical and billing records concerning their participation in this trial. The Investigator will obtain, as part of the informed consent, permission for trial monitors or regulatory authorities to review, in confidence, any records identifying the patients in this trial. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the patient's personal and private information.

10.7 SOURCE DATA

10.7.1 DEFINITION AND RESPONSIBILITY

Source data includes all information in original records, certified copies of original records (including imaging records) and original data recorded on worksheets, and includes all original recordings or certified copies of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the study.

The Investigator is responsible for maintaining complete and accurate documentation of the trial including but not limited to medical records, trial progress records, laboratory results, case report forms, signed informed consent forms, device accountability records, correspondence with the IRB as well as trial monitors and sponsor, adverse event reports, and information regarding subject discontinuations.

The Investigator is required to maintain information in the subject’s medical records which documents and corroborates data entered in the case report forms. As a minimum, the subject record should contain:

- Documentation of subject’s consent and subject ID number in the trial
- Medical history/physical exam documenting that subject meets inclusion/exclusion criteria
- Dated and signed notes from each subject visit
- Adverse events reported and their resolution or lack thereof including supporting documents such as hospital records, discharge summaries, catheterization reports, ECGs, etc.
- Record of clinical investigation plan required medications during the trial

- Record of the subject's condition upon completion of or withdrawal from the trial.

10.7.2 SOURCE DATA VERIFICATION

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits reported data are reviewed for accuracy, completeness and will be verified from source documents (e.g. patient files, physician notes, discharge summaries, imaging reports etc.). All data reported in CRFs should be supported by source documents unless otherwise specified.

Patient follow-up form on hospitalizations and survival documenting the follow-up call conducted by the study personnel will be considered as a source document.

10.7.3 RECORDS RETENTION

ICH guidelines require that essential documents be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

To comply with these requirements, the investigator will not dispose of any records relevant to this trial without either (1) written permission from the Sponsor, or (2) providing an opportunity for the Sponsor to archive the records. The investigator shall take responsibility for maintaining adequate and accurate source documents of all observations and data generated as required during this trial, including any data clarification forms received from the Sponsor or its designees. Such documentation is subject to inspection by the Sponsor or its agents, the IRB/EC, or other regulatory agencies.

The Investigator will be notified by the Sponsor of the date of marketing approval or discontinuation of the trial. The Investigator will obtain permission from the Sponsor in writing before destroying or transferring control of any trial records.

10.8 SELECTION OF CLINICAL SITES AND INVESTIGATORS

The sponsor will select Investigators who are qualified by training and experience and are legally entitled to perform clinical research and to participate in the investigation of the study device. Sites will be selected based upon review of a recent site assessment and the qualifications of the Primary Investigator at the site.

10.9 TRAINING

10.9.1 SITE TRAINING

All Investigators and trial personnel are required to be trained by either Sponsor, or a previously trained Investigator. This training may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions including training utilizing electronic media. Training of Investigators and trial personnel will include, but is not limited to, the investigational plan, investigational device usage, clinical investigation plan requirements, case report form completion and trial personnel responsibilities. All Investigators and trial personnel who are trained must sign a training log (or an equivalent) upon completion of the training. Investigator and trial personnel must not perform any trial- related procedures prior to being trained. All Investigators must be trained to the clinical investigation plan and trial procedures prior to enrolling patients.

10.9.2 TRAINING OF SPONSOR'S MONITORS

The trial monitors will be trained to the clinical investigational plan, case report forms, and investigational device usage in accordance with the Sponsor's and/or designee's standard procedures.

10.10 QUALITY ASSURANCE ASSESSMENTS

The Sponsor and/or designee may conduct periodic compliance assessments (on-site audits) at the investigational study sites. A Sponsor representative or designee may request access to all trial records, including source documentation, for inspection and duplication during a compliance assessment. The Investigator and research coordinator must be available to respond to reasonable requests and queries made during the compliance assessment process.

10.11 REGULATORY AGENCY INSPECTION

If an Investigator is contacted by a Regulatory Agency in relation to this trial, the Investigator will notify the Sponsor immediately. The Investigator and research coordinator must be available to respond to reasonable requests and inspection queries made during the inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of this trial. The Sponsor will provide any needed assistance in response to regulatory inspections.

10.12 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation, and completion. A quality management plan will be developed to describe a study's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated and collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.13 PROCEDURES USED FOR DATA REVIEW, DATABASE CLEANING, AND ISSUING AND RESOLVING DATA QUERIES

Cardiovascular Research foundation (New York, NY) will provide the electronic data capture (EDC) services for the trial. The sites are responsible for completing the clinical electronic CRF (eCRF) from the EDC clinical database. The data cleaning routines are performed during data entry through automatic edit checks that occur during data entry by the sites into the EDC system. The auto-queries are generated by the EDC system and are resolved by the site. Those auto-queries will be cleared when the revised data entry meets the edit check criteria, or the monitor accepts the revised entry. The manual queries are created by the site monitors. The Data Manager from Cardiovascular Research Foundation can create manual queries on data as well for the sites to review. The EDC system flags the records with data queries which are resolved by the site, and the manual queries are cleared by the originating personnel. Tracking of data cleaning query status is facilitated by listings from the EDC system. Data listings needed for data review are also created within the EDC system. Refer to the separate Data Management Plan for specific details.

10.13. PROCEDURES FOR VERIFICATION, VALIDATION, AND ELECTRONIC CLINICAL DATA

The trial website will be managed by Cardiovascular Research Foundation (New York, NY). The EDC will meet patient confidentiality requirements consistent with applicable regulations such as the US HIPAA (Health Insurance Portability and Accountability Act). The trial website will enforce restricted access control mechanisms under the management of Cardiovascular Research Foundation and will incorporate encrypted point-to-point data transfer via secure HTTP protocols. Trial Investigators/sites will enter data online; data will be stored at a secure and confidential location and will be reviewed and analyzed on a regular basis. Further details of verification, validation, and securing of electronic clinical data systems can be found in the trial specific Data Management Plan.

10.14 PROTOCOL DEVIATIONS

10.14. STATEMENT SPECIFYING THAT THE INVESTIGATOR IS NOT TO DEVIATE FROM THE

No investigative procedures other than those defined in this clinical investigational plan will be undertaken on the enrolled subjects without the written agreement of the IRB and Sponsor.

It is the Investigator's responsibility to ensure that there are no deviations from the clinical investigational plan and full compliance with all established procedures of the IRB is maintained. The Investigator will not deviate from the clinical investigational plan for any reason except in cases of medical emergencies when the deviation is necessary to protect the life or physical well-being of the subject. Such deviations must be reported to IRBs/ECs and Sponsor within 24 hours from the time of the deviation.

10.14. PROCEDURES FOR RECORDING, REPORTING, AND DEVIATION

A deviation is an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the Clinical Investigation Plan. All deviations must be reported to the Sponsor. The occurrence of clinical investigational plan deviations will be monitored by the Sponsor or designee. It is the Investigator's responsibility to inform their IRB of clinical investigational plan deviations in accordance with their specific IRB reporting policies and procedures.

If a study site does not comply with the Investigator Agreement or Clinical Investigational Plan, the Sponsor will notify the Investigator of the site’s non-compliance. Continued non-compliance may result in further escalation in accordance with the Sponsor’s standard procedures.

10.14. NOTIFICATION

Major protocol deviations shall be reported to the trial Sponsor and to the reviewing IRB per their reporting requirements. Sponsor approved personnel will also observe and record any protocol deviations during routine monitoring visits and follow up accordingly.

10.14. CORRECTIVE AND PREVENTATIVE ACTIONS AND INVESTIGATOR DISQUALIFICATION

Protocol deviations and site/Primary-Investigator non-compliance will be closely monitored by the Sponsor and appointed sponsor personnel. Identifying deviations and taking corrective actions at the earliest possible stage will increase the potential for clinical trial success and reduced patient risk. The initiation of a corrective and preventative action (CAPA) to investigate and establish corrective actions may be required in some cases. The Sponsor reserves the right to close a clinical study site or replace a PI if non-compliance is observed.

10.14.5 PUBLICATION AND DATA SHARING

The Sponsor of this trial, recognizing the seminal importance of this investigation, is committed to the unrestricted and widespread dissemination of all primary and secondary endpoint results and tertiary analyses. At the conclusion of the trial, a multicenter abstract reporting the primary results will be prepared by the Executive Committee Investigators and presented at an annual scientific meeting. A multicenter publication will similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any single center experience within the trial is not allowed until both the presentation and publication of the multicenter results.

10.14. CONFLICT OF INTEREST

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Executive Committee have established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11 ABBREVIATIONS

6MWT	6-Minute Walk Test
ACE	Angiotensin Converting Enzyme Inhibitor
ADHF	Acute Decompensated Heart Failure
AE	Adverse Event
AF	Atrial Fibrillation
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor-Neprilysin Inhibitor
ASD	Atrial Septal Defect
BARC	Bleeding Academic Research Consortium
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CSAP	Canadian Special Access Program
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
DVT	Deep Venous Thrombosis
EC	Ethics Committee
eCRF	Electronic Case Report Forms
eGFR	Estimated Glomerular Filtration Rate
EQ-5D	EQ-5D is a standardized measure of health status developed by the EuroQol Group
FDA	Food and Drug Administration
FEC	Final Exclusion Criteria
FIM	First-in-Man
FO	Fossa Ovalis
GCP	Good Clinical Practice
GDMT	Guideline-directed Medical Therapy
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HCN	Hyperpolarization-activated Cyclic Nucleotide Channel Blocker
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICD	Implantable Cardioverter/Defibrillator
ICE	Intracardiac Echocardiogram
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IFU	Instructions-for-Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention-To-Treat

KCCQ	Kansas City Cardiomyopathy Questionnaire
LAP	Left Atrial Pressure
LV	Left Ventricle
LVAD	Left Ventricular Assist Device, including any form of Mechanical Circulatory Support
LVEF	Left Ventricular Ejection Fraction
MACNE	Major Acute Cardiovascular or Neurological Event
MAUDE	Manufacturer and User Facility Device Experience
MOP	Manual of Operations
MRA	Mineralocorticoid Receptor Inhibitor
NCT	National Clinical Trial
NIH	National Institutes of Health
NYHA	New York Heart Association Functional Class
OUS	Outside of the United States
PAP	Pulmonary Artery Pressure
PFO	Patent Foremen Ovale
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
Qp:Qs	Pulmonary to Systemic Blood Flow Ratio
RV	Right Ventricle
RVFAC	Right Ventricular Factional Area Change
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
TAPSE	Tricuspid Annular Plane Systolic Excursion
TEE	Transesophageal Echocardiogram
TMF	Trial Master File
TTE	Transthoracic Echocardiogram
US	United States
VTE	Venous Thromboembolism

12 REFERENCES

1 Adams KF, Lindenfeld J, Arnold J M. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. J Heart Failure 2006; 12:10-38.

2 Ambrosy P, Fonarow GC, Butler J, et al. The Global Health and Economic Burden of Hospitalizations for Heart Failure. Lessons Learned From Hospitalized Heart Failure Registries. J Am Coll Cardiol. 2014;63:1123–1133.

3 Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics-2009 Update. A Report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009; 119:e1-e161.

4 Butler J, Braunwald E, Gheorghiade M. Recognizing worsening chronic heart failure as an entity and an end point in clinical trials. JAMA. 2014;312(8):789-90.

5 Schiff GD, Fung S, Speroff T, et al. Decompensated heart failure: symptoms, patterns of onset, and contributing factors. The American journal of medicine 2003;114(8):625-30.

6 Adamson PB, Magalski A, Braunschweig F, et al. Ongoing right ventricular hemodynamics in heart failure: clinical value of measurements derived from an implantable monitoring system. Journal of the American College of Cardiology 2003;41(4):565-71.

7 Fonarow GC, Adams KF, Abraham WT, et al. Risk Stratification for in-hospital mortality in acutely decompensated heart failure. JAMA 2005;293:572-580.

8 Ritzema J, Troughton R, Melton I, Crozier I, Doughty R, Krum H, Walton A, Adamson P, Kar S, Shah PK, Richards M, Eigler NL, Whiting JS, Haas GJ, Heywood JT, Frampton CM, Abraham WT; Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) Study Group. Physician-directed patient self-management of left atrial pressure in advanced chronic heart failure. Circulation. 2010 Mar 9;121(9):1086-95.

9 Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119(14):e391-479.

10 McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–1847.

11 Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. New Engl J Med. 2006;355:251-259.

12 Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Current heart failure reports. 2013;10(4):401-410.

13 Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. Journal of the American College of Cardiology. 2004;43(3):317-327.

14 Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240-e327. DOI: 10.1161/CIR.0b013e31829e8776.

15 Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;000:e000–e000. DOI: 10.1161/CIR.0000000000000509.

16 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016 Aug;18(8):891-975. doi: 10.1002/ejhf.592. Epub 2016 May 20.

17 Abraham WT1, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomized controlled trial. Lancet. 2011 Feb 19;377(9766):658-66. doi: 10.1016/S0140-6736(11)60101-3.

18 Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2015 Update: A Report From the American Heart Association. Circulation. 2014.

19 Popovic JR, Kozak LJ. Vital and health statistics from the Centers for Disease Control and Prevention/National Center for Health Statistics: national hospital discharge survey annual summary, 1998.

20 Adams KF, Fonarow GC, Emerman CL, et. al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: Rationale, design and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National registry (ADHERE). Am Heart J 2005; 149: 209-216.

21 Fonarow GC, Gattis Strough W, Abraham WT. et. al. Characteristics, Treatments and Outcomes of Patients with Preserved Systolic Function Hospitalized for Heart Failure. JACC 2007; 50(8): 768-777.

22 Gheorghiade M, Zannad FZ, Sopko G, et. al. Acute Heart Failure Syndromes, Current State and Framework for Future Research. Circulation 2005; 112: 3958-3968.

23 Chen J, Norman SLT, Wan Y, Krumhollz HM, National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. JAMA 2011;306:1669-1678.

24 Owan TE, Hodge DO, Herges RM, Jacobsen SJ, et al. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. N Engl J Med 2006;355:251-9.

25 Krumholz HM, Merrill AR, Schone EM, Schreiner GC, Chen J, Bradley EH, Wang Y, Wang Y, Lin Z, Straube BM, Rapp MT, Normand SL, Drye EE. Patterns of hospital performance in acute myocardial infarction and heart failure 30-day mortality and readmission. Circ Cardiovasc Qual Outcomes. 2009;2:407–413.

26 Chun S, Tu JV, Wijeysundera HC, Austin PC, Wang X, Levy D, Lee DS. Lifetime analysis of hospitalizations and survival of patients newly-admitted with heart failure. Circ Heart Fail. May 2, 2012.

27 Cleland JGF, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme--a survey on the quality of care among patients with heart failure in Europe: Part 1: patient characteristics and diagnosis. Eur Heart J 2003;24:442-463.

28 Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of Tolvaptan, a Vasopressin Antagonist, in Patients Hospitalized With Worsening Heart Failure: A Randomized Controlled Trial. JAMA 2004;291:1963-1971.

29 Setogoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. Am Heart J 2007;154:260-266.

30 Ritzema J, Troughton R, Melton I, Crozier I, Doughty R, Krum H, Walton A, Adamson P, Kar S, Shah PK, Richards M, Eigler NL, Whiting JS, Haas GJ, Heywood JT, Frampton CM, Abraham WT; Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) Study Group. Physician-directed patient self-management of left atrial pressure in advanced chronic heart failure. Circulation. 2010 Mar 9;121(9):1086-95.

31 Abraham WT, Stevenson LW, Bourge RC, et al. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomized trial. Lancet. 2016 Jan 30;387(10017):453-61. doi: 10.1016/S0140-6736(15)00723-0. Epub 2015 Nov 9.

32 Adamson PB, Abraham WT, Bourge RC et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail 2014;7:935-944.

33 Drazner MH, Hamilton MA, Fonarow G, et al. Relationship between right and left-sided filling pressures in 1000 patients with advanced heart failure. J Heart Lung Transplant 1999;18:1126-1132.

34 Viaene D, Vermeersch P, Van den Branden F. Pulmonary oedema after percutaneous ASD-closure. Acta Cardiol. 2010 Apr;65(2):257-60.

35 Beyer J, Brunner L, Hugel W, Kreuzer E, Reichart B, Sunder-Plassmann L, et al. Acute left heart failure following repair of atrial septal defects. Its treatment by reopening. Thoraxchir Vask Chir 1975; 23: 346-349.

36 Schubert S, Peters B, Abdul-Khaliq H, Nagdyman N, Lange PE, Ewert P. Left ventricular conditioning in the elderly patient to prevent congestive heart failure after transcatheter closure of atrial septal defect. Catheter Cardiovasc Interv 2005; 64: 333-337.

37 Seib PM, Faulkner SC, Erickson CC, Van Devanter SH, Harrell JE, Fasules JW, Frazier EA, Morrow WR. Blade and balloon atrial septostomy for left heart decompression in patients with severe ventricular dysfunction on extracorporeal membrane oxygenation. Catheter Cardiovasc Interv. 1999 Feb;46(2):179-86.

38 Burkhoff D, Mirsky I, Suga H, Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Phsiol Heart Circ Physiol 2005;289:H501-H512.

39 Eigler NL, del Rio CL, Verheye S. et al. Cardiac unloading with an implantable interatrial shunt in heart failure: serial observations in an ovine model of ischemic cardiomyopathy. Structural Heart 2017; 1:1-2, 40-48.

40 Del Trigo M, Bergeron S, Bernier M, et al. Unidirectional left-to-right interatrial shunting for treatment of patients with heart failure with reduced ejection fraction: a safety and proof-of-principle cohort study. The Lancet;387:1290-1297.

41 Hasenfuß G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, Malek F, Van der Heyden J, Lang I, Petrie MC, Cleland JG, Leon M, Kaye DM; REDUCE LAP-HF study investigators. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. Lancet. 2016 Mar 26;387(10025):1298-304. doi: 10.1016/S0140-6736(16)00704-2.

42 Kaye DM, Hasenfuß G, Neuzil P, Post MC, Doughty R, Trochu JN, Kolodziej A, Westenfeld R, Penicka M, Rosenberg M, Walton A, Muller D, Walters D, Hausleiter J, Raake P, Petrie MC, Bergmann M, Jondeau G, Feldman T, Veldhuisen DJ, Ponikowski P, Silvestry FE, Burkhoff D, Hayward C. One-Year Outcomes After Transcatheter Insertion of an Interatrial Shunt Device for the Management of Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2016 Dec;9(12). pii: e003662.

43 Feldman T, Komtebedde J, Burkhoff D, Massaro J, Maurer MS, Leon MB, Kaye D, Silvestry FE, Cleland JG, Kitzman D, Kubo SH, Van Veldhuisen DJ, Kleber F, Trochu JN, Auricchio A, Gustafsson F, Hasenfuβ G, Ponikowski P, Filippatos G, Mauri L, Shah SJ. Transcatheter Interatrial Shunt Device for the Treatment of Heart Failure: Rationale and Design of the Randomized Trial to REDUCE Elevated Left Atrial Pressure in Heart Failure (REDUCE LAP-HF I). Circ Heart Fail. 2016 Jul;9(7). pii: e003025. doi: 10.1161/CIRCHEARTFAILURE.116.003025.

44 Cappato R, Calkins H, Chen SA, et al. Prevalence and causes of fatal outcome in catheter ablation of atrial fibrillation. J Am Coll Cardiol 2009;53:1798-803.

45 Belhassen B. A 1 per 1,000 mortality rate after catheter ablation of atrial fibrillation, an acceptable risk? J Am Coll Cardiol 2009;804-8-5.

46 Feldman T, Foster E, Glower DD, et al, for the EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. J Engl J Med 2011;364:395-406.

47 De Ponti R, Cappato R, Curnis A, et al. Trans-septal catheterization in the electrophysiology laboratory, data from a multicenter survey spanning 12 years. J Am Coll Cardiol 2006;47:1037-1042.

48 Holmes DR, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy. J Am Coll Cardiol 2014;64:1-12.

49 Percutaneous mitral valve repair with the MitraClip clip delivery system in high surgical risk patient. Briefing document for the Circulatory Systems Device Panel Advisory Committee. 20 March 2013.

50 Howell MD, Geraci JM, Knowlton AA. Congestive heart failure and outpatient risk of venous thromboembolism: a retrospective, case-control study. J Clin Epidemiol. 2001;54:810–816.

51 Beemath A, Skaf E, Stein PD. Pulmonary embolism as a cause of death in adults who died with heart failure. Am J Cardiol. 2006;98:1073–1075.

52 Chiche O, Castellani M, et al. E. Prevalence of patent foramen ovale and stroke in pulmonary embolism patients. Eur Heart J. 2013;34:1142.

53 Bannan A, Shen R, Silvestry FE, et al. Characteristics of adult patients with atrial septal defects presenting with paradoxical embolism. Catheter Cardiovasc Interv 2009;74:1066–9.

54 Geva T, Martins JD, Wald RM. Atrial septal defects. Lancet 2014;383:1921–32.

55 McClean D, Aragon J, Jamali A, et al. Noninvasive calibration of cardiac pressure transducers in patients with heart failure: An aid to implantable hemodynamic monitoring and therapeutic guidance. J Card Fail 2006;12:567-576.

56 Haeusler KG, Laufs U, Endres M. Chronic heart failure and ischemic stroke. Stroke 2011;42:2977-2982.

57 Abdul-Rahim AH, Perez AC, Fulton RL et al. Risk of stroke in chronic heart failure patients without atrial fibrillation. Analysis of the controlled Rosuvastatin in multinational trial heart failure (COROMA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) trial. Circulation 2015;131:1486-1494.

58 Arboix A, Alio J. Cardioembolic stroke: clinical feature, specific cardiac disorders and prognosis. Current Cardiol Rev 2010:6:150-161.

59 Krumsdorf U, Ostermayer S, Billinger K, et al. Incidence and clinical course of thrombus formation on atrial septal defect and patent foramen ovale closure devices in 1,000 consecutive patients. J Am Coll Cardiol 2004;43:302–9.

60 Baumgartner H, Bonhoeffer P, Groot NMS, et al. ESC guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 2010;31:2915-2957.

61 Therrien J, Warnes C, Daliento L, et al. Canadian Cardiovascular Society Consensus Conference 2001 update: recommendations for the management of adults with congenital heart disease part III. Can J Cardiol. 2001;17:1135–1158.

62 Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008 Dec 2;52(23):e143-263.

63 Webb G, Gatzoulis MA. Atrial septal Defects in the Adult: Recent progress and overview. Circulation 2006;114:1645:1653.

64 Chan NY, Choy CC, Lau CL, et al. Persistent iatrogenic atrial septal defect after pulmonary vein isolation by cryoballoon: an under-recognized complication. Europace 2011 Oct;13(10):1406-10.

65 Rillig A, Meyerfeldt U, Kunze M, et al. Persistent iatrogenic atrial septal defect after a single-puncture, double-transseptal approach for pulmonary vein isolation using a remote robotic navigation system: results from a prospective study. Europace 2010 Mar;12(3):331-6.

66 McGinty PM, Smith TW, Rogers JH. Transseptal left heart catheterization and the incidence of persistent iatrogenic atrial septal defects. J Interv Cardiol. 2011 Jun;24(3):254-63.

67 Hoffman R, Altiok E, Rieth S. Functional effect of new atrial septal defect after percutaneous mitral valve repair using the MitraClip device. Am J Cardiol 2014;113:1228-1233.

68 Korkmaz S, Demirkan B, Guray Y, et al. Long-term follow-up of iatrogenic atrial septal defect: after percutaneous mitral balloon valvuloplasty. Tex Heart Inst J. 2011;38(5):523-7.

69 Hammerstingl C, Licfett L, Jeong KM, et al. Persistence of iatrogenic atrial septal defect after pulmonary vein isolation—an underestimated risk? Am Heart J 2006;152:e1-362.e5.

70 Yousuf MA, Haqwue S, O'donnell R, et al. Right heart failure from persistent iatrogenic atrial septal defect following atrial fibrillation ablation. J Am Coll Cardiol 2014;63:A661.

71 Shueler R, Ozturk C, Wedekind JA, et al. Persistence of iatrogenic atrial septal defect after interventional mitral valve repair with the MitraClip system, A note of caution. J Am Coll Cardiol Intv 2015;8:450-459.

72 FDA. FDA Executive Summary P130013 Boston Scientific Watchman Left Atrial Appendage Closure Therapy. 2013;

73 Percutaneous mitral valve repair with the MitraClip clip delivery system in high surgical risk patient. Briefing document for the Circulatory Systems Device Panel Advisory Committee. 20 March 2013.

74 Cox ZL, Lai P, Lindenfeld J. Eur J Heart Fail. 2020; 22:1045-1046.

75 Umapathi P, et al. J Card Fail 2020; 26:637-638.

76 Okumura N, et al. Circulation 2016; 133:2254-2262. (PARADIGM-HF)

77 Vaduganathan M, et al. J Am Coll Cardiol HF 2021; 9:374-382. (PARAGON-HF)

78 Docherty KF, et al. Circulation 2020; 142:1623-1632. (DAPA-HF)

79 Packer M, et al. Circulation 2021; 143:326-336. (EMPEROR-Reduced)

80 Packer M, et al. Circulation published online August 29, 2021 (EMPEROR-Preserved)

81 Finkelstein DM, Shoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Statistics in Medicine. 1999;18:1341-1344.

82 Abraham WT, et al. JACC Heart Fail 2020; 8:961-972.

83 Lansky AJ, et al. Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative. J AM Coll Cardiol. 2017;69(6):679-691. doi.org/10.1016/j.jacc.2016.11.045.

84 Bourge RC, Abraham WT, Adamson PB, et al. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure. The COMPASS-HF Study. JACC 2008;51:1073-9.

85 Abraham WT, Adamson PB, Constanzo MR, et al. Hemodynamic Monitoring in Advanced Heart Failure: Results from the LAPTOP-HF Trial. Journal of Cardiac Failure: 22(11):940.

86 Stone GW, Lindenfeld JA, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018 Sep 23; [e-pub]. (*https://doi.org/10.1056/NEJMoa1806640*)

87 Cui L, Hung HMJ, Wang S-J. Modification of sample size in group sequential clinical trials. Biometrics 1999;55:853-857.

Summary of Changes from Previous Version:

Version	Release Date	Description of Changes
0.0	February 13, 2018	Initial Release
1.0	March 23, 2018	1) Replaced Executive Committee signature page with Sponsor's signature page. 2) Added language to require removal of delivery sheath immediately post implantation. 3) Included description of medication to be provided to US and international sites. 4) Expanded number of clinical sites to 75. 5) Minor typographical corrections.
2.0	April 16, 2018	1) Added NCT Number. 2) Added language to clarify that healthcare economic analysis will only include U.S. patients at U.S. sites. 3) Added language requiring patients randomized to therapy who have an unsuccessful implant and who are not on anticoagulation or antiplatelet therapy for prior indications should receive aspirin and placebo for clopidogrel. 4) Added clarification that death, heart transplant and LVAD implantation will be considered terminal endpoints from an effectiveness analysis standpoint. 5) Minor typographical corrections. 6) Deleted Section 12 – Protocol Amendment History which was duplicated.
3.0	July 2, 2018	1) Clarified that only cardiovascular, anticoagulant, and antiplatelet therapy medications need to be collected during follow-up. 2) Clarified that time-based Inclusion/Exclusion criteria are reference to the Baseline Visit. 3) Clarified Final Exclusion Criteria based on PASP and PVR. 4) Changed BB stability requirement for inclusion from 3 months to 1 month for compatibility with other major HF clinical trials. 5) Added language to allow exclusion of OUS patients that may not be allowed to take study required medications. 6) Clarified that all study enrolled patients (Roll-In, Treatment and Control) must be admitted for a hospital overnight stay post study intervention visit.

Version	Release Date	Description of Changes
		7) Clarified that RHC during Study Intervention must be performed from femoral venous access. 8) Clarified blinding procedures. 9) Removed Patient Self-Assessment at Baseline. 10) Minor typographical corrections.
4.0	October 12, 2018	1) Added Group SVP Clinical and Commercial Affairs to signature page 2) Clarified that BNP/NT-pro BNP measurements need to happen during a clinically stable period and at least 1 month after CRT or mitral valve repair device implantation. 3) Clarified that HF hospitalization must happen 1 months after CRT or mitral repair device implantation. 4) Clarified that nickel allergy must be known, not suspected, to be considered an exclusion criterion. 5) Added reference to patient blinding assessment on schedule of activities table. 6) Updated time of BNP or NT-pro BNP collection up to 90 days prior to baseline visit. 7) Added collection of cardiac troponins at study intervention procedure. 8) Changed duration of mock transseptal catheterization for control patients to 10 minutes. 9) Added requirement to collect imaging and hemodynamic data at the time of Study Intervention. 10) Clarified that blinded investigators that become unblinded to any given patient must be replaced by another blinded investigator for further blinded interactions for that patient. 11) Clarified that the patient blinding questionnaire will be applied at the 12-month follow-up visit. 12) Clarified that for control patients to be able to cross-over, the cross-over phase of the study must be active. 13) Clarified that control patients that cross-over will be followed for the first 12 months after receiving the implant according to the first 12-month follow-up schedule and then yearly thereafter until they reach 5 years post implantation. 14) Added recommendation that post enrollment echo core lab findings consistent with COAPT eligibility criteria are recommended before undergoing mitral valve device implantation. 15) Clarified that the MRI or CT head for neurological event assessment should be done per standard of care.

Version	Release Date	Description of Changes
		16) Clarified that heart transplantation, right or left ventricular assist device implantation or other intervention procedures for worsening heart failure (e.g. MitraClip) will be counted as a HF Hospitalization. 17) Clarified that Eligibility Committee members cannot review patient candidates from their own site. 18) Clarified that blinding procedures other than described in the protocol can also be used by sites. 19) Clarified that blinded Field Monitors will be responsible for monitoring blinded study activities and records. 20) Other minor typographical corrections or clarifications.
5.0	June 25, 2019	1) Added reference that the trial will be conducted according to 21 CFR parts 50, 56, 812 for US and 812.28.a.1 for International sites. 2) Clarified inclusion criteria for NYHA such that historical assessment is documented at the Baseline Screening visit. 3) Clarified inclusion criteria language regarding GDMT for HFrEF vs HFpEF patients. 4) Added outpatient HF Clinic treatment for ADHF is considered equivalent to a HFH for the purpose of meeting Inclusion criteria. 5) Increased BMI exclusion criterion to >45 Kg/m^2. 6) Lowered RVFAC for baseline exclusion criterion to 25%. 7) Clarified that MitraClip implantation within 3 months of Baseline Visit is considered an exclusion criterion for the study. 8) Clarified exclusion for coagulopathy or known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically. 9) Clarified that screening assessments should be completed with the patient in stable condition as an outpatient. Consenting a patient pre-discharge or at discharge is acceptable. 10) Clarified FEC criterion where patients are excluded if not stable to undergo the procedure. 11) Clarified Final Exclusion Criterion such that transient hypotension or bradycardia during anesthesia or catheterization, manifest as a vagal or similar acute episode or dehydration responding promptly to IV fluids or IV push vasopressors or chronotropic agents is not considered an exclusion criterion.

Version	Release Date	Description of Changes
		12) Updated allowable maximal septal thickness to 6mm. 13) Reverted duration of mock transseptal catheterization for control patients back to 15 minutes to prevent potential patient unblinding. 14) Added hemoptysis as a foreseeable adverse event. 15) Clarified the primary safety endpoint analysis to say that the primary safety endpoint analysis will be conducted using an intention to treat analysis including patients randomized to the Therapy arm regardless of whether the implantation procedure was successful. 16) Clarified the language for secondary endpoint for heart failure hospitalization adjusted for all-cause mortality. 17) Clarified that the Implant Guidelines comprises Best Practices and Tips and Tricks documents contained in the study Manual of Operations. 18) Added that SGLT2 medications for the treatment of diabetes will be collected during follow-up. 19) Clarified that intervention procedure can be up to 45 days from Eligibility Committee approval. 20) Clarified that baseline TTE may be done with saline contrast. 21) Added that if FEC cannot be completed during Intervention Procedure, the case will have to be rereviewed by Eligibility Committee. 22) Updated site reporting timeline for SAEs and device deficiencies that could have led to an SAE. 23) Clarified that checking labs for PT, PTT and /or INR is according to institutional standards. 24) Expanded number of clinical sites to 100. 25) Other minor grammatical or typographical corrections.
6.0	May 19, 2020	1) Inclusion of “high risk” NYHA Class II patients that meet criteria of one HFH AND BMI corrected BNP≥300 pg/ml or a corrected NT-proBNP≥1500 pg/ml 2) Replace 6MHW with KCCQ in the primary effectiveness hierarchical composite endpoint 3) MACNE on LVADS under additional safety endpoints should be same as primary safety endpoint 4) Clarify verbiage on baseline screening of Screening / Study Intervention visit (+ 60 days from Start of baseline assessment to FEC 5) Ventura branding and updates to add investigational V-Wave Introducer Sheath

Version	Release Date	Description of Changes
		6) Ventura branding and respective Model Numbers for VWave Shunt, Delivery System and Sheath 7) Statistical updates to address FDA Study Design Considerations 8) Add an additional 20 sites for US for total of 85 sites in US and 120 total worldwide 9) Clarify that roll-in phase to close once reach 100 patients; change the number of roll-in patients per site from 3 to 2. 10) Clarify ACT language 11) Update Adverse Event Section 12) Other minor typographical corrections or clarifications, (de-specify drug co name, i.e. Teva)
7.0		1) Modified Primary effectiveness hierarchical composite endpoint to include worsening HF events treated as an outpatient. 2) Reranked hierarchical tested secondary effectiveness endpoints; 6MWT is now ranked last. 3) Clarified the investigator statement for better alignment with US FDA Part 812.43. 4) Clarify Exclusion #26 requires a documented liver function test. 5) Clarified Troponin requirements as 'cardiac Troponin T, I or C'. 6) Added assessment of worsening HF events treated as an outpatient to all applicable follow-up visits 7) Capture assessment of COVID-19 history at all visits. 8) Clarified timing of COVID-19 serological testing 9) Revised the Planned Interim Analysis to allow trial expansion by up to 600 additional subjects in alignment with FDA approved SAP. 10) Other minor clarifications or typographical corrections

Statistical Analysis

Protocol CL7018

RELIEVE-HF TRIAL:

REducing Lung congestIon symptoms using the v-wavE shunt in advanced Heart Failure

Statistical Analysis Plan (SAP)

Version: 1.0

Date: 11-DEC-2018

Statistical Analysis

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Statistical Analysis

TABLE OF CONTENTS

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1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) provides the detailed methodology for summaries and statistical analyses of the data collected in the RELIEVE-HF trial. This document provides additional details of analysis plans outlined in the study protocol; future modifications of this document or the study protocol will be reconciled so that requirements and procedures in the two documents remain consistent. This SAP is based on the trial protocol version 3.0.

1.1 Study Objectives

The objective of this study is to provide reasonable assurance of safety and effectiveness of the V-Wave Interatrial Shunt System to improve clinical outcomes in a certain high-risk subset of symptomatic patients suffering from HF.

1.2 Study Design

The study is a prospective, multi-center, 1:1 randomized, patient and observer blinded trial, with a Shunt Treatment arm and a non-implant Control arm. All patients will be screened for eligibility in a 3-stage process. Each site may implant up to 3 Roll-in patients in an open-label (unblinded) manner to become familiar with the device and procedures. The roll-in arm is anticipated to enroll approximately 100 patients.

During the Randomized Access (blinded) phase, approximately 400 patients will be randomized 1:1 into a Shunt Treatment arm or a Control arm, with a possible increase to approximately 600 total patients based on interim analysis results. Randomization will be stratified by site and left ventricular ejection fraction (HFrEF, LVEF≤40% or HFpEF, LVEF>40%) as determined by the Echocardiography Core Laboratory on the baseline transthoracic echocardiogram and balanced between treatment arms within sites using permuted block sizes. Treatment arm patients will undergo transseptal catheterization and Shunt implantation. Control patients will not have transseptal catheterization or shunt placement but will undergo all other study procedures. All patients are blinded to study assignment in the Cath Lab.
After randomization, all patients and study personnel involved in endpoint collections will remain blinded to data or treatment assignment for active patients in the study until the last enrolled patient reaches the 12-month follow-up. Patients reaching 24 months prior to the last enrolled patient reaching 12 months will be unblinded. Patients randomized to the Control group who still meet inclusion/exclusion criteria may have the opportunity to cross-over and receive a shunt implant when they complete their follow-up requirements.

All implanted patients (Roll-Ins, Randomized to Treatment and Control patients that cross-over and receive the shunt) will be followed for a total of 5 years from the time of the Study Device implantation. Roll-in patients will additionally undergo TEE imaging at 6 and 12 months to assess Shunt patency.

2.0 ENDPOINTS: DEFINITIONS AND CONVENTIONS

2.1 Primary Endpoints

2.1.1 Primary Safety Endpoint

The percentage of Treatment Group patients experiencing device-related Major Adverse Cardiovascular and Neurological Events (MACNE) during the first 30-days after randomization, compared to a pre- specified Performance Goal. MACNE is defined as all-cause death, stroke, systemic embolism, need for open cardiac surgery or major endovascular surgical repair. Specifically, percutaneous drainage of a pericardial effusion, percutaneous catheter snaring and removal of an embolized but otherwise uncomplicated Study Device and non-surgical treatment of access site complications are excluded from the definition of MACNE.

All events contributing to the primary safety endpoint will be adjudicated and classified by an independent Clinical Events Committee (CEC).

2.1.2 Primary Effectiveness Endpoint

Comparison between Shunt and Control groups of the hierarchical composite ranking of all-cause death, cardiac transplantation or left ventricular assist device (LVAD) implantation, recurrent HF hospitalizations (including Emergency Room HF Visits with duration >6 hours) and change in 6-minute walk test (6MWT) distance. The primary effectiveness analysis will be performed when the last enrolled patient has been followed for a minimum of 12 months from randomization. The analysis is based on the method of Finkelstein and Schoenfeld (1). In addition to the Finkelstein and Schoenfeld test, the unmatched Win ratio with 95% confidence intervals will be used to measure the ratio of wins in the Shunt group described by Pocock et al (2).

2.2 Secondary Endpoints

The difference between study groups will be hierarchically tested for the following secondary effectiveness endpoints in the order shown below, if the primary effectiveness endpoint is met.

Hierarchically Tested Secondary Effectiveness Endpoints:

- 6MWT changes from Baseline to 12 months
- KCCQ changes from Baseline to 12 months

- All-cause mortality and heart failure hospitalizations
- Time to all-cause death, LVAD/Transplant or heart failure hospitalization
- Time to all-cause death or first heart failure hospitalization
- Cumulative heart failure hospitalizations
- Time to first heart failure hospitalization
  - Modified Primary Effectiveness Endpoint including all-cause death, LVAD/Transplant and HF Hospitalizations but without 6MWT

2.3 Additional Endpoints

The following endpoints are considered exploratory, and there are no associated tests of hypotheses. They will be summarized using descriptive statistics appropriate to the data distribution of the individual endpoints.

2.3.1 Additional Effectiveness Endpoints:

- NYHA Class (I, II, III, IV)
- Patient Global Assessment
- Combined all-cause death and all-cause hospitalizations
- All-cause death
- Time to all-cause death (KM analysis)
- Time to cardiovascular death (KM analysis)
- Time to all-cause death, transplant or LVAD (KM analysis)
- Time to cardiovascular death, transplant or LVAD (KM analysis)
  - The Nelson-Aalen cumulative distribution functions for the combined occurrences of heart failure hospitalizations (HFH), LVAD implants, and heart transplant events in the Shunt and Control groups
- Days alive free from heart failure hospitalization
- Outpatient intensification of heart failure therapy
- Emergency room HF visits
  - HF Clinical Composite Assessment (improved, unchanged, or worsened) as described by Packer comprised of all-cause mortality, HF hospitalization, and changes in NYHA functional class ranking and Patient Global Assessment
  - Comparison of transthoracic echocardiographic parameters as listed in Echocardiography Core Laboratory Manual
- Incidence of loss of shunt flow as measured on TTE and/or TEE
- Absolute Changes in 6MWT
- Death: All-cause; Cardiovascular cause (with breakdown by cause, e.g. sudden death, myocardia

infarction, pump failure, stroke); Non-Cardiovascular cause; Undetermined cause; and relationship to device, study intervention or other cardiovascular procedure

- Hospitalization: All-cause; HF hospitalization, Non-HF hospitalization (with breakdown for cause including if associated with secondary worsening of9 HF)
- Change in renal function
- Medication utilization including type, dose, frequency and changes
- Cost and cost-effectiveness data
- Technical success defined as successful delivery and deployment of the shunt and removal of the delivery catheter
- Technical success
- Device success
- Procedural success
- For Roll-in patients, transesophageal or intracardiac echocardiography at 6 and 12 months to assess shunt patency and other parameters as listed in the Echocardiography Core Laboratory Manual
- Additional exploratory subgroup or multivariable analyses may be performed to further understand the relationship between baseline and treatment variables and the outcomes observed

2.3.2 Additional Safety Endpoints:

- Major Adverse Cardiovascular and Neurological Events (MACNE) and Bleeding Academic Research Consortium (BARC) types 3 and 5 bleeding at 30 days
- Percentage of Treatment Group patients with device-related MACNE at 12 months
- Incidence of all Serious Adverse Events by type at study duration
- Incidence of cerebrovascular events at study duration with sub-classification of CNS infarction, CNS hemorrhage, and TIA and their relationship to device or study procedures (per NeuroARC)
- Incidence of MI events at study duration after implantation
- Incidence of systemic embolization events at study duration after implantation
- Incidence of pulmonary embolism events at study duration after implantation
- Incidence of shunt implant embolization at study duration
- Device-related MACNE annually through 5 years

2.4 Effectiveness Endpoints: Qualifying Definitions

2.4.1 Hospitalization (all-cause)

Defined as an admission to an acute care facility, inpatient unit, observation unit or emergency room, or some combination thereof, for at least 24 hours. Excludes hospitalizations planned for pre-existing

conditions (elective admissions) unless there is worsening in the baseline clinical condition prior to the planned admission. Overnight stays at nursing home facilities, physical rehabilitation or extended care facilities, including hospice, do not meet the definition of hospitalization. Hospitalizations will be adjudicated by the Clinical Events Committee as Heart Failure Hospitalization, Other Cardiovascular Hospitalization, or Non-Cardiovascular Hospitalization.

2.4.2 Heart Failure Hospitalization

Meets the definition of all-cause hospitalization above and the primary reason for admission is acute decompensated heart failure (ADHF) meeting the following criteria:

1) Patient has one or more symptoms of ADHF such as worsening or new onset of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, reduced exercise capacity and/or lower extremity/abdominal swelling;

AND

2) Patient has one or more signs or laboratory evidence of ADHF such as: rapid weight gain, pulmonary edema or rales, elevated jugular venous pressure, radiological signs of pulmonary congestion or increased pulmonary venous pressure, increasing peripheral edema or ascites, S3 gallop, hepatojugular reflux, and/or elevated BNP or NT pro-BNP above most recent baseline, right heart catheterization within 24 hours of admission showing elevated PCWP or low cardiac index;

AND

3) Admission results in the initiation of intravenous heart failure therapies such as diuretics, vasodilators, inotropes, or mechanical or surgical intervention (e.g., ultrafiltration, intra-aortic balloon pump, mechanical assistance) or the intensification of these therapies or at least doubling of the oral diuretic dose with the clear intent of promoting increased diuresis for the treatment of ADHF.;

AND

4) No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

For the endpoint event of heart failure requiring hospitalization, the diagnosis of HF would need to be the primary disease process accounting for the above signs and symptoms. All hospitalizations where the primary reason for admission is other than ADHF, if accompanied by worsening HF or subsequently complicated by ADHF, do not meet the criteria for HF Hospitalization. Outpatient Intensification of Heart

Failure Therapy whether managed in a Heart Failure clinic, other clinic setting, or done remotely, does not meet the definition of HF Hospitalization. Admissions for heart transplant or LVAD implantation and MitraClip procedure will also, by definition, be considered a HF hospitalization.

2.4.3 Other Cardiovascular Hospitalization

Meets the definition of all-cause hospitalization for conditions such as coronary artery disease, acute coronary syndromes, hypertension, cardiac arrhythmias, pericardial effusion, atherosclerosis, peripheral vascular disease, pulmonary embolisms, stroke and aortic dissection and not classified as a HF Hospitalization.

2.4.4 Non-Cardiovascular Hospitalization

Meets the definition of all-cause hospitalization for conditions and does not meet the definition of HF Hospitalization or other cardiovascular hospitalization.

2.4.5 Emergency Room Heart Failure Visit

Admission to an emergency room for less than 24 hours, where the primary reason for admission is ADHF otherwise meeting the same criteria defined for HF Hospitalization when the patient is not transferred to an inpatient unit or observation unit, but is discharged home.

2.4.6 Outpatient Intensification of Heart Failure Therapy

Outpatient intensification of HF therapy requires that the patient has worsening symptoms, signs or laboratory evidence of worsening heart failure and the dose of diuretics was increased and sustained for a month, or intravenous treatment given for HF, or a new drug was added for the treatment of worsening HF.

2.4.7 Heart Failure Endpoint Qualifying Events

All Hospitalizations and Emergency Room Visits lasting at least 6 hours as
defined will be adjudicated by the CEC to determine if they qualify as Heart Failure Endpoint Events for inclusion in the Primary Effectiveness Endpoint analysis.

2.4.8 Technical Success

Technical success will be measured at exit from cath lab and is defined as alive, with successful access, delivery and retrieval of the transcatheter V-Wave delivery system, with deployment and correct positioning of the single intended device and no need for additional emergency surgery or reintervention related to either the device or the access procedure.

2.4.9 Device Success

Device success will be measured at 30 days and all post-procedural intervals and is defined as alive and stroke free, with original intended device in place and no additional surgical or interventional procedures related to access or the device and intended performance of the device with no device migration, embolization, detachment, fracture, hemolysis or endocarditis, and expected hemodynamic performance including patent device with Qp:Qs <1.5, and no detected para-device

complications including device leak, erosion, systemic or pulmonary thromboembolization.

2.4.10 Procedural Success

Procedural success will be measured at 30 days and is defined as device success and no device or procedure related SAEs including life threatening bleeding (>4 units of packed red blood cells), acute kidney injury (stage 2 or 3, including renal replacement therapy), major vascular complications or tamponade requiring intervention, myocardial infarction or coronary ischemia requiring PCI or CABG, severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatment (e.g. ultrafiltration or hemodynamic assist devices including intraaortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for ≥ 48 hours).

2.4.11 Neurological Success

Neurological events will be classified according to Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative (NeuroARC). Events will be classified as CNS injury (Type 1) including ischemic stroke, with or without hemorrhagic conversion, along with other Type 1 subtypes, and neurological dysfunction without CNS injury (Type 3) including TIA. Clinical assessment will include a neurological consultation, assessment of the National Institutes of Health Stroke Scale, and assessment of neurological deficits and cognitive function according to institutional standards. Patients experiencing a neurological event will have an MRI or a head CT (if MRI is contraindicated) and will undergo transesophageal echocardiography (TEE) to evaluate cardiac origin, device patency and involvement in their neurological event.

2.4.12 Cost and Cost-Effectiveness Analyses

A prospective health economic evaluation in order to provide rigorous, prospective data with respect to the cost-effectiveness of the interatrial shunt procedure compared with standard medical therapy for U.S. patients in the trial from the time of randomization through a minimum of 1 and a maximum of 2 years of follow up (at which point some patients assigned to the control group may cross over to the shunt procedure). These data will include hospital billing data (UB-04 summary bills and itemized hospital bills) for all U.S. patients, which will be used, along with supplementary material from the case report forms, to determine the initial treatment costs. Follow-up costs will be assessed from the perspective of the U.S. healthcare system based on resource utilization data including follow-up hospitalizations, office visits, medications, etc. At the completion of the trial, these data will be used in conjunction with quality of life and utility data collected from the trial to develop a long-term Markov model in order to project patient-level survival, quality-adjusted life expectancy, and costs beyond the time frame of the trial in order to estimate the incremental cost-effectiveness ratio for the interatrial shunt procedure compared with standard medical therapy for the trial population. These analyses will be out of scope of the clinical data analyses covered by this SAP.

3.0 ANALYSIS SETS

The statistical analysis for the RELIEVE-HF Trial will be presented on the following analysis populations. Data for all subjects will be assessed to determine if subjects meet the criteria for in each analysis population prior to unblinding.

3.1 Roll-in populations:

Sites will first familiarize themselves with the V-Wave system by implanting the shunt in up to 3 Roll-in patients and follow them in an open-label (unblinded) manner. Implantation performance during Roll-in will be assessed during the implant by a Sponsor provided qualified Proctor. Roll-in patients will otherwise be followed and analyzed identically as Randomized patients, but their study data will be presented separately. The detailed information regarding any additional statistical analyses in roll-in patients, such as those related to shunt patency, is specified in a separate monitoring plan (Appendix 2).

3.2 Intention-to-Treat(ITT):

Subjects who were randomized to the Shunt Implant or Control study arms, analyzed according to their original assignment regardless of treatment received or crossovers. Subjects with missing baseline or follow-up data preventing evaluation of specific endpoints will be excluded from ITT analyses of that endpoint.

3.3 Per Protocol (PP):

Randomized subjects who met all initial and final inclusion/exclusion criteria, had no major protocol deviations which may have impacted study outcomes, were treated according to randomization (i.e. study device patients who underwent a V-Wave implant procedure, and control patients who did not undergo a V-Wave implant procedure) and who have available follow-up data for the endpoint being evaluated. The protocol deviations leading to PP exclusion will identified prior to analysis of any data.

3.4 Safety Population:

Randomized subjects who met the initial inclusion and exclusion criteria, signed an informed consent form and underwent any invasive procedure associated with evaluation of the final exclusion criteria.

The analysis data sets that will be used for each analysis are summarized in Table 1. Table 1:

Analyses and analysis sets

Endpoint	ITT Analysis Set	PP Analysis Set	Safety Analysis Set
Primary safety endpoint	X	X	

Primary effectiveness endpoint	X	X	
Secondary effectiveness endpoints	X	X	
Additional effectiveness endpoints	X	X	
Additional safety endpoints (AEs)			X
Demographics/baseline characteristics	X	X	X

4.0 GENERAL METHODOLOGY AND CONVENTIONS

Primary analysis will occur when the last patient enrolled completes 12 months of follow-up. Patients will be followed for the primary data analysis for a minimum of 12 months and a maximum of 24 months from the time of randomization at the Study Intervention Procedure. Patients with less than 24 months of follow-up will complete randomized blinded follow-up when the last randomized patient has completed the 12-month visit. Patients reaching 24 months prior to the last enrolled patient reaching 12 months will be unblinded. Patients randomized to the Control group who still meet inclusion/exclusion criteria may have the opportunity to cross-over and receive a shunt implant when they complete their follow-up requirements, and data collected after crossover will be summarized and reported upon separately.

All implanted patients (Roll-Ins, Randomized to Treatment and Control patients that cross-over and receive the shunt) will be followed for a total of 5 years from the time of the Study Device implantation. Control group patients who do not cross-over to receive a shunt implant, will cease to be followed once unblinding has occurred.

4.1 Sample Size and Controlling for Multiplicity

4.1.1 Primary Safety Endpoint

The hypothesis for safety is:

H_o: R ≥ PG

H_1: R < PG

where R is the percentage of Shunt group patients experiencing device-related Major Adverse Cardiovascular and Neurological Events (MACNE) during the first 30-days after randomization Assuming an alpha level of 0.025 (one-sided), a sample size of 200 evaluable Treatment group patients from the Randomized cohort would achieve a power of 87% to detect a difference between the expected safety endpoint rate of 5% and a Performance Goal of 11%. Primary safety endpoint analysis

will be conducted in all patients implanted with the device using an intention to treat analysis including patients randomized to Therapy only.

4.1.2 Primary Effectiveness Endpoint

The hypothesis for effectiveness is:

H_o: $T_{Shunt} \leq 0$

H_1: $T_{Shunt} > 0$

Where, T_{Shunt} equals sum of ranks in the Shunt group

The assumptions for the effect size in the hierarchical components of the composite primary effectiveness endpoints in HFrEF and HFpEF are pre-specified and based on the best available external information.

Table 2. Six-Month Event Rates, One-Month Hazard Rates (in parentheses), Hazard Ratios (HR), and 6MWT Assumptions by Treatment Group and Ejection Fraction Subpopulation

	Reduced Ejection Fraction (HFrEF)			**Preserved Ejection Fraction (HFpEF)**		
Type of Event	**Control**	**Shunt**	**HR**	**Control**	**Shunt**	**HR**
Loss to Follow-up	**1.7%** (0.002927)	**1.7%** (0.002927)	---	**1.7%** (0.002927	**1.7%** (0.002927	---
Death	**5.1%** (0.008742)	**4.2%** (0.007080)	0.810	**3.6%** (0.006025)	**2.9%** (0.004926)	0.818
LVAD	**1.6%** (0.002620)	**1.2%** (0.001941)	0.741	**0**	**0**	---
HFH1	**27.5%** (0.053379)	**20.7%** (0.038750)	0.726	**21.4%** (0.040101)	**11.5%** (0.020399)	0.509
HFH2	**30.1%** (0.059793)	**22.8%** (0.043171)	0.722	**23.5%** (0.044698)	**12.7%** (0.022583)	0.505
HFH3+	**32.9%** (0.066463)	**24.9%** (0.047712)	0.718	**25.7%** (0.049425)	**13.8%** (0.024796)	0.502
6MWT(*)	**2 (27)**	**12 (27)**	---	**0 (27)**	**10 (27)**	---

* Mean (SD) percentage change from baseline at time of evaluation

Primary effectiveness endpoint analysis will be performed on a combined HFrEF and HFpEF population in the ITT population. The homogeneity of the treatment effect will be examined in an analysis of the interaction between treatment effect and the HFrEF/HFpEF subpopulations. It is estimated that 20%-25% of the total study population will be HFpEF patients. The rank of a subject relative to other subjects is based on consideration of the following factors: level of an observed event in above hierarchical list, the time of the event(s) after randomization, the number of events, the observed time in study, and 6MWT performance. Based on 10,000 simulated trials, a study of 400 patients (200 per arm) would achieve an

expected power of 90% to detect a sum of ranks greater than zero in the treatment group, with a one- sided alpha of 0.025.

Based on above power calculations, the total sample size for RELIEVE-HF trial will be 400 to ensure enough power for both primary safety and effectiveness endpoints.

4.2 Interim Analyses and Summaries

A single, midpoint interim analysis with adaptive sample size re-estimation is planned at the point when approximately 50% of the study population have completed approximately a minimum of 6 months of follow-up, but no later than 3 months prior to completion of enrollment of the original 400 subjects.
This interim analysis would consider only data collected for the composite primary effectiveness endpoint and be based on validation of the original planning assumptions for the components of the endpoint. The interim analysis would be performed by an independent third party, who would communicate results only to the study DSMB, who will make a recommendation to the sponsor about possible changes to the study sample size.

The interim analysis will be limited to data collected in an identified study cohort (e.g., the first 200 evaluable subjects). Using the analysis method specified for evaluation of the primary effectiveness endpoint (Finkelstein-Schoenfeld), the unconditional power to meet the endpoint at the conclusion of the study will be re-estimated. At that time a decision will be taken to possibly increase the sample size. This decision will utilize maximum likelihood estimates of the design parameters displayed in Table 2.
The sample size of the trial will be re-computed by assuming that the updated maximum likelihood estimates are the true design parameters. To be specific, the entire trial will be redesigned with these updated design parameters so as to obtain the new sample size required to achieve 90% power. If the new sample size is less than 400, the trial will proceed as planned initially, with 400 subjects. If, however, the new sample size is greater than 400, the sample size will be increased appropriately, up to a maximum of 600 subjects, if the sponsor accepts the recommendation from the DSMB to increase the study size. Additional details regarding the interim analysis and sensitivity of power to deterioration in treatment effect can be found in the attached statistical methodology for RELIEVE-HF trial (2). The following guidelines are provided to the DSMB for making a recommendation (zone and associated recommended action to be taken) based on the estimated unconditional power:

Table.3 DSMB recommendation guidelines based on interim analysis

Interim Analysis Results	DSMB Recommendation
P400 ≥ 90%	Zone 1: Continue trial with no expansion
P400 < 90% and P600 ≥ 90%, or P600 ≥ 50% and P600 – P400 ≥ 10%	Zone 2: Expand trial by 1-200 subjects to increase power, up to 90% design target

P400 > 20% and none of the above conditions apply	Zone 3: Continue trial with no expansion (futility for expansion)
P400 ≤ 20%	Zone 4: Consider early termination for trial (futility for treatment effect)
Definitions: P400/P600 – statistical power associated with 400/600 evaluable subjects	

In making their recommendation, the DSMB will not reveal specific details of the interim analysis results or estimated power achieved and will also consider all available safety information collected to date. The DSMB recommendation will be made to Executive Committee for the trial, who will review the recommendation and make any necessary decisions about future actions to be taken.

4.3 General Methods

All data collected will be summarized overall and by randomized treatment arms. Descriptive statistics of continuous variables will include mean, standard deviation, median, quartiles, range, and sample size. Mean differences in continuous variables between the randomized treatment arms, where appropriate, will be summarized with the estimated mean difference of the two means, 95% confidence intervals for the difference between the means, and p-values based on a t-test. The distributions within each group will be tested for normality using the Shapiro-Wilks test and if normality cannot be assumed then a Wilcoxon rank-sum test for medians will be performed. The confidence interval for the difference of two means will be calculated under the assumption of unequal variances.

For categorical variables, descriptive statistics will include count, percentage, and sample size. Categorical data will be presented as n/N (%), and percentages will be rounded and reported to a single decimal point (xx.x %). Unless otherwise noted, subjects with missing data will be excluded from the denominator. Differences between the two randomized treatment arms, where specified, will be summarized with the difference in percentages, the exact binomial (Clopper Pearson) 95% confidence interval for the difference of two percentages, and a p-value based on Fisher's exact test.

Survival analysis techniques will be used to analyze the time-to-event variables that occur at or after 30 days of follow-up. Time to event analysis will be performed for each time point separately (i.e. up to 30 days, 6-months (180 days), 1 year (365 days), 2 years (730 days), 3 years (1095 days), 4 years (1460 days), and 5 years (1825 days)) and summarized using the Kaplan-Meier estimated event rates and number of events. The log-rank test will be used for comparing treatments. Hazard ratios and the associated two- sided confidence intervals (Wald's CI) will be estimated by Cox proportional hazards model, including treatment as a covariate.

All time-to-event analyses will be performed with time defined from date of randomization to first occurrence of an event. Subjects without events will be censored at their early withdrawal date or the

last known event-free time point. If this event-free time point occurs after the analysis time point, the days to event variable will be set equal to the analysis time point so that the patient will be included in the analysis (e.g. if the last data point was collected at 1 year and 2 weeks post-procedure, for the 1-year analysis, this subject will be censored at exactly 1 year (365 days)). When analyzing composite endpoints, time is measured from randomization to the first event (days).

All statistical analyses will be performed using SAS 9.4 or higher, IBM/SPSS Version 24 or higher, StatXact Version 11 or higher and software scripts necessary for implementing the evaluation of the composite primary effectiveness endpoint in the above software packages.

4.4 Methods to Manage Missing Data

Reasonable efforts will be made to obtain complete data for all patients; however, missing observations may occur. The reasons for missing data will be reported (e.g., patient is deceased, lost to follow up, withdrew consent, missed follow-up visit, etc.).

All secondary endpoints analyses will be performed using all available data in the ITT and Per Protocol populations.

Missing Safety data:

Completely or partially missing AE start dates will be imputed with the earliest possible date since enrollment/randomization, i.e., the randomization date, if date is completely missing, the first of the month if day is missing (provided that the first of the month is after enrollment), etc.

4.5 Definition and Use of Visit Windows in Reporting

Following the intervention procedure, patients will be followed up to 5 years. The scheduled visits and windows in chronological order can be found at below table:

Table 4. Study visit schedule and follow-up windows

Scheduled visits	Windows
2-week telephone follow up	± 7 Days
One month in-clinic follow up	± 7 Days
3 months in-clinic follow up	± 14 Days
6 months in-clinic follow up	± 30 Days
9 months telephonic follow up	± 30 Days
12 months in-clinic follow up	± 30 Days
15 months telephonic follow up	± 30 Days
18 months in-clinic follow up	± 30 Days
21 months telephonic follow up	± 30 Days

24 months in-clinic follow up	± 30 Days
Close-out telephonic visit	± 30 Days
Follow-up schedule for crossed over control	± 30 Days
2,3,4 and 5 years Post-unblinding annual in-clinic follow up	± 60 Days

Study Day will be calculated from the date of randomization (Day 1 is the day of randomization), and will be used to display the start/stop day of events in the data listings. Study day will be calculated as: Study Day = (date of event – randomization date) + 1.

5.0 ANALYSES AND SUMMARIES

Baseline and Other Summaries and Analyses

Descriptive statistics will be used to summarize all subject baseline and outcome data collected during the study. Continuous variables will be summarized using means, standard deviations, medians, and ranges and categorical variables will be summarized in frequency distributions as described in the general methodology section.

5.1.1 Study Conduct and Subject Disposition

The frequency and percentage of subjects enrolled by site will be provided as a table. A tabulation of patient disposition will be presented overall and by treatment arm, and will include the number of subjects screened, enrolled (randomized), and discontinued, with reasons for discontinuations (e.g., subject died, withdrew consent, was lost to follow-up, etc.) as documented on the case report form. Adherence to study inclusion/exclusion criteria and protocol deviations as documented on the case report form will be descriptively tabulated. A by-subject listing will include the reference data for these tables.

Compliance to 2-weeks, 30-day, 3, 6, 9, 15, 18, 21-months, and 1, 2, 3, 4, and 5-year follow-up visit schedules will be summarized for all subjects in the ITT population and PP population by site.

5.1.2 Baseline Summaries

Baseline patient characteristics will be presented descriptively and will be compared between two treatment arms using the methodology described in Section 4.3. Baseline measurements consist of subject demographics, heart failure history, cardiovascular disease history, other significant medical history, vital signs, and physical examination.

5.1.3 Procedural Characteristics

Procedural characteristics will be presented descriptively and will be compared between two treatment arms using the methodology described in Section 4.3. Procedural measurements consist of right heart catheterization data, procedural measurement and procedure related medications.

5.2 Primary Endpoints

The primary analysis will be performed when the last enrolled patient has been followed for a minimum of 12 months from randomization. The duration of follow-up evaluated by the primary effectiveness endpoint will range from a minimum of 12 to a maximum of 24 months.

5.2.1 Primary Safety Endpoint

The Primary Safety Endpoint is the percentage of Treatment Group patients experiencing any device related Major Adverse Cardiovascular and Neurological Events (MACNE) during the first 30-days after randomization.

5.2.1.1 Primary Analysis

Statistically, the hypothesis can be stated as:

H_o: $R \geq PG$

H_1: $R < PG$

Where R is the expected rate of observed Device/Procedure-related MACNE and PG =11%. The proportion of subjects with MACNE events will be tested against a Performance Goal of 11% with an exact binomial test, with a one-sided significance level of 0.025.

For the primary safety endpoint, only subjects who experience a MACNE event by the end of the 30-day visit window or whose last known event free day on the trial is at least 23 days (i.e., beginning of the 30- day visit window) from randomization and who meet the applicable analysis population will be included in the analysis. A subject will be considered a failure for MACNE if the subject dies or experiences stroke, systemic embolism, need for open cardiac surgery or major endovascular surgical repair.

5.2.1.2 Sensitivity/Robustness Analysis

To support the interpretation of the primary safety analysis, a tipping point analysis will be performed as a sensitivity analysis to assess the impact of missing 30-day MACNE from subjects with insufficient 30- day follow-up. Tipping point analysis involves performing the primary repeatedly for every possible scenario involving the missing outcome data. The analysis will include the worst-case scenario (i.e., all missing outcome data are assumed to be MACNE events) as the most extreme case.

5.2.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint will be evaluated with a sum of ranks (T_{Shunt}) test statistic in the

Shunt group using the method of Finkelstein and Schoenfeld, based on adjudicated endpoint events when last enrolled patients has minimum 12month follow-up since randomization. In addition, the unmatched win-ratio approach will be used to evaluate the primary effectiveness endpoint. In addition, the unmatched win-ratio approach will be used to evaluate the primary effectiveness endpoint. The win- ratio will be calculated as the total number of shunt arm patient wins divided by the number of Shunt arm loses (win-ratio) and 95% confidence interval after all the pairwise comparisons. All subjects have a scheduled minimum follow-up period of 12 months, and all data collected through 24 months of follow- up will be included in the final analyses.

5.2.2.1 **Primary Analysis**

Statistically, the hypothesis can be stated as:

H_o: $T_{Shunt} \leq 0$ H_1: $T_{Shunt} > 0$

Where, T_{Shunt} = sum of ranks in the Shunt group. The Finkelstein-Schoenfeld statistic is evaluated by comparing every subject *i* to every other subject j in the dataset and assigning a rank U_{ij} in accordance with the following hierarchical ranking algorithm across the total evaluable study population (Shunt and Control groups).

1. Death (all-cause)
2. Heart transplant or LVAD implant
3. HF hospitalizations (including qualifying ER visits >6 hours)
4. Six-Minute Walk Distance Test (6MWT, measured as % change from baseline)

At each level, the following comparisons will be done:

1. Death

First, an attempt is made to compare the two subjects based on their Death event.

a. If subject *i* died and subject *j* did not die, we check whether subject j was followed at least as long as the death time of subject i, in which case U_{ij} = -1. But if subject j was followed for less than the death time of subject *i*, the ranking cannot be based on Death events and we proceed to ranking based on LVAD/Transplant events.
b. If the opposite is true, where subject j died and subject i survived at least as long as the death time of subject *j*, U_{ij} = 1. But if subject i was followed for less than the death time of subject *j*, the ranking cannot be based on Death events and we proceed to ranking based on LVAD/Transplant events.
c. In case both subjects have a Death event, where subject i died at least 7 days after subject j, U_{ij} = 1. If the opposite is true and subject j died at least 7 days after subject

i, U_{ij} = -1. If both subjects died within 7 days of each other, the ranking can not be assigned based on Death events and we proceed to ranking based on LVAD/Transplant events.

2. LVAD/Transplant events:

In cases where the two subjects cannot be compared and ranked based on their Death events, LVAD/Transplant events are used next to compare them and assign ranks. The comparison and ranking of two subjects based on LVAD/Transplant events is exactly the same as for Death events.

a. If subject *i* had an LVAD/Transplant event and subject j did not, we check whether subject *j* was followed at least as long as the time that the LVAD/Transplant event occurred for subject *i*, in which case U_{ij} = -1. But if subject j was followed for less than the LVAD/Transplant time of subject i, the ranking cannot be based on LVAD/Transplant events and we proceed to ranking based on HF hospitalization events.

b. If the opposite is true, where subject *j* had an LVAD/Transplant event and subject *i* did not, we check whether subject i was followed at least as long as the time that the LVAD/Transplant event occurred for subject j, in which case U_{ij} = 1. But if subject i was followed for less than the LVAD/Transplant time of subject *j*, the ranking cannot be based on LVAD/Transplant events and we proceed to ranking based on HF hospitalization events.

c. In cases where both subjects have had the LVAD/Transplant event, if subject *i* had the LVAD/Transplant event at least 7 days after subject j, then U_{ij} = 1, or if subject j had the LVAD/Transplant event at least 7 days after subject *i*, then assign U_{ij} = -1. If both subjects had the LVAD/Transplant event within 7 days interval, the ranking cannot be assigned based on LVAD/Transplant event and we proceed to ranking based on HF hospitalization events.

3. Heart Failure Hospitalization (HFH):

In cases where the two subjects cannot be compared and ranked based on their Death or LVAD/Transplant events, HFH events are used next to compare them and assign ranks.

a. The two subjects are first compared on the basis of the number of HFH events, where the subject with the fewer HFH events has the better rank. This comparison is made over the time period of the subject with the shorter follow-up time.

b. In case the two subjects have the same number of HFH events, the first HFH times are compared and if subject *i* 's first HFH event time is 7 days earlier than that of subject *j*, we assign U_{ij} = -1. If the opposite is true so that subject j's first HFH event time is 7 days earlier than that of subject i, we assign U_{ij} = 1.

c. When both subjects have the same number of HFH events and the first HFH event times for the two subjects are within a 7-day interval, ranking cannot be assigned based on HFH event times and we proceed with the investigation of their 6MWT measurements.

d. In all other cases where the two subjects cannot be compared (such as if one subject has been followed without any events for less time than the first HFH time of the other) we proceed with the investigation of their 6MWT measurements.

4. Six-Minute Walk Test (6MWT)

If subject *i* 's change from baseline in 6MWT is 5% more than that of subject *j*, we set *Uij* = 1, and if the same is true for subject *j*, U_{ij} = -1. In case the comparison cannot be made between the two subjects based on their 6MWD, the comparison is considered a tie, with U_{ij} = 0. Note that if a subject cannot walk during follow-up because of a cardiac limitation, his/her follow-up 6MWT will be set to 0. Conversely, if a subject cannot walk during follow-up because of a non-cardiac disability (e.g. orthopedic limitation), that patient will not be considered for the paired assessment of 6MWT.

Suppose m subjects are randomized to the Shunt arm, n subjects are randomized to the control arm, and N = m + n is the total sample size. In the RELIEVE-HF trial, m=n. Each subject will be assigned a score $U_i = \sum_{i=1(j\neq i)}^{N} U_{ij}$ based on the above algorithm. Let D_i = 1 if subject *i* is randomized to receive the VWAVE shunt device, the F-S statistic can be written as

$$T = \sum_{i=1}^{N} D_i U_i$$

The statistic T is asymptotically normal with mean E(T) =2mn(θ – ½) , where θ is the probability that a random subject *i* in the treatment group has a better outcome than a random subject *j* in the control group. The null hypothesis of no treatment effect with respect to death, LVAD, HFH or 6MWT is thus equivalent to H_0: θ = ½. Under H_0 the variance of T is $\text{var}(T) = \frac{mn}{N(N-1)} \sum_{i=1}^{N} U_i^2$ (Equation 1), which reduced in the absence of ties to $\text{var}(T) = \frac{mn(N+1)}{3}$ (Equation 2).

As is generally the case for normal statistics derived from independent multinomial distributions, under local alternatives (values of θ approaching ½) one may use the null variance to standardize the distribution of T. When source data are available we shall compute the variance of T by Equation 1.
Otherwise we shall use Equation 2 to estimate the variance of T.

For clarification, heart transplant and LVAD implant are considered terminal endpoints from an effectiveness analysis standpoint and will be censored for HF hospitalizations and 6MWT after the date of admission that results in heart transplant or LVAD placement. The hypothesis will be tested by comparing the test statistic (T_{Shunt} / $\sqrt{var(T)}$) to the normal distribution, with a one-sided significance level of 0.025.

In additional to the F-S statistics, the effective size for primary effectiveness endpoint will be calculated as

$$R_W = \frac{N_W}{N_L}$$

where N_W equals the number of Shunt wins and N_L equals the number of Shunt losses. The standard error is estimated by assuming the estimated standard error (s) will match the theoretical standard error z. That is, $\frac{\log(R_W)}{s} = z$. We can solve this equation to compute the standard error as

$s = \log(\mathrm{R}_W) / z$, the standardized normal deviates. An approximate 95% confidence intervals will be estimated by adding and subtracting s x 1.96 to $\log(\mathrm{R}_W)$ and exponentiating both results.

5.2.2.2 Sensitivity/Robustness Analysis

Multiple imputation methods will be used in a sensitivity analysis to address the impact of any missing data for the primary effectiveness endpoint outcome. The ITT population is the primary analysis population for the primary effectiveness endpoint, with supportive analyses in the PP population. As a sensitivity analysis, the standard error for the win-ratios will also be estimated from 10,000 bootstrapped samples of the data.

Secondary Endpoints

If the primary effectiveness endpoint is met, then the difference between treatment groups will be hierarchically tested for the following secondary effectiveness endpoints in the order shown below. The same significance level (one-sided, alpha = 0.025) used for the primary effectiveness endpoint will be applied at each step in the hierarchical testing.

Secondary endpoints will be analyzed when the last subject completes 12 months of follow-up. All available follow-up through 24 months at the time of data cut-off will be included in the analysis. Subjects who die or who receive an LVAD or a heart transplant will be censored on the date of that event. Subjects who withdraw from the trial without an endpoint event will be censored on the date of withdrawal.

The ITT population is the primary analysis population for these secondary endpoints, with supportive analyses performed in the PP population.

Where indicated, the analyses of secondary endpoints will be covariate adjusted. The list of pre- specified covariates will include

- Stratification factor of HFrEF and HFpEF
- Ischemic vs. non-ischemic cardiomyopathy
- Sex
- Age
- eGFR

1. 6MWT changes from Baseline to 12 months

Statistical Analysis:

H_o: $\mu_{Shunt} \leq \mu_{Control}$ H_1: $\mu_{Shunt} > \mu_{Control}$

Where μ is the percentage change in 6MWT measurement from baseline to 12 months, adjusted in the analysis for the baseline value in 6MWT in each group. We will use an ANCOVA adjusting for the baseline value to test if the difference in the mean percentage changes from baseline to 12 months is higher in the Shunt arm compared to the Control arm.

2. KCCQ changes from Baseline to 12 months

If the difference in the mean percentage changes in 6MWT from baseline to 12 months is found to be significantly greater in the Shunt arm compared to the Control arm, we will then compare the KCCQ changes from baseline to 12 months between two treatment arms.

Statistical Analysis:

H_o: $\mu_{Shunt} \leq \mu_{Control}$ H_1: $\mu_{Shunt} > \mu_{Control}$

Where μ is the absolute change in KCCQ scores from baseline to 12 months, adjusted in the analysis for the baseline KCCQ value in each group. We will use an ANCOVA to test if the difference in the mean changes from baseline to 12 months is higher in the Shunt arm compared to the Control arm.

3. All-cause mortality and all heart failure hospitalizations at study duration

If the difference in the mean percentage changes in KCCQ from baseline to 12 months is found to be significantly greater in the Shunt arm compared to the Control arm, we will then compare the rate ratio (RR) of HFH in the Shunt vs. Control groups accounting for all-cause mortality risk.

Statistical Analysis:

H_o: $RR_{Shunt\ vs\ Control} \geq 1$ H_1: $RR_{Shunt\ vs\ Control} < 1$

We will use a parametric joint model specifying the distributions for recurrent HFH and all-cause mortality with a common frailty term to induce an association between the two distributions. A Poisson model will be assumed for HFH events and a log-logistic model will be assumed for the time to all-cause death, conditional on the frailty terms, with individual frailties assumed to follow a Gamma distribution. HFH rates will follow negative binomial distributions and the rates in the Shunt vs. Control groups will be used to estimate the rate ratio (RR). The hazard rate associated with all-cause mortality in the joint modeling will also be estimated and reported.

4. Time to first death, LVAD/Transplant, or heart failure rehospitalization event

If the null hypothesis for all-cause mortality and heart failure hospitalization is rejected, we will then proceed with the time-to-first event analysis of the composite endpoint of death, LVAD/transplant or heart failure hospitalization.

Statistical Analysis:

H_o: $HR_{Shunt\ vs\ Control} \geq 1$ H_1:
$HR_{Shunt\ vs\ Control} < 1$

We will use the Cox regression with pre-specified covariates to analyze the composite endpoint and to estimate the hazard ratio (HR) associated with the hazard rates for the Shunt vs. Control.

5. Time to death or first heart failure hospitalization

If the null hypothesis for all-cause mortality, LVAD/transplant and heart failure hospitalization is rejected, we will then proceed with time-to-event analyses of death or first heart failure hospitalization:

Statistical Analysis:

H_o: $HR_{Shunt\ vs\ Control} \geq 1$ H_1: $HR_{Shunt\ vs\ Control} < 1$

We will use the Cox regression with pre-specified covariates to analyze the composite endpoint and to estimate the hazard ratio (HR) associated with the hazard rates for the Shunt vs. Control.

6. Cumulative heart failure hospitalizations at study duration

If the null hypothesis for time to death or first heart failure hospitalization is rejected, we will then compare the cumulative heart failure hospitalizations.

Statistical Analysis:
Statistical Analysis:

H_o: $F_{Shunt} - F_{Control} \leq 0$ for some n H_1:
$F_{Shunt} - F_{Control} > 0$ for some n

Where F is the cumulative distribution function (Nelson-Aalen estimate) for the occurrence of heart failure hospitalization and n is the number of heart failure hospitalizations for each arm. We will use non-parametric Kolmogorov-Smirnov (4) test to compare of distribution of cumulative heart failure hospitalization events

7. Time to first heart failure hospitalization

If the null hypothesis for cumulative heart failure hospitalizations is rejected, we will then proceed with time-to-event analyses of first heart failure hospitalization.

Statistical Analysis:

H_o: $HR_{Shunt\ vs\ Control} \geq 1$ H_1:
$HR_{Shunt\ vs\ Control} < 1$

We will use the Cox regression with pre-specified covariates to analyze the time-to-first heart failure rehospitalization and to estimate the hazard ratio (HR) associated with the hazard rates for the Shunt vs. Control.

8. Modified Primary Effectiveness Endpoint including mortality, LVAD/Transplant, and HF Hospitalizations but without 6MWT

If the null hypothesis for time to first hear failure hospitalization is rejected, we will then proceed with testing the modified primary effectiveness endpoint without 6MWT.

Statistical Analysis:
We will analyze modified primary effectiveness endpoint without 6MWT using the same methodology specified in the section 5.2.2.1.

5.4 Additional Safety Endpoints

The following additional safety data will be evaluated. There are no tests of hypotheses associated with these analyses.

- Comparison of Major Adverse Cardiovascular and Neurological Events (MACNE) and Bleeding

Academic Research Consortium (BARC) types 3 and 5 bleeding at 30 days

This endpoint will be evaluated by estimating the rates of MACNE and BARC events at 30 days, togethers with the associated exact, 95% confidence intervals.

- Percentage of Treatment Group patients with device-related MACNE at 12 months.

This endpoint will be evaluated by estimating the MACNE rate at 12 months, together with its exact, 95% confidence intervals and a Kaplan-Meier analysis of the time-to-events.

5.5 Subgroup Analyses

The consistency of the primary safety endpoint and primary effectiveness endpoint in the ITT and PP populations will be examined in subgroups defined by age (median), sex, BMI (median), diabetes, hypertension, ischemic vs. non-ischemic cardiomyopathy, LVEF stratification factor of HFrEF and HFpEF, baseline NYHA (III vs. IV), baseline BNP/NT-proBNP (median), eGFR (median), baseline 6MWT (median), baseline KCCQ score (median), shunt encapsulation process (two provider sources), US vs. non-US clinical sites, and by sites based on number of enrolled subjects. No formal hypothesis testing for subgroup analyses will be performed. The subgroup analyses described below will be performed for descriptive purposes only. For each subgroup, a test for the difference in the primary safety and effectiveness endpoints will be performed to assess whether there is an interaction between treatment effect and subgroup.

For each of the dichotomous subgroups identified above, the following analyses will be performed:

Primary Safety Endpoint: The primary safety endpoint of MACNE rates at 30 days will be evaluated in each subgroup and compared using a Fisher's Exact test.

Primary Effectiveness Endpoint: The relative treatment effects for the primary effectiveness endpoint within each subgroup will be compared using Z-test based on the Finkelstein- Schoenfeld estimates of the test statistic and its variance in each subgroup.

5.6 Multicenter Studies

For the primary safety endpoint, the appropriateness of pooling data across sites will be assessed by Mantel-Haenszel analysis to examine the homogeneity of the odds ratios at sites as well as by including a random effect for site in a random effects model assessing the primary safety endpoint using the logit link. If a test of the variance from the mixed effects model is significant at alpha=0.15, then it will be concluded that evidence of heterogeneity by site may exist. A significant result will require further inspection of the by-site results to assess the reasons for site differences and if poolability is

appropriate. Sites with less than 10 subjects will be pooled according to study region as defined previously.

The consistency of the primary effectiveness endpoint across sites will be examined by summarizing the distribution of the within-site Finkelstein estimates of the test statistic and its variance.

5.7 Safety Summaries and Analyses

5.7.1 Adverse Events

All adverse events collected will be coded using the most recent version of MedDRA to system organ class (SOC) and preferred term (PT) and summarized based on the Safety Population. The following adverse event summaries will be presented for all subjects and by treatment arms:

- Frequency (number and percent) of subjects with adverse events (AEs) by MedDRA system organ class and preferred term
- Frequency (number and percent) of subjects with serious adverse events (SAEs) by MedDRA system organ class and preferred term
- Frequency (number and percent) of subjects with adverse device effects and serious adverse device effects by MedDRA system organ class and preferred term
- Frequency (number and percent) of subjects with unanticipated adverse device effects (UADEs) by MedDRA system organ class and preferred term
- Frequency (number and percent) of subjects with AE or SAE, by relationship to the study intervention/device. Relationship information will be based on CEC adjudicated data, when available.

In addition, subject data listings of deaths, adverse events and serious adverse events, with their relationship to study device/intervention, AE onset date, outcome, and date of resolution (if resolved), will be presented in the data listings.

5.7.2 Device Deficiencies, Malfunctions

Device Deficiency: A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.
Device deficiencies include malfunctions, use errors, and inadequate labeling.

Malfunction: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or protocol.

Use Error: Act or omission of an act that results in a different medical device response than intended by

the manufacturer or expected by the user.

The following summaries of device deficiencies will be presented, and summary statistics will follow the same analysis as described in the general methods in section 4.3.

All device deficiencies, malfunctions, use errors, and any (serious) adverse events associated with device malfunctions/deficiencies/use errors, as documented in the case report form, will be summarized descriptively by frequency (number and percentage of subjects) in the Safety Population for all subjects and by treatment arms.

A supportive subject data listing of Listings of device deficiencies/malfunction/user errors will be presented in the data listings.

5.7.3 Vital signs, physical examination data

Vital signs, including weight and pulse oximetry data will be collected at each in-clinic visits and summarized overall and by randomized treatment arms using rules specified at general methodology.

5.7.4 NYHA functional class

NYHA Functional Class by blinded assessor by will be collected at baseline screening, 1, 3, 6, 12, 18 and 24 months and annual 3-5 follow-up and summarized overall and by randomized treatment arm using the rules specified in the general methodology.

5.7.5 ECHO Core Lab Data

Transthoracic echo (TTE) measurement will be recorded in baseline screening, 1, 6, 12 and 24 months and annual 3-5 follow-up. Once unblinded, shunted patients will have transesophageal echo (TEE) if no shunt flow seen on prior TTE. And Roll-in patients will have routine follow-up TEE/ICE (intra cardiac echo).

5.7.6 ECG Data

An ECG will be performed at screening/baseline visit. Any abnormal findings will be recorded in the electronic case report forms and summarized overall and by randomized treatment arm using the rules specified in the general methodology.

5.7.7 Laboratory Data

Clinical laboratory measurements will be collected at baseline screening, final screening, post enrollment prior to discharge, and at, 1, 6, 12, and 24 month in-clinic visits. All laboratory parameters will be presented descriptively by applicable visit for all subjects in the ITT population and by randomized treatment arms. The peak lab measurement will be presented if measurements are collected multiple times in one in-clinic visit. Units of all laboratory measurements will be converted into
U.S. Conventional units before any descriptive analyses are performed.

5.7.8 Concomitant Medications

All detailed medication information related to heart failure condition management will be documented in the Case Report Form and summarized overall and by randomized treatment arm and separately for HFrEF and HFpEF patients using the rules specified in the general methodology at all visits.

5.7.9 Quality of Life

Quality of life assessment including KCCQ and EQ5D by blinded assessors will be collected at baseline screening, 1, 3, 6, 12, 18 and 24 months and annual 3-5 follow-up and summarized overall and by randomized treatment arms using the rules specified in the general methodology.

6.0 REFERENCES

1. Finkelstein DM, Schoenfeld, DA (1999). Combining mortality and longitudinal measures in clinical trials. Statistics in Medicine, 18, 1341-1344.
2. Pocock, Stuart J., et al. "The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities." European heart journal 33.2 (2011): 176-182

3. Cyrus R Mehta, Pranab Ghosh and Natasa Rajicic , Statistical Methodology for RELIEVE-HF Trial. Provided by V-WAVE
4. Hollander, Wolfe and Chicken. Nonparametric Statistical Methods. Wiley; 3rd edition (2013)

7.0 APPENDICES

Appendix 1. SAS Code for Patient Level Data Analysis

7.1 SAS Code for Patient Level Data Analysis

7.1.1 Continuous Data

Normality is tested using the Shapiro-Wilks test with NORMAL option in PROC UNIVARIATE. The CLASS statement identifies the treatment group variable (TRT). The VAR statement names the continuous variable in the analysis (OUTCOME).

```
PROC UNIVARIATE NORMAL; BY
TRT;
VAR OUTCOME;
RUN;
```

Student's t-test is performed using PROC TTEST if normality assumption is satisfied. The CLASS statement identifies the treatment group variable (TRT). The VAR statement names the continuous variable in the analysis (OUTCOME).

```
PROC TTEST;
CLASS TRT;
VAR OUTCOME;
RUN;
```

The Wilcoxon Rank-Sum test is performed using PROC NPAR1WAY when normality assumption is not met. The CLASS statement identifies the treatment group variable (TRT). The VAR statement names the continuous variable in the analysis (OUTCOME).

```
PROC NPAR1WAY; CLASS
TRT; VAR OUTCOME;
RUN;
```

7.1.2 Categorical Data

The Chi-square test and Fisher's exact test are performed using PROC FREQ. The TABLES statement produces a cross tabulation of the treatment group (TRT) and interested categorical variable (OUTCOME).
The CHISQ option performs the Chi-square test.

```
PROC FREQ;
TABLES TRT*OUTCOME/CHISQ;
RUN;
```

The FISHER option performs Fisher's exact test when expected values in any of the cells of a contingency table are below 5.

```
PROC FREQ;
TABLES TRT*OUTCOME/FISHER;
RUN;
```

7.1.3 Time to Event Data

PROC LIFETEST calculates Kaplan-Meier estimates and performed the log rank test. The STRATA statement identifies the treatment group (DCS). The TIME statement identifies the variables to be used as the failure time (TIME) and censoring variable (EVENT).

```
PROC LIFETEST;
STRATA TRT;
TIME EVENTDAYS *EVENT(0);
run;
```

7.2 SAS Code for poolability

The Chi-square test and Fisher's exact test are performed using PROC FREQ. The TABLES statement produces a cross tabulation of the treatment group (TRT) and interested categorical variable (OUTCOME).

```
PROC FREQ;
TABLES TRT*OUTCOME/CMH;
RUN;
```

7.3 SAS Code for Cox Model

The Cox regressions are performed using PROC PHREG. The MODEL statement identifies the variables to be used as the failure time (TIME) and censoring variable (EVENT) and treatment group and interested pre-specified covariates. The Efron method will be used to handle ties in the failure time.

```
PROC PHREG;
CLASS  TRT COVARS /DESC ;
MODEL AEVENTDAYS *EVENT(0) = TRT COVARS / RL TIES = EFRON;
RUN;
```

Appendix 2. Data Analysis Plan for Roll-in Patients

Each site may implant up to 3 Roll-in patients and follow them in an open-label (unblinded) manner to become familiar with the device and procedures. Implantation performance during Roll-in will be assessed during the implant by a Sponsor provided qualified Proctor. Roll-in patients will otherwise be followed, and their data analyzed in a manner similar to that from patients implanted with shunts in the Randomized Study, including notification of any identified safety concerns to the DSMB, but with no comparisons to control patients. Data and analysis results from roll-in patients will be summarized and presented separately. The roll-in arm is anticipated to enroll approximately 100 patients.

Transesophageal or intracardiac echocardiography will also be performed at 6 and 12 months in roll-in patients to assess shunt patency and other echo parameters. Additional statistical analyses in roll-in patients beyond those performed for all randomized patients receiving shunts, such as those related to shunt patency, are described below. Since data from roll-in patients will be unblinded to the sponsor, and relatively, that data collection will begin earlier than that from the randomized phase. the monitoring and analyses of their collected data may begin with the first roll-in patients and occur

continuously during the study to identify and intervene early in any issues of safety or performance that may arise.

Enrollment: Reporting of the numbers of roll-in patients, timing, and completion of roll-in phase requirements by active study sites

Assessment of Implant Performance by Proctors: Numbers of roll-in patients required by individual sites to demonstrate implant proficiency

Shunt Patency: Number and rates of patients exhibiting any evidence of shunt closure, classification of the degree of patency loss (%) in those patients, and times to occurrence of first evidence and estimation of the progression of closure; descriptive statistical summaries of other collected echocardiographic parameters

Primary Effectiveness Endpoint: Estimates of events rates and 6MWT outcomes for components of the primary effectiveness endpoint

Compliance Assessment: Early evaluation of compliance with protocol requirements (protocol deviations) to identify potential study conduct or implementation issues at individual sites prior to enrollment of patients in the randomized phase

8.0 VERSION HISTORY

This Statistical Analysis Plan (SAP) for study RELIEVE-HF is based on protocol version 2.0 dated 16April2018.

Table 5. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable

Statistical Analysis

Protocol CL7018

RELIEVE-HF TRIAL:

REducing Lung congestIon symptoms using the v-wavE shunt in advanced Heart Failure

Statistical Analysis Plan (SAP)

Version: 5.1

Date: November 2023

Statistical Analysis

Signature Page

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Statistical Analysis Plan

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1.0 INTRODUCTION

This Statistical Analysis Plan (SAP) provides the detailed methodology for summaries and statistical analyses of the data collected in the RELIEVE-HF trial. This document provides additional details of analysis plans outlined in the study protocol; future modifications of this document or the study protocol will be reconciled so that requirements and procedures in the two documents remain consistent. This SAP is based on the trial protocol version 6.0.

1.1 Study Objectives

The objective of this study is to provide reasonable assurance of safety and effectiveness of the V-Wave Interatrial Shunt System to improve clinical outcomes in a certain high-risk subset of symptomatic patients suffering from HF.

1.2 Study Design

The study is a prospective, multi-center, 1:1 randomized, patient and observer blinded trial, with a Shunt Treatment arm and a non-implant Control arm. All patients will be screened for eligibility in a 3-stage process. Each site may implant up to 2 Roll-in patients in an open-label (unblinded) manner to become familiar with the device and procedures. The roll-in arm is anticipated to enroll approximately 100 patients.

During the Randomized Access (blinded) phase, approximately 400 patients will be randomized 1:1 into a Shunt Treatment arm or a Control arm, with a possible increase up to approximately 1000 total patients based on interim analysis results. Randomization will be stratified by site and left ventricular ejection fraction (HFrEF, LVEF≤40% or HFpEF, LVEF>40%) as determined by the Echocardiography Core Laboratory on the baseline transthoracic echocardiogram and balanced between treatment arms within sites using permuted block sizes. Treatment arm patients will undergo transseptal catheterization and Shunt implantation. Control patients will not have transseptal catheterization or shunt placement but will undergo all other study procedures. All patients are blinded to study assignment in the Cath Lab.
After randomization, all patients and study personnel involved in endpoint collections will remain blinded to data or treatment assignment for active patients in the study until the last enrolled patient reaches the 12-month follow-up. Patients reaching 24 months follow-up prior to the last enrolled patient reaching 12 months will be unblinded. Patients randomized to the Control group who still meet inclusion/exclusion criteria may have the opportunity to cross-over and receive a shunt implant when they complete their follow-up requirements.

All implanted patients (Roll-Ins, Randomized to Treatment and Control patients that cross-over and receive the shunt) will be followed for a total of 5 years from the time of the Study Device implantation. Roll-in patients will additionally undergo TEE imaging at 6 and 12 months to assess Shunt patency.

2.0 ENDPOINTS: DEFINITIONS AND CONVENTIONS

2.1 Primary Endpoints

2.1.1 Primary Safety Endpoint

The percentage of Treatment Group patients experiencing device-related Major Adverse Cardiovascular and Neurological Events (MACNE) during the first 30-days after randomization, compared to a pre- specified Performance Goal. MACNE is defined as all-cause death, stroke, systemic embolism, need for open cardiac surgery or major endovascular surgical repair. Specifically, percutaneous drainage of a pericardial effusion, percutaneous catheter snaring and removal of an embolized but otherwise uncomplicated Study Device and non-surgical treatment of access site complications are excluded from the definition of MACNE.

All events contributing to the primary safety endpoint will be adjudicated and classified by an independent Clinical Events Committee (CEC).

2.1.2 Primary Effectiveness Endpoint

Comparison between Shunt and Control groups of the hierarchical composite ranking of all-cause death, cardiac transplantation or left ventricular assist device (LVAD) implantation, recurrent HF hospitalizations (including Emergency Room HF Visits with duration ≥6 hours), recurrent worsening heart failure treated as an outpatient (including ER HF visits with duration of < 6 hours), and change in KCCQ overall score of at least 5. The primary effectiveness analysis will be performed when the last enrolled patient has been followed for a minimum of 12 months from randomization. The analysis is based on the method of Finkelstein and Schoenfeld (1). P-value will be calculated from the Finkelstein and Schoenfeld test, and the unmatched Win ratio with 95% confidence intervals will be used to measure the ratio of wins in the Shunt group described by Pocock et al (2).

2.2 Secondary Endpoints

The difference between study groups will be hierarchically tested for the following secondary effectiveness endpoints in the order shown below, if the primary effectiveness endpoint is met.

Hierarchically Tested Secondary Effectiveness Endpoints:

- KCCQ changes from Baseline to 12 months

- All-cause mortality and heart failure hospitalizations
- Time to all-cause death, LVAD/Transplant or heart failure hospitalization
- Time to all-cause death or first heart failure hospitalization
- Cumulative heart failure hospitalizations
- Time to first heart failure hospitalization
  - Primary Effectiveness Endpoint including all-cause death, LVAD/Transplant, HF Hospitalizations, and Worsening Heart Failure treated as an outpatient, but without KCCQ
- 6MWT changes from Baseline to 12 months

2.3 Additional Endpoints

The following endpoints are considered exploratory, and there are no associated tests of hypotheses. They will be summarized using descriptive statistics appropriate to the data distribution of the individual endpoints.

2.3.1 Additional Effectiveness Endpoints:

- NYHA Class (I, II, III, IV)
- Patient Global Assessment
- Combined all-cause death and all-cause hospitalizations
- All-cause death
- Time to all-cause death (KM analysis)
- Time to cardiovascular death (KM analysis)
- Time to all-cause death, transplant or LVAD (KM analysis)
- Time to cardiovascular death, transplant or LVAD (KM analysis)
  - The Nelson-Aalen cumulative distribution functions for the combined occurrences of heart failure hospitalizations (HFH), LVAD implants, and heart transplant events in the Shunt and Control groups
- Days alive free from heart failure hospitalization
- Outpatient clinic HF visit and/or Outpatient intensification of heart failure therapy
- Emergency room HF visits
  - HF Clinical Composite Assessment (improved, unchanged, or worsened) as described by Packer comprised of all-cause mortality, HF hospitalization, and changes in NYHA functional class ranking and Patient Global Assessment
  - Comparison of transthoracic echocardiographic parameters as listed in Echocardiography Core Laboratory Manual
- Incidence of loss of shunt flow as measured on TTE and/or TEE
- Absolute and Percentage Changes in 6MWT

- Death: All-cause; Cardiovascular cause (with breakdown by cause, e.g. sudden death, myocardial infarction, pump failure, stroke); Non-Cardiovascular cause; Undetermined cause; and relationship to device, study intervention or other cardiovascular procedure
- Hospitalization: All-cause; HF hospitalization, Non-HF hospitalization (with breakdown for cause including if associated with secondary worsening of HF)

- Change in renal function
- Medication utilization including type, dose, frequency and changes
- Cost and cost-effectiveness data
  - Technical success defined as successful delivery and deployment of the shunt and removal of the delivery catheter
- Technical success
- Device success
- Procedural success
- Absolute Changes in KCCQ from baseline by intervals of 5 points
  - For Roll-in patients, transesophageal or intracardiac echocardiography at 6 and 12 months to assess shunt patency and other parameters as listed in the Echocardiography Core Laboratory Manual
  - Additional exploratory subgroup or multivariable analyses may be performed to further understand the relationship between baseline and treatment variables and the outcomes observed

2.3.2 Additional Safety Endpoints:

- Major Adverse Cardiovascular and Neurological Events (MACNE) and Bleeding Academic Research Consortium (BARC) types 3 and 5 bleeding at 30 days
- Percentage of Treatment Group patients with device-related MACNE at 12 months
- Incidence of all Serious Adverse Events by type at study duration
  - Incidence of cerebrovascular events at study duration with sub-classification of CNS infarction, CNS hemorrhage, and TIA and their relationship to device or study procedures (per NeuroARC)
- Incidence of MI events at study duration after implantation
- Incidence of systemic embolization events at study duration after implantation
- Incidence of pulmonary embolism events at study duration after implantation
- Incidence of shunt implant embolization at study duration
- Device-related MACNE annually through 5 years

2.4 Effectiveness Endpoints: Qualifying Definitions

2.4.1 Hospitalization (all-cause)

Defined as an admission to an acute care facility, inpatient unit, observation unit or emergency room, or some combination thereof, for at least 24 hours. Excludes hospitalizations planned for pre-existing conditions (elective admissions) unless there is worsening in the baseline clinical condition prior to the planned admission. Overnight stays at nursing home facilities, physical rehabilitation or extended care facilities, including hospice, do not meet the definition of hospitalization. Hospitalizations will be adjudicated by the Clinical Events Committee as Heart Failure Hospitalization, Other Cardiovascular Hospitalization, or Non-Cardiovascular Hospitalization.

2.4.2 Heart Failure Hospitalization

Meets the definition of all-cause hospitalization above and the primary reason for admission is acute decompensated heart failure (ADHF) meeting the following criteria:

1) Patient has one or more symptoms of ADHF such as worsening or new onset of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, reduced exercise capacity and/or lower extremity/abdominal swelling;

AND

2) Patient has one or more signs or laboratory evidence of ADHF such as: rapid weight gain, pulmonary edema or rales, elevated jugular venous pressure, radiological signs of pulmonary congestion or increased pulmonary venous pressure, increasing peripheral edema or ascites, S3 gallop, hepatojugular reflux, and/or elevated BNP or NT pro-BNP above most recent baseline, right heart catheterization within 24 hours of admission showing elevated PCWP or low cardiac index;

AND

3) Admission results in the initiation of intravenous heart failure therapies such as diuretics, vasodilators, inotropes, or mechanical or surgical intervention (e.g., ultrafiltration, intra-aortic balloon pump, mechanical assistance) or the intensification of these therapies or at least doubling of the oral diuretic dose with the clear intent of promoting increased diuresis for the treatment of ADHF.;

AND

4) No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

For the endpoint event of heart failure requiring hospitalization, the diagnosis of HF would need to be the primary disease process accounting for the above signs and symptoms. All hospitalizations where the primary reason for admission is other than ADHF, if accompanied by worsening HF or subsequently complicated by ADHF, do not meet the criteria for HF Hospitalization. Outpatient Intensification of Heart Failure Therapy whether managed in a Heart Failure clinic, other clinic setting, or done remotely, does not meet the definition of HF Hospitalization. Admissions for heart transplant or LVAD implantation and MitraClip procedure will also, by definition, be considered a HF hospitalization.

2.4.3 Other Cardiovascular Hospitalization

Meets the definition of all-cause hospitalization for conditions such as coronary artery disease, acute coronary syndromes, hypertension, cardiac arrhythmias, pericardial effusion, atherosclerosis, peripheral vascular disease, pulmonary embolisms, stroke and aortic dissection and not classified as a HF Hospitalization.

2.4.4 Non-Cardiovascular Hospitalization

Meets the definition of all-cause hospitalization for conditions and does not meet the definition of HF Hospitalization or other cardiovascular hospitalization.

2.4.5 Emergency Room Heart Failure Visit

Admission to an emergency room for less than 24 hours, where the primary reason for admission is ADHF otherwise meeting the same criteria defined for HF Hospitalization when the patient is not transferred to an inpatient unit or observation unit, but is discharged home.

2.4.6 Worsening Heart Failure Events Without Hospitalization or Qualifying ER Visit

Standardized definition from Heart Failure Collaboratory Academic Research Consortium (HFC-ARC)[88]. Broadly characterized as unscheduled outpatient medical contact associated with changes in heart failure therapy and requires:

- Documented new or worsening symptoms due to heart failure
- Objective evidence of new or worsening heart failure
- Treatment specifically for worsening heart failure
    - Significant augmentation in oral diuretic therapy (including at least a doubling of loop diuretic dose, initiation of loop diuretic therapy, initiation of combination diuretic therapy)
    - Initiation of intravenous diuretic (even a single dose)
    - Initiation of an intravenous vasoactive agent (catecholamine, phosphodieaterase-3 inhibitor, other vasopressor, vasodilator)
    - Mechanical fluid removal (ultrafiltration, hemofiltration, initiation of dialysis for what is felt to be a primary cardiac rather than renal cause)
- Documented response to treatment

2.4.7 Outpatient Intensification of Heart Failure Therapy

Outpatient intensification of HF therapy requires that the patient has worsening symptoms, signs or laboratory evidence of worsening heart failure and the dose of diuretics was increased and sustained for a month, or intravenous treatment given for HF, or a new drug was added for the treatment of worsening HF. This event category excludes patients meeting the definition of Outpatient Clinic Heart Failure Visit described in Section 2.4.6.

2.4.8 Heart Failure Endpoint Qualifying Events

All Hospitalizations and Emergency Room Visits lasting at least 6 hours as well as worsening HF event treated as an outpatient (including ER HF visits with duration of < 6 hours) as defined will be adjudicated by the CEC to determine if they qualify as Heart Failure Endpoint Events for inclusion in the Primary Effectiveness Endpoint analysis.

2.4.9 Technical Success

Technical success will be measured at exit from cath lab and is defined as alive, with successful access, delivery and retrieval of the transcatheter V-Wave delivery system, with deployment and correct positioning of the single intended device and no need for additional emergency surgery or reintervention related to either the device or the access procedure.

2.4.10 Device Success

Device success will be measured at 30 days and all post-procedural intervals and is defined as alive and stroke free, with original intended device in place and no additional surgical or interventional procedures related to access or the device and intended performance of the device with no device migration, embolization, detachment, fracture, hemolysis or endocarditis, and expected hemodynamic performance including patent device with Qp:Qs <1.5, and no detected para-device complications including device leak, erosion, systemic or pulmonary thromboembolization.

2.4.11 Procedural Success

Procedural success will be measured at 30 days and is defined as device success and no device or procedure related SAEs including life threatening bleeding (>4 units of packed red blood cells), acute kidney injury (stage 2 or 3, including renal replacement therapy), major vascular complications or tamponade requiring intervention, myocardial infarction or coronary ischemia requiring PCI or CABG, severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatment (e.g. ultrafiltration or hemodynamic assist devices including intraaortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for ≥ 48 hours).

2.4.12 Neurological Success

Neurological events will be classified according to Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative (NeuroARC). Events will be classified as CNS injury (Type 1) including ischemic stroke, with or without hemorrhagic conversion, along with other Type 1 subtypes, and neurological dysfunction without CNS injury (Type 3) including

TIA.

Clinical assessment will include a neurological consultation, assessment of the National Institutes of Health Stroke Scale, and assessment of neurological deficits and cognitive function according to institutional standards. Patients experiencing a neurological event will have an MRI or a head CT (if MRI is contraindicated) and will undergo transesophageal echocardiography (TEE) to evaluate cardiac origin, device patency and involvement in their neurological event.

2.4.13 Cost and Cost-Effectiveness Analyses

A prospective health economic evaluation in order to provide rigorous, prospective data with respect to the cost-effectiveness of the interatrial shunt procedure compared with standard medical therapy for U.S. patients in the trial from the time of randomization through a minimum of 1 and a maximum of 2 years of follow up (at which point some patients assigned to the control group may cross over to the shunt procedure). These data will include hospital billing data (UB-04 summary bills and itemized hospital bills) for all U.S. patients, which will be used, along with supplementary material from the case report forms, to determine the initial treatment costs. Follow-up costs will be assessed from the perspective of the U.S. healthcare system based on resource utilization data including follow-up hospitalizations, office visits, medications, etc. At the completion of the trial, these data will be used in conjunction with quality of life and utility data collected from the trial to develop a long-term Markov model in order to project patient-level survival, quality-adjusted life expectancy, and costs beyond the time frame of the trial in order to estimate the incremental cost-effectiveness ratio for the interatrial shunt procedure compared with standard medical therapy for the trial population. These analyses will be out of scope of the clinical data analyses covered by this SAP.

3.0 ANALYSIS SETS

The statistical analysis for the RELIEVE-HF Trial will be presented on the following analysis populations. Data for all subjects will be assessed to determine if subjects meet the criteria for in each analysis population prior to unblinding.

3.1 Roll-in populations:

Sites will first familiarize themselves with the V-Wave system by implanting the shunt in up to 2 Roll-in patients and follow them in an open-label (unblinded) manner. Implantation performance during Roll-in will be assessed during the implant by a Sponsor provided qualified Proctor. Roll-in patients will otherwise be followed and analyzed identically as Randomized patients, but their study data will be presented separately. The detailed information regarding any additional statistical analyses in roll-in patients, such as those related to shunt patency, is specified in a separate monitoring plan (Appendix 2).

3.2 Intention-to-Treat (ITT):

Subjects who were randomized to the Shunt Implant or Control study arms, analyzed according to their original assignment regardless of treatment received or crossovers. Subjects with missing baseline or follow-up data preventing evaluation of specific endpoints will be excluded from ITT analyses of that endpoint.

3.3 Per Protocol (PP):

Randomized subjects who met all initial and final inclusion/exclusion criteria, had no major protocol deviations which may have impacted study outcomes, were treated according to randomization (i.e. study device patients who underwent a V-Wave implant procedure, and control patients who did not undergo a V-Wave implant procedure) and who have available follow-up data for the endpoint being evaluated. The major protocol deviations leading to PP exclusion are: failure to obtain informed consent, randomization or enrollment error and inclusion/exclusion criteria violation.

3.4 Safety Population:

Randomized subjects who met the initial inclusion and exclusion criteria, signed an informed consent form and underwent any invasive procedure associated with evaluation of the final exclusion criteria.

The analysis data sets that will be used for each analysis are summarized in Table 1. Table 1:

Analyses and analysis sets

Endpoint	ITT Analysis Set	PP Analysis Set	Safety Analysis Set
Primary safety endpoint	X	X	
Primary effectiveness endpoint	X	X	
Secondary effectiveness endpoints	X	X	
Additional effectiveness endpoints	X	X	
Additional safety endpoints (AEs)			X
Demographics/baseline characteristics	X	X	X

4.0 GENERAL METHODOLOGY AND CONVENTIONS

Primary analysis will occur when the last patient enrolled completes 12 months of follow-up as defined in the Protocol. Patients will be followed for the primary data analysis for a minimum of the time of their 12-month follow-up and a maximum of the time of their 24 months follow-up from the time of randomization at the Study Intervention Procedure. Patients with less than 24 months of follow-up will complete randomized blinded follow-up when the last randomized patient has completed the 12-month visit. Patients reaching 24 months prior to the last enrolled patient reaching 12 months will be unblinded. Patients randomized to the Control group who still meet inclusion/exclusion criteria may have the opportunity to cross-over and receive a shunt implant when they complete their follow-up requirements, and data collected after crossover will be summarized and reported upon separately.

All implanted patients (Roll-Ins, Randomized to Treatment and Control patients that cross-over and receive the shunt) will be followed for a total of 5 years from the time of the Study Device implantation. Control group patients who do not cross-over to receive a shunt implant, will cease to be followed once unblinding has occurred.

4.1 Sample Size and Controlling for Multiplicity

4.1.1 Primary Safety Endpoint

The hypothesis for safety is:

H_o: $R \geq PG$

H_1: $R < PG$

where R is the percentage of Shunt group patients experiencing device-related Major Adverse Cardiovascular and Neurological Events (MACNE) during the first 30-days after randomization Assuming an alpha level of 0.025 (one-sided), a sample size of 200 evaluable Treatment group patients from the Randomized cohort would achieve a power of 87% to detect a difference between the expected safety endpoint rate of 5% and a Performance Goal of 11%. Primary safety endpoint analysis will be conducted in all patients implanted with the device using an intention to treat analysis including patients randomized to the Therapy arm regardless of whether the implantation procedure was successful.

4.1.2 Primary Effectiveness Endpoint

The null hypothesis of this test is that the components of the composite endpoint are not affected by treatment, and the alternative is that at least one demonstrates improvement in favor of the intervention. The assumptions for the effect size in the hierarchical components of the composite primary effectiveness endpoints in HFrEF and HFpEF are pre-specified and based on the best available external information.

Table 2. Six-Month Event Rates, One-Month Hazard Rates (in parentheses), Hazard Ratios (HR), and KCCQ Assumptions by Treatment Group and Ejection Fraction Subpopulation

	Reduced Ejection Fraction (HFrEF)			Preserved Ejection Fraction (HFpEF)		
Type of Event	**Control**	**Shunt**	**HR**	**Control**	**Shunt**	**HR**
Loss to Follow-up	**1.7%** (0.002927)	**1.7%** (0.002927)	---	**1.7%** (0.002927	**1.7%** (0.002927	---
Death	**5.1%** (0.008742)	**4.2%** (0.007080)	0.810	**3.6%** (0.006025)	**2.9%** (0.004926)	0.818
LVAD/Transplant	**1.6%** (0.002620)	**1.2%** (0.001941)	0.741	**0**	**0**	---
HFH1	**27.5%** (0.053379)	**20.7%** (0.038750)	0.726	**21.4%** (0.040101)	**11.5%** (0.020399)	0.509
HFH2	**30.1%** (0.059793)	**22.8%** (0.043171)	0.722	**23.5%** (0.044698)	**12.7%** (0.022583)	0.505
HFH3+	**32.9%** (0.066463)	**24.9%** (0.047712)	0.718	**25.7%** (0.049425)	**13.8%** (0.024796)	0.502
KCCQ(*)	**8(22)**	**16(22)**	---	**11(26)**	**22(26)**	---

* Mean (SD) absolute change from baseline at time of evaluation.

Primary effectiveness endpoint analysis will be performed on a combined HFrEF and HFpEF population in the ITT population. The difference in the primary effectiveness endpoint test statistics between the HFrEF and HFpEF subpopulations will be examined using a Z-test.. It is estimated that approximately 50% of the total study population will be HFpEF patients. The rank of a subject relative to other subjects is based on consideration of the following factors: level of an observed event in above hierarchical list, the time of the event(s) after randomization, the number of events, the observed time in study, and KCCQ overall score. Based on 10,000 simulated trials, a study of 400 patients (200 per arm) would achieve an expected power of 90% to detect a sum of ranks greater than zero in the treatment group, with a one-sided alpha of 0.025.

Based on above power calculations, the total sample size for RELIEVE-HF trial will be 400 to ensure enough power for both primary safety and effectiveness endpoints.

4.2 Randomization and Blinding

The study is anticipated to include up to 120 centers in the United States and other countries with a majority of sites located in the US (Protocol, Section 4.1). If the recommendation from the interim analysis results in an increase in the original maximum total sample size of 600 subjects, then approval

may be sought from the FDA for increase up to 150 sites with the majority of sites located in the US. At each site, treatment assignment will be allocated using randomly selected blocks of size 2 and 4. Patient randomization will be via an automated interactive system, which will require entry of the site's ID, and the patient's participant number. The system will have knowledge of the site and the patient's LVEF as determined by the Echo Core Lab for stratification purposes. After data are verified, a randomization code will be given. The randomization assignment will be kept by the Implanter-Investigator or unblinded designate and kept separate from other study documents until the patient has been unblinded (Protocol, Section 6.3.1).

The trial is a double-blind study and comprehensive effort will be made to maintain the blinding so as not to compromise the integrity of the trial. Trial statisticians, except a designated unblinded statistician, will not have access to data that combines outcomes with treatment assignment prior to performing the final analysis. The designated unblinded statistician will act as a liaison to the DSMB and have responsibility for the planned interim analysis. No sponsor personnel or other trial statisticians will have access to outcome data summarized by treatment until the completion of the blinded phase of the trial. Efforts will also be made to blind the Clinical Events Committee (CEC) to the subject's treatment assignment, unless unblinding is required for event adjudication on a case-by-case basis.

4.3 Interim Analyses and Summaries

A single, midpoint interim analysis with adaptive sample size re-estimation is planned at the point when approximately 50% of the study population have completed approximately a minimum of 6 months of follow-up, but no later than 3 months prior to completion of enrollment of the original 400 subjects.
This interim analysis would consider only data collected for the composite primary effectiveness endpoint and be based on validation of the original planning assumptions for the components of the endpoint. The interim analysis would be performed by an independent third party, who would communicate results only to the study DSMB, who will make a recommendation to the sponsor about possible changes to the study sample size.

The interim analysis will be limited to data collected in an identified study cohort (e.g., the first 200 evaluable subjects). Using the analysis method specified for evaluation of the primary effectiveness endpoint (Finkelstein-Schoenfeld), the unconditional power to meet the endpoint at the conclusion of the study will be re-estimated. At that time a decision will be taken to possibly increase the sample size. This decision will utilize maximum likelihood estimates of the design parameters displayed in Table 2.
The sample size of the trial will be re-computed by assuming that the updated maximum likelihood estimates are the true design parameters. To be specific, the entire trial will be redesigned with these updated design parameters so as to obtain the new sample size required to achieve 90% power. If the new sample size is less than 400, the trial will proceed as planned initially, with 400 subjects. If, however, the new sample size is greater than 400, the sample size will be increased appropriately, up to

a maximum of 1000 subjects. Sequential design by Cui, Huang and Wang (Modification of Sample Size in Group Sequential Trials, Biometrics, 55: 853-857, 1999) will be used to combine the separable results during the first phase (prior to interim analysis) and the second phase (post-interim analysis) to control the type I error.

Let m and n denote the pre-specified sample sizes for the experimental and control groups, respectively. (Here, for example, m = n = 200 for the original total sample size of 400.) Suppose the pre-specified plan is to use the data from the first m_1 subjects in the experimental group and the first n_1 subjects in the control group for the interim analysis. Let $m_2 = m - m_1$ and $n_2 = n - n_1$ denote the pre-specified incremental sample sizes for the second stage in the absence of a sample size increase. (Here m1 = n1 = m2 = n2 = 100). If the sample size is increased at the interim analysis, let m* and n* be the new total sample sizes for the experimental and control groups. Let T_1 denote the F-S statistic for the (m1; n1) subjects in the first cohort evaluated at the time of the final analysis. Similarly let T_2 denote the F-S statistic for the (m_2; n_2) subjects in the second cohort if there is no sample size change and T^*_2 denote the F-S statistic for the (m^*_2 , n^*_2) subjects in the second cohort if the sample size is increased. The CHW statistic is a weighted sum of the two incremental F-S statistics of the form:

$$Tchw = \begin{cases} w1\left(\frac{T1}{\sqrt{var\ (T1)}}\right) + w2\left(\frac{T2}{\sqrt{var\ (T2)}}\right) \\ w1\left(\frac{T1}{\sqrt{var\ (T1)}}\right) + w2\left(\frac{T^*2}{\sqrt{var\ (T^*2)}}\right) \end{cases}$$

Where the bottom equation corresponds to test statistics when there is sample size re-assessment and weights are pre-specified as:

$$w1 = \sqrt{\frac{m1+n1}{m+n}} \quad \text{and} \quad w2 = \sqrt{\frac{m2+n2}{m+n}}$$

The weights w1 and w2 remain the same whether the sample sizes are increased from (m; n) to (m*; n*). This is necessary in order to prevent inflation of the type-1 error, as shown originally by Cui, Hung and Wang (1999). The null hypothesis of no treatment effect can be rejected at the one-sided level-of significance if Tchw ≥ z_α. In the absence of same size re-assessment, Tchw is asymptotically equivalent to the F-S statistic T evaluated from the complete dataset of m subjects on the experimental arm and n subjects on the control arm as defined by $T = \sum^{N} D_i U_{i=1}$ without any weighting.

Note: Because of COVID-19 issues, it is expected that the adaptive sample size re-estimation will increase the needed sample size beyond the original 400 subjects. In response, the pre-specified weights will be based on a total sample size of 600 subjects (the original upper limit after adaptive re- estimation, since revised to a maximum of 1000). The pre-specified weights, as required by the Cui, Huang and Wang method, used during the interim analysis and in the final analysis for the study will be *w1* = $(200/600)^{1/2}$ and *w2* = $(400/600)^{1/2}$ for the two stages, instead of equal weighting.

The following guidelines are provided to the DSMB for making a recommendation (zone and associated recommended action to be taken) based on the estimated unconditional power:

Table.3 DSMB recommendation guidelines based on interim analysis

Interim Analysis Results	DSMB Recommendation
P400 ≥ 90%	Zone 1: Continue trial with no expansion
P400 < 90% and P1000 ≥ 90%, or P1000 ≥ 50% and P1000 – P400 ≥ 10%	Zone 2: Expand trial by 1-600 subjects to increase power, up to 90% design target
P400 > 20% and none of the above conditions apply	Zone 3: Continue trial with no expansion (futility for expansion)
P400 ≤ 20%	Zone 4: Consider early termination for trial (futility for treatment effect)
Definitions: P400/P1000 – statistical power associated with 400/1000 evaluable subjects	

In making their recommendation, the DSMB will not reveal specific details of the FS component event rates or estimated power achieved and will also consider all available safety information collected to date. The DSMB may consider the results from both the primary and supplemental analyses of the primary effectiveness endpoint in their decision making. The supplemental analysis is described in Section 5.2.2.1 below. The DSMB recommendation will be made to Executive Committee for the trial, who will review the recommendation and make any necessary decisions about future actions to be taken.

4.4 General Method

All data collected will be summarized overall and by randomized treatment arms. Descriptive statistics of continuous variables will include mean, standard deviation, median, quartiles, range, and sample size. Mean differences in continuous variables between the randomized treatment arms, where appropriate, will be summarized with the estimated mean difference of the two means, 95% confidence intervals for the difference between the means, and p-values based on a t-test. The distributions within each group will be tested for normality using the Shapiro-Wilks test and if normality cannot be assumed then a Wilcoxon rank-sum test for medians will be performed. The confidence interval for the difference of two means will be calculated under the assumption of unequal variances.

For categorical variables, descriptive statistics will include count, percentage, and sample size. Categorical data will be presented as n/N (%), and percentages will be rounded and reported to a single decimal point (xx.x %). Unless otherwise noted, subjects with missing data will be excluded from the denominator. Differences between the two randomized treatment arms, where specified, will be

summarized with the difference in percentages, the exact binomial (Clopper Pearson) 95% confidence interval for the difference of two percentages, and a p-value based on Fisher's exact test.

Survival analysis techniques will be used to analyze the time-to-event variables that occur at or after 30 days of follow-up. Time to event analysis will be performed for each time point separately (i.e. up to 30 days, 6-months (180 days), 1 year (365 days), 2 years (730 days), 3 years (1095 days), 4 years (1460 days), and 5 years (1825 days)) and summarized using the Kaplan-Meier estimated event rates and number of events. The log-rank test will be used for comparing treatments. Hazard ratios and the associated two-sided confidence intervals (Wald's CI) will be estimated by Cox proportional hazards model, including treatment as a covariate.

All time-to-event analyses will be performed with time defined from date of randomization to first occurrence of an event. Subjects without events will be censored at their early withdrawal date or the last known event-free time point. If this event-free time point occurs after the analysis time point, the days to event variable will be set equal to the analysis time point so that the patient will be included in the analysis (e.g. if the last data point was collected at 1 year and 2 weeks post-procedure, for the 1-year analysis, this subject will be censored at exactly 1 year (365 days)). When analyzing composite endpoints, time is measured from randomization to the first event (days).

Unless otherwise noted, all statistical tests will be two-sided and performed at the 5% significance level, when applicable. All statistical analyses will be performed using SAS 9.4 or higher or R-Studio and software scripts necessary for implementing the evaluation of the composite primary effectiveness endpoint in the above software packages.

4.5 Methods to Manage Missing Data

Reasonable efforts will be made to obtain complete data for all patients; however, missing observations may occur. The reasons for missing data will be reported (e.g., patient is deceased, lost to follow up, withdrew consent, missed follow-up visit, etc.).

All secondary endpoints analyses will be performed using all available data in the ITT and Per Protocol populations.

Missing Safety data:

Completely or partially missing AE start dates will be imputed with the earliest possible date since enrollment/randomization, i.e., the randomization date, if date is completely missing, the first of the month if day is missing (provided that the first of the month is after enrollment), etc.

4.6 Definition and Use of Visit Windows in Reporting

Following the intervention procedure, patients will be followed up to 5 years. The scheduled visits and windows in chronological order can be found at below table:

Table 4. Study visit schedule and follow-up windows

Scheduled visits	Windows
2-week telephone follow up	± 7 Days
One month in-clinic follow up	± 7 Days
3 months in-clinic follow up	± 14 Days
6 months in-clinic follow up	± 30 Days
9 months telephonic follow up	± 30 Days
12 months in-clinic follow up	± 30 Days
15 months telephonic follow up	± 30 Days
18 months in-clinic follow up	± 30 Days
21 months telephonic follow up	± 30 Days
24 months in-clinic follow up	± 30 Days
Close-out telephonic visit	± 30 Days
Follow-up schedule for crossed over control	± 30 Days
2,3,4 and 5 years Post-unblinding annual in-clinic follow up	± 60 Days

Study Day will be calculated from the date of randomization (Day 1 is the day of randomization), and will be used to display the start/stop day of events in the data listings. Study day will be calculated as: Study Day = (date of event – randomization date) + 1.

5.0 ANALYSES AND SUMMARIES

5.1 Baseline and Other Summaries and Analyses

Descriptive statistics will be used to summarize all subject baseline and outcome data collected during the study. Continuous variables will be summarized using means, standard deviations, medians, and ranges and categorical variables will be summarized in frequency distributions as described in the general methodology section.

5.1.1 Study Conduct and Subject Disposition

The frequency and percentage of subjects enrolled by site will be provided as a table. A tabulation of patient disposition will be presented overall and by treatment arm, and will include the number of subjects screened, enrolled (randomized), and discontinued, with reasons for discontinuations (e.g., subject died, withdrew consent, was lost to follow-up, etc.) as documented on the case report form.

Adherence to study inclusion/exclusion criteria and protocol deviations as documented on the case report form will be descriptively tabulated. A by-subject listing will include the reference data for these tables.

Compliance to 2-weeks, 30-day, 3, 6, 9, 15, 18, 21-months, and 1, 2, 3, 4, and 5-year follow-up visit schedules will be summarized for all subjects in the ITT population and PP population by site. Subjects with insufficient follow-up due to restrictions posed by the COVID-19 pandemic will be denoted as "COVID-19 affected" subjects in the compliance listing. [FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (updated April 16, 2020) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials- medical-products-during-covid-19-pandemic]

5.1.2 Baseline Summaries

Baseline patient characteristics will be presented descriptively and will be compared between two treatment arms using the methodology described in Section 4.3. Baseline measurements consist of subject demographics, heart failure history, cardiovascular disease history, other significant medical history, vital signs, and physical examination.

5.1.3 Procedural Characteristics

Procedural characteristics will be presented descriptively and will be compared between two treatment arms using the methodology described in Section 4.3. Procedural measurements consist of right heart catheterization data, procedural measurement and procedure related medications.

5.2 Primary Endpoints

The primary analysis will be performed when the last enrolled patient has been followed for a minimum of 12 months from randomization. The duration of follow-up evaluated by the primary effectiveness endpoint will range from a minimum of 12 to a maximum of 24 months.

5.2.1 Primary Safety Endpoint

The Primary Safety Endpoint is the percentage of Treatment Group patients experiencing any device related Major Adverse Cardiovascular and Neurological Events (MACNE) during the first 30-days after randomization.

5.2.1.1 Primary Analysis

Statistically, the hypothesis can be stated as:

H_o: $R \geq PG$ H_1: $R < PG$

Where R is the expected rate of observed Device/Procedure-related MACNE and PG =11%. The proportion of subjects with MACNE events will be tested against a Performance Goal of 11% with an exact binomial test, with a one-sided significance level of 0.025.

For the primary safety endpoint, only subjects who experience a MACNE event by the end of the 30-day visit window or whose last known event free day on the trial is at least 23 days (i.e., beginning of the 30- day visit window) from randomization and who meet the applicable analysis population will be included in the analysis. A subject will be considered a failure for MACNE if the subject dies or experiences stroke, systemic embolism, need for open cardiac surgery or major endovascular surgical repair. The safety analysis population will include any patients for whom the device implant was attempted, regardless of whether the implantation was successful.

5.2.1.2 Sensitivity/Robustness Analysis

To support the interpretation of the primary safety analysis, a tipping point analysis will be performed as a sensitivity analysis to assess the impact of missing 30-day MACNE from subjects with insufficient 30- day follow-up. Tipping point analysis involves performing the primary repeatedly for every possible scenario involving the missing outcome data. The analysis will include the worst-case scenario (i.e., all missing outcome data are assumed to be MACNE events) as the most extreme case.

5.2.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint will be evaluated with a sum of ranks (T_{Shunt}) test statistic in the Shunt group using the method of Finkelstein and Schoenfeld, based on adjudicated endpoint events when last enrolled patients has minimum 12month follow-up since randomization. In addition, the unmatched win-ratio approach will be used to evaluate the primary effectiveness endpoint. In addition, the unmatched win-ratio approach will be used to evaluate the primary effectiveness endpoint. The win- ratio will be calculated as the total number of shunt arm patient wins divided by the number of Shunt arm loses (win-ratio) and 95% confidence interval after all the pairwise comparisons. All subjects have a scheduled minimum follow-up period of 12 months, and all data collected through 24 months of follow- up will be included in the final analyses.

5.2.2.1 Primary Analysis

The null hypothesis of this test is that the components of the composite endpoint are not affected by treatment, and the alternative is that at least one demonstrates improvement in favor of the intervention. The Finkelstein-Schoenfeld statistic is evaluated by comparing every subject *i* to every other subject j in the dataset and assigning a rank U_{ij} in accordance with the following hierarchical

ranking algorithm across the total evaluable study population (Shunt and Control groups).

1. Death (all-cause)
2. Heart transplant or LVAD implant
3. HF hospitalizations (including qualifying ER visits ≥6 hours)
4. Worsening heart failure treated as an outpatient (including ER HF visits < 6 hours)
5. KCCQ Overall Score (KCCQ measured as absolute point change from baseline), with at least a 5-point difference viewed as significant

At each level, the following comparisons will be done:

1. Death

First, an attempt is made to compare the two subjects based on their Death event.

a. If subject *i* died and subject *j* did not die, we check whether subject j was followed at least as long as the death time of subject i, in which case U_{ij} = -1. But if subject j was followed for less than the death time of subject *i*, the ranking cannot be based on Death events and we proceed to ranking based on LVAD/Transplant events.
b. If the opposite is true, where subject j died and subject i survived at least as long as the death time of subject *j*, U_{ij} = 1. But if subject i was followed for less than the death time of subject *j*, the ranking cannot be based on Death events and we proceed to ranking based on LVAD/Transplant events.
c. In case both subjects have a Death event, where subject i died at least 7 days after subject j, U_{ij} = 1. If the opposite is true and subject j died at least 7 days after subject *i*, U_{ij} = -1. If both subjects died within 7 days of each other, the ranking can not be assigned based on Death events and we proceed to ranking based on LVAD/Transplant events.

2. LVAD/Transplant events:

In cases where the two subjects cannot be compared and ranked based on their Death events, LVAD/Transplant events are used next to compare them and assign ranks. The comparison and ranking of two subjects based on LVAD/Transplant events is exactly the same as for Death events.

a. If subject *i* had an LVAD/Transplant event and subject j did not, we check whether subject *j* was followed at least as long as the time that the LVAD/Transplant event occurred for subject *i*, in which case U_{ij} = -1. But if subject j was followed for less than the LVAD/Transplant time of subject i, the ranking cannot be based on

LVAD/Transplant events and we proceed to ranking based on HF hospitalization events.

b. If the opposite is true, where subject *j* had an LVAD/Transplant event and subject *i* did not, we check whether subject i was followed at least as long as the time that the LVAD/Transplant event occurred for subject j, in which case U_{ij} = 1. But if subject i was followed for less than the LVAD/Transplant time of subject *j*, the ranking cannot be based on LVAD/Transplant events and we proceed to ranking based on HF hospitalization events.

c. In cases where both subjects have had the LVAD/Transplant event, if subject *i* had the LVAD/Transplant event at least 7 days after subject j, then U_{ij} = 1, or if subject j had the LVAD/Transplant event at least 7 days after subject *i*, then assign U_{ij} = -1. If both subjects had the LVAD/Transplant event within 7 days interval, the ranking cannot be assigned based on LVAD/Transplant event and we proceed to ranking based on HF hospitalization events.

3. Heart Failure Hospitalization (HFH):

In cases where the two subjects cannot be compared and ranked based on their Death or LVAD/Transplant events, HFH events are used next to compare them and assign ranks.

a. The two subjects are first compared on the basis of the number of HFH events, where the subject with the fewer HFH events has the better rank. This comparison is made over the time period of the subject with the shorter follow-up time.

b. In case the two subjects have the same number of HFH events, the first HFH times are compared and if subject *i* 's first HFH event time is 7 days earlier than that of subject *j*, we assign U_{ij} = -1. If the opposite is true so that subject j's first HFH event time is 7 days earlier than that of subject i, we assign U_{ij} = 1.

c. When both subjects have the same number of HFH events and the first HFH event times for the two subjects are within a 7-day interval, ranking cannot be assigned based on HFH event times and we proceed with the investigation of their worsening heart failure events .

d. In all other cases where the two subjects cannot be compared (such as if one subject has been followed without any events for less time than the first HFH time of the other) we proceed with the investigation of their worsening heart failure events.

4. Worsening Heart Failure Events without Hospitalization or Qualifying ER Visit

If the HFH level of the hierarchical ranking is reached and ranking between subjects cannot be assigned, then the numbers of Worsening Events will be compared between subjects. The

subject with fewer Worsening Events, over the longest time period in common between two subjects, will have the better rank. If the subjects have the same number of Worsening Events, then the ranking procedure will proceed to Step 5.

5. KCCQ Overall Score

If x_i is subject to i's change from baseline and x_j is subject to j's change from baseline in KCCQ overall score, then:

a) If $x_i - x_j \geq 5$, $U_{ij} = 1$
b) If $x_i - x_j \leq -5$, $U_{ij} = -1$
c) Otherwise, $U_{ij} = 0$

Blinded research staff will perform in-clinic follow-up visits at 1, 3, 6, 12, 18, and 24 months, including the evaluation of KCCQ (Protocol, Section 6.3.2). For purposes of hierarchical ranking, the last KCCQ values for the longest follow-up interval in common between two subjects being compared will be used, consistent with the hierarchical ranking procedure for other primary endpoint components.

Supplemental Primary Analysis

The above analysis of the primary effectiveness endpoint will be performed without the component of Worsening Heart Failure, as a supplemental analysis.

Test Statistic

Suppose m subjects are randomized to the Shunt arm, n subjects are randomized to the control arm, and N = m + n is the total sample size. In the RELIEVE-HF trial, m=n. Each subject will be assigned a score $U_i = \sum_{i=1(j\neq i)}^{N} U_{ij}$ based on the above algorithm. Let D_i = 1 if subject *i* is randomized to receive the VWAVE shunt device, the F-S statistic can be written as

$$T = \sum_{i=1}^{N} D_i U_i$$

The statistic T is asymptotically normal with mean E(T) =2mn(θ – ½) , where θ is the probability that a random subject *i* in the treatment group has a better outcome than a random subject *j* in the control group. The null hypothesis of no treatment effect with respect to death, LVAD, HFH or KCCQ is thus equivalent to H_0: θ = ½. Under H_0 the variance of T is $\text{var}(T) = \frac{mn}{N(N-1)} \sum_{1}^{N} U_i^2$ (Equation 1), which reduced in the absence of ties to $\text{var}(T) = \frac{mn(N+1)}{3}$ (Equation 2).

As is generally the case for normal statistics derived from independent multinomial distributions, under local alternatives (values of θ approaching ½) one may use the null variance to standardize the distribution of T. When source data are available, we shall compute the variance of T by Equation 1.
Otherwise we shall use Equation 2 to estimate the variance of T.

For clarification, heart transplant and LVAD implant are considered terminal endpoints from an effectiveness analysis standpoint and will be censored for HF hospitalizations and KCCQ after the date of admission that results in heart transplant or LVAD placement. The hypothesis will be tested by comparing the test statistic (T_{Shunt} / $\sqrt{var(T)}$) to the normal distribution, with a one-sided significance level of 0.025.

In additional to the F-S statistics, the effect size for primary effectiveness endpoint will be calculated as

$$R_W = \frac{N_W}{N_L}$$

where N_W equals the number of Shunt wins and N_L equals the number of Shunt losses. The standard error is estimated by assuming the estimated standard error (s) will match the theoretical standard error z. That is, $\frac{\log(R_W)}{s} = z$. We can solve this equation to compute the standard error as

$s = \log(R_W) / z$, the standardized normal deviates. An approximate 95% confidence intervals will be estimated by adding and subtracting s x 1.96 to $\log(R_W)$ and exponentiating both results.

The WIN ratio (R_W) the end of the trial will be estimated in a manner analogous to that of the FS statistic for the primary effectiveness endpoint described above. The effect size will use the same pre-specified weights for combing (R_W) in the two phases (interim and post-interim analysis cohorts), with the sum of estimated variances used to construct the associated estimate of the 95% confidence interval.

5.2.2.2 Sensitivity/Robustness Analysis

Multiple imputation methods will be used in a sensitivity analysis to address the impact of any missing data for the primary effectiveness endpoint outcome. The ITT population is the primary analysis population for the primary effectiveness endpoint, with supportive analyses in the PP population. As a sensitivity analysis, the standard error for the win-ratios will also be estimated from 10,000 bootstrapped samples of the data. These covariates will be used for multiple imputation purposes:

- Randomized treatment
- Stratification factor of HFrEF and HFpEF
- Ischemic vs. non-ischemic cardiomyopathy
- Sex

- Age
- eGFR

5.3 Secondary Endpoints

If the primary effectiveness endpoint is met, then the difference between treatment groups will be hierarchically tested for the following secondary effectiveness endpoints in the order shown below. The same significance level (one-sided, alpha = 0.025) used for the primary effectiveness endpoint will be applied at each step in the hierarchical testing.

Secondary endpoints will be analyzed when the last subject completes 12 months of follow-up. All available follow-up through 24 months at the time of data cut-off will be included in the analysis. Subjects who die or who receive an LVAD or a heart transplant will be censored on the date of that event. Subjects who withdraw from the trial without an endpoint event will be censored on the date of withdrawal.

The ITT population is the primary analysis population for these secondary endpoints, with supportive analyses performed in the PP population.

Where indicated, the analyses of secondary endpoints will be covariate adjusted. The list of pre- specified baseline covariates will include:

- Randomized treatment
- Stratification factor of HFrEF and HFpEF
- Ischemic vs. non-ischemic cardiomyopathy
- Sex
- Age
- eGFR

1. KCCQ changes from Baseline to 12 months

We will compare the KCCQ changes from baseline to 12 months between two treatment arms.

Statistical Analysis:

$$H_o: \mu_{Shunt} \leq \mu_{Control} \quad H_1: \mu_{Shunt} > \mu_{Control}$$

Where μ is the absolute change in KCCQ scores from baseline to 12 months, adjusted in the analysis for

the baseline KCCQ value in each group. We will use an ANCOVA to test if the difference in the mean changes from baseline to 12 months is higher in the Shunt arm compared to the Control arm.

2. Heart failure hospitalization adjusted for all-cause mortality through 24 months.

If the difference in the mean percentage changes in KCCQ from baseline to 12 months is found to be significantly greater in the Shunt arm compared to the Control arm, we will then compare the rate ratio (RR) of HFH in the Shunt vs. Control groups accounting for all-cause mortality risk.

Statistical Analysis:

H_o: $RR_{Shunt\ vs\ Control} \geq 1$ H_1:
$RR_{Shunt\ vs\ Control} < 1$

A semi-parametric joint model will be use that specifies the distributions for recurrent HFH and all-cause mortality with a common frailty term to induce an association between the two distributions. The joint frailty method will be used to model the recurrent hospitalization event and estimate the RR, where RR = Hazard Ratio of Shunt vs. Control = e^{β} where β is the regression coefficient of the recurrent HF hospitalization in the joint frailty model.

See Appendix 3 for additional details on the joint frailty analysis model.

3. Time to first death, LVAD/Transplant, or heart failure hospitalization event at 12 months

If the null hypothesis for heart failure hospitalization adjusted for all-cause mortality is rejected, we will then proceed with the time-to-first event analysis of the composite endpoint of death, LVAD/transplant or heart failure hospitalization.

Statistical Analysis:

H_o: $HR_{Shunt\ vs\ Control} \geq 1$ H_1:
$HR_{Shunt\ vs\ Control} < 1$

We will use the Cox regression with the pre-specified covariates to analyze the composite endpoint and to estimate the hazard ratio (HR) associated with the hazard rates for the Shunt vs. Control. The above analysis without covariate adjustment will be performed as a supportive analysis. See Appendix 4.

4. Time to death or first heart failure hospitalization at 12 months

If the null hypothesis for all-cause mortality, LVAD/transplant and heart failure hospitalization is

rejected, we will then proceed with time-to-event analyses of death or first heart failure hospitalization:

Statistical Analysis:

H_o: $HR_{Shunt\ vs\ Control} \geq 1$ H_1:
$HR_{Shunt\ vs\ Control} < 1$

We will use the Cox regression with the pre-specified covariates to analyze the composite endpoint and to estimate the hazard ratio (HR) associated with the hazard rates for the Shunt vs. Control. The above analysis without covariate adjustment will be performed as a supportive analysis. See Appendix 4.

5. Cumulative heart failure hospitalizations at study duration through 24 months

If the null hypothesis for time to death or first heart failure hospitalization is rejected, we will compare the cumulative heart failure hospitalizations.

Statistical Analysis:

H_o: $F_{Shunt} - F_{Control} \leq 0$ for some n H_1:
$F_{Shunt} - F_{Control} > 0$ for some n

Where F is the cumulative distribution function (Nelson-Aalen estimate) for the occurrence of heart failure hospitalization and n is the number of heart failure hospitalizations for each arm. We will use non-parametric Kolmogorov-Smirnov (4) test to compare of distribution of cumulative heart failure hospitalization events

6. Time to first heart failure hospitalization at 12 months

If the null hypothesis for cumulative heart failure hospitalizations is rejected, we will then proceed with time-to-event analyses of first heart failure hospitalization.

Statistical Analysis:

H_o: $HR_{Shunt\ vs\ Control} \geq 1$ H_1:
$HR_{Shunt\ vs\ Control} < 1$

We will use the Cox regression with the pre-specified covariates to analyze the time-to-first heart failure rehospitalization and to estimate the hazard ratio (HR) associated with the hazard rates for the Shunt vs. Control. The above analysis without covariate adjustment will be performed as a supportive analysis.
See Appendix 4.

7. Primary Effectiveness Endpoint including mortality, LVAD/Transplant, HF Hospitalizations, and

Worsening Heart Failure treated as an outpatient, but without KCCQ

If the null hypothesis for time to first heart failure hospitalization is rejected, we will then proceed with testing the modified primary effectiveness endpoint without KCCQ.

Statistical Analysis:
We will analyze modified primary effectiveness endpoint without KCCQ using the same methodology specified in the section 5.2.2.1.

8. If the null hypothesis for Secondary Endpoint 7 above is rejected, we will then proceed with evaluating the 6MWT changes from Baseline to 12 months.

Statistical Analysis:

$$H_o: \mu_{Shunt} \leq \mu_{Control} \quad H_1: \mu_{Shunt} > \mu_{Control}$$

Where μ is the percentage change in 6MWT measurement from baseline to 12 months, adjusted in the analysis for the baseline value in 6MWT in each group. We will use an ANCOVA adjusting for the baseline value to test if the difference in the mean percentage changes from baseline to 12 months is higher in the Shunt arm compared to the Control arm. Note that if a subject cannot walk during follow- up because of a cardiac limitation, his/her follow-up 6MWT will be set to 0.

5.4 Additional Safety Endpoints

The following additional safety data will be evaluated. There are no tests of hypotheses associated with these analyses.

• Comparison of Major Adverse Cardiovascular and Neurological Events (MACNE) and Bleeding Academic Research Consortium (BARC) types 3 and 5 bleeding at 30 days

This endpoint will be evaluated by estimating the rates of MACNE and BARC events at 30 days, togethers with the associated exact, 95% confidence intervals.

• Percentage of Treatment Group patients with device-related MACNE at 12 months.

This endpoint will be evaluated by estimating the MACNE rate at 12 months, together with its exact, 95% confidence intervals and a Kaplan-Meier analysis of the time-to-events.

5.5 Subgroup Analyses

The consistency of the primary safety endpoint and primary effectiveness endpoint in the ITT and PP populations will be examined in subgroups defined by age (median), sex, BMI (median), diabetes, hypertension, ischemic vs. non-ischemic cardiomyopathy, LVEF stratification factor of HFrEF and HFpEF, baseline NYHA (III vs. IV), baseline BNP/NT-proBNP (median), eGFR (median), baseline 6MWT (median), baseline KCCQ score (median), shunt encapsulation process (two provider sources), US vs. non-US clinical sites, prior COVID-19 infection (yes/no), and by sites based on number of enrolled subjects. If any non-patent shunts are observed, additional subgroup analyses will be conducted to compare safety and effectiveness endpoints between patent and non-patent groups in shunt implanted patients. No formal hypothesis testing for subgroup analyses will be performed. The subgroup analyses described below will be performed for descriptive purposes only. For each subgroup, a test for the difference in the primary safety and effectiveness endpoints will be performed to assess whether there is an interaction between treatment effect and subgroup.

For each of the dichotomous subgroups identified above, the following analyses will be performed:

Primary Safety Endpoint: The primary safety endpoint of MACNE rates at 30 days will be evaluated in each subgroup and compared using a Fisher's Exact test.

Primary Effectiveness Endpoint: The relative treatment effects for the primary effectiveness endpoint within each subgroup will be compared using Z-test based on the Finkelstein- Schoenfeld estimates of the test statistic and its variance in each subgroup.

5.5.1 Impact of COVID-19

To examine the potential impact of COVID-19 on the components of the primary effectiveness endpoint, data for these outcomes will be summarized by annual periods during the study, beginning in 2018 through the end of the study. To enable comparisons with the annual period believed to be of highest COVID impact (March 1, 2020 – February 28, 2021), that period and annual periods before and after defined by those monthly dates will be used.

Event rates for mortality, LVAD/Transplant, and heart failure hospitalizations will be descriptively summarized for the Treatment and Control group using Kaplan-Meier analyses by those defined annual periods, with the difference between groups within each year evaluated using log rank test statistics.

Changes from baseline for KCCQ will be descriptively summarized by treatment group by those annual periods, with differences between treatment group evaluated using Student's t-tests.

5.6 Multicenter Studies

For the primary safety endpoint, the assessment of site poolability will be performed using a logistic regression model including site as a random intercept to test whether sites have a significant variability in the primary safety event rates.. If the test is significant at alpha=0.15, then it will be concluded that evidence of heterogeneity by site may exist. A significant result will require further inspection of the by- site results to assess the reasons for site differences and if poolability is appropriate. Sites with less than 10 subjects will be pooled according to study region as defined previously.

The above analysis will also be performed including only sites with a minimum of 10 enrolled subjects.

The consistency of the primary effectiveness endpoint across sites will be examined by summarizing the distribution of the within-site Finkelstein estimates of the test statistic and its variance.

5.7 Safety Summaries and Analyses

5.7.1 Adverse Events

All adverse events collected will be coded using the most recent version of MedDRA to system organ class (SOC) and preferred term (PT) and summarized based on the Safety Population. The following adverse event summaries will be presented for all subjects and by treatment arms:

- Frequency (number and percent) of subjects with adverse events (AEs) by MedDRA system organ class and preferred term
- Frequency (number and percent) of subjects with serious adverse events (SAEs) by MedDRA system organ class and preferred term
- Frequency (number and percent) of subjects with adverse device effects and serious adverse device effects by MedDRA system organ class and preferred term
- Frequency (number and percent) of subjects with unanticipated adverse device effects (UADEs) by MedDRA system organ class and preferred term
- Frequency (number and percent) of subjects with AE or SAE, by relationship to the study intervention/device. Relationship information will be based on CEC adjudicated data, when available.

In addition, subject data listings of deaths, adverse events and serious adverse events, with their relationship to study device/intervention, AE onset date, outcome, and date of resolution (if resolved), will be presented in the data listings.

5.7.2 Device Deficiencies, Malfunctions

Device Deficiency: A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Device deficiencies include malfunctions, use errors, and inadequate labeling.

Malfunction: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or protocol.

Use Error: Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

The following summaries of device deficiencies will be presented, and summary statistics will follow the same analysis as described in the general methods in section 4.3.

All device deficiencies, malfunctions, use errors, and any (serious) adverse events associated with device malfunctions/deficiencies/use errors, as documented in the case report form, will be summarized descriptively by frequency (number and percentage of subjects) in the Safety Population for all subjects and by treatment arms.

A supportive subject data listing of Listings of device deficiencies/malfunction/user errors will be presented in the data listings.

5.7.3 Vital signs, physical examination data

Vital signs, including weight and pulse oximetry data will be collected at each in-clinic visits and summarized overall and by randomized treatment arms using rules specified at general methodology.

5.7.4 NYHA functional class

NYHA Functional Class by blinded assessor by will be collected at baseline screening, 1, 3, 6, 12, 18 and 24 months and annual 3-5 follow-up and summarized overall and by randomized treatment arm using the rules specified in the general methodology.

5.7.5 ECHO Core Lab Data

Transthoracic echo (TTE) measurement will be recorded in baseline screening, 1, 6, 12 and 24 months and annual 3-5 follow-up. Once unblinded, shunted patients will have transesophageal echo (TEE) if no shunt flow seen on prior TTE. And Roll-in patients will have routine follow-up TEE/ICE (intra cardiac echo).

5.7.6 ECG Data

An ECG will be performed at screening/baseline visit. Any abnormal findings will be recorded in the electronic case report forms and summarized overall and by randomized treatment arm using the rules specified in the general methodology.

5.7.7 Laboratory Data

Clinical laboratory measurements will be collected at baseline screening, final screening, post enrollment prior to discharge, and at, 1, 6, 12, and 24 month in-clinic visits. All laboratory parameters will be presented descriptively by applicable visit for all subjects in the ITT population and by randomized treatment arms. The peak lab measurement will be presented if measurements are collected multiple times in one in-clinic visit. Units of all laboratory measurements will be converted into
U.S. Conventional units before any descriptive analyses are performed.

5.7.8 Concomitant Medications

All detailed medication information related to heart failure condition management will be documented in the Case Report Form and summarized overall and by randomized treatment arm and separately for HFrEF and HFpEF patients using the rules specified in the general methodology at all visits.

5.7.9 Quality of Life

Quality of life assessment including KCCQ and EQ5D by blinded assessors will be collected at baseline screening, 1, 3, 6, 12, 18 and 24 months and annual 3-5 follow-up and summarized overall and by randomized treatment arms using the rules specified in the general methodology.

6.0 REFERENCES

1. Finkelstein DM, Schoenfeld, DA (1999). Combining mortality and longitudinal measures in clinical trials. Statistics in Medicine, 18, 1341-1344.
2. Pocock, Stuart J., et al. "The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities." European heart journal 33.2 (2011): 176-182.
3. Hollander, Wolfe and Chicken. Nonparametric Statistical Methods. Wiley; 3rd edition (2013)
4. Cui L, Hung HMJ, Wang S-J (1999). Modification of sample size in group sequential clinical trials. Biometrics, 55, 853-857.

7.0 APPENDICES

7.1 Appendix 1: SAS Code for Patient Level Data Analysis

7.1.1 Continuous Data

Normality is tested using the Shapiro-Wilks test with NORMAL option in PROC UNIVARIATE. The CLASS statement identifies the treatment group variable (TRT). The VAR statement names the continuous variable in the analysis (OUTCOME).

```
PROC UNIVARIATE NORMAL; BY
TRT;
VAR OUTCOME;
RUN;
```

Student's t-test is performed using PROC TTEST if normality assumption is satisfied. The CLASS statement identifies the treatment group variable (TRT). The VAR statement names the continuous variable in the analysis (OUTCOME).

```
PROC TTEST;
CLASS TRT;
VAR OUTCOME;
RUN;
```

The Wilcoxon Rank-Sum test is performed using PROC NPAR1WAY when normality assumption is not met. The CLASS statement identifies the treatment group variable (TRT). The VAR statement names the continuous variable in the analysis (OUTCOME).

```
PROC NPAR1WAY; CLASS
TRT; VAR OUTCOME;
RUN;
```

7.1.2 Categorical Data

The Chi-square test and Fisher's exact test are performed using PROC FREQ. The TABLES statement produces a cross tabulation of the treatment group (TRT) and interested categorical variable (OUTCOME).
The CHISQ option performs the Chi-square test.

```
PROC FREQ;
TABLES TRT*OUTCOME/CHISQ;
RUN;
```

The FISHER option performs Fisher's exact test when expected values in any of the cells of a contingency table are below 5.

```
PROC FREQ;
TABLES TRT*OUTCOME/FISHER;
RUN;
```

7.1.3 Time to Event Data

PROC LIFETEST calculates Kaplan-Meier estimates and performed the log rank test. The STRATA statement identifies the treatment group (DCS). The TIME statement identifies the variables to be used as the failure time (TIME) and censoring variable (EVENT).

```
PROC LIFETEST;
STRATA TRT;
TIME EVENTDAYS *EVENT(0);
run;
```

7.1.4 SAS Code for poolability of safety outcome

```
proc glimmix;
class SITE SUBJECT;
model ENDPOINT = SITE / dist = binary;
random _residual_ / group = SITE subject = SUBJECT; covtest
'common variance' homogeneity;
run;
```

7.1.5 SAS Code for Cox Model

The Cox regressions are performed using PROC PHREG. The MODEL statement identifies the variables to be used as the failure time (TIME) and censoring variable (EVENT) and treatment group and interested pre-specified covariates. The Efron method will be used to handle ties in the failure time.

```
PROC PHREG;
CLASS  TRT COVARS /DESC ;
MODEL AEVENTDAYS *EVENT(0) = TRT COVARS / RL TIES = EFRON;
RUN;
```

7.2 Appendix 2: Data Analysis Plan for Roll-in Patients

Each site may implant up to 2 Roll-in patients and follow them in an open-label (unblinded) manner to become familiar with the device and procedures. Implantation performance during Roll-in will be assessed during the implant by a Sponsor provided qualified Proctor. Roll-in patients will otherwise be followed, and their data analyzed in a manner similar to that from patients implanted with shunts in the Randomized Study, including notification of any identified safety concerns to the DSMB, but with no comparisons to control patients. Data and analysis results from roll-in patients will be summarized and presented separately. The roll-in arm is anticipated to enroll approximately 100 patients.

Transesophageal or intracardiac echocardiography will also be performed at 6 and 12 months in roll-in patients to assess shunt patency and other echo parameters. Additional statistical analyses in roll-in patients beyond those performed for all randomized patients receiving shunts, such as those related to shunt patency, are described below. Since data from roll-in patients will be unblinded to the sponsor, and relatively, that data collection will begin earlier than that from the randomized phase. the monitoring and analyses of their collected data may begin with the first roll-in patients and occur continuously during the study to identify and intervene early in any issues of safety or performance that may arise.

Enrollment: Reporting of the numbers of roll-in patients, timing, and completion of roll-in phase requirements by active study sites

Assessment of Implant Performance by Proctors: Numbers of roll-in patients required by individual sites to demonstrate implant proficiency

Shunt Patency: Number and rates of patients exhibiting any evidence of shunt closure, classification of the degree of patency loss (%) in those patients, and times to occurrence of first evidence and estimation of the progression of closure; descriptive statistical summaries of other collected echocardiographic parameters

Primary Effectiveness Endpoint: Estimates of events rates and KCCQ outcomes for components of the primary effectiveness endpoint

Compliance Assessment: Early evaluation of compliance with protocol requirements (protocol deviations) to identify potential study conduct or implementation issues at individual sites prior to enrollment of patients in the randomized phase

7.3 Appendix 3: Secondary Endpoint 2 - Joint Frailty Model

The proposed joint frailty model is based on the approach described by Rogers *et al* (2014) and expanded upon by Rogers *et a*l (2016). A similar formulation of the model was previously described by Liu *et al* (2004) and Rondeau *et al* (2007).

The joint frailty model is defined through the hazard functions associated with recurrent heart failure hospitalizations (HFH), $r_i(t \mid \omega_i)$ and all-cause death, $\lambda_i(t \mid \omega_i)$, conditional on random frailty, ω_i, for an individual patient (i). Recurrent event times in the interval from $t_{i0} = 0$ to t_{iNi} for patient (i) are included up to N_i, representing all events before the minimum of death time or the time of a censoring event.

$$r_i(t \mid \omega_i) = \omega_i \exp\{\boldsymbol{\beta}_1' \mathbf{Z}_i\} r_0(t) = \omega_i r_i(t)$$
$$\lambda_i(t \mid \omega_i) = \omega_i^{\alpha} \exp\{\boldsymbol{\beta}_2' \mathbf{Z}_i\} \lambda_0(t) = \omega_i^{\alpha} \lambda_i(t).$$

The parameters $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_2$ are 2 × 1 vectors of regression coefficients associated with vectors of covariates $\mathbf{Z}_1$ and $\mathbf{Z}_2$, respectively, where the covariates reflect treatment group and the two strata of HFrEF and HFpEF patients, based on ejection fraction levels. A supportive analysis will also be done without inclusion of the covariate for the ejection fraction strata representing HFrEF and HFpEF.

The patient-specific random frailty effect (ω_i) will be assumed conventionally to follow a gamma distribution with a mean of 1 and a variance θ, with the parameter θ representing the correlation of recurrent HFH. The parameter α represents the relationship between recurrent HFH and time to all- cause death.

The likelihood of the events associated with patient (i) can then expressed by the following:

$$L_i = \int_{\omega_i} \prod_{j=1}^{N_i} \left[\omega_i r_i(t_{ij})\right]^{\delta_{ij}} \exp\left\{\int_0^{x_i} \omega_i r_i(t)dt\right\} \left[\omega_i^{\alpha} \lambda_i(x_i)\right]^{\Delta_i} \exp\left\{\int_0^{x_i} \omega_i^{\alpha} \lambda_i(t)dt\right\} f_{\theta}(\omega_i)d\omega_i.$$

Where, t_{ij} and x_i represent the observed recurrent event times and follow-up, respectively. The indicator of a recurrent event at time t_{ij} is given by δ_{ij} , and the indicator of a death at time x_i is given by Δ_{ij} .

Since there is no closed form solution for the likelihood function, it will be assumed that there are piecewise constant hazards for the recurrent HFH and all-cause death, permitting estimation of the likelihood by Gaussian quadrature, as suggested by Rogers *et al* (2016). This estimation is incorporated in the SAS 9.1 (or above) procedure Proc NLMIXED.

The joint model gives two distinct hazard ratio estimates, RR_{HFH} and RR_{Death}. Both will be reported, but RR_{HFH} is the outcome evaluated in Secondary Endpoint 3 (that is, *Heart failure hospitalizations adjusted for all-cause mortality*). The frailty parameters θ and α will both be estimated from the observed data. Since it is believed that a higher risk of HFH is positively associated with a higher risk of all-cause mortality, it is expected that α will be greater than zero and in the interval of 0.5 to 1.0.

References

LIU, L., WOLFE, R. A. AND HUANG, X. (2004). Shared frailty models for recurrent events and a terminal event. *Biometrics* **60**, 747–756.

ROGERS, J.K., POCOCK, S.J., MCMURRAY, J.V., GRANGER, C.B., MICHELSON, E.L., OSTERGREN, J., PFEFFER, M.A., SOLOMON, S.D., SWEDBERG, K., AND YUSUF, S. (2014). Analysing recurrent hospitalizations in heart failure: a review of statistical methodology, with application to CHARM-Preserved. *Eur J Heart Failure* **16**, 33-40.

ROGERS, J.K., YAROSHINSKY, A., POCOCK, S.J., STOKAR, D., AND PAGODA, J. (2016). Analysis of recurrent events with an associated informative dropout time: application of the joint frailty model. *Statistics in Medicine* **35**, 2195- 2205.

RONDEAU, V., MATHOULIN-PELISSIER, S., JACQMIN-GADDA, H., BROUSTE, V., AND SOUBEYRAN, P. (2007). Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events. *Biostatistics* **8**, 708-721

7.4 Appendix 4: Secondary Endpoint 3, 4 and 6 – Cox Regressions

There are multiple approaches (graphical, goodness-of-fit tests, time-dependent variables) to the evaluation of the proportional hazard (PH) assumptions in a Cox model. In this study the PH assumptions will be evaluated using the Wald test for individual predictors and the partial likelihood ratio test for the global test. This will be performed using the PROC PHREG in SAS by creating time varying covariates (variable x time) in an extended Cox model and using the test statement. Scaled Schoenfeld residuals as a function of time will also be examined to visualize possible patterns of time- related changes.

If the predictor representing treatment group has satisfied the PH assumption, then it together with any baseline factors also satisfying the PH assumption (non-significant evidence of violation) will be evaluated using the planned Cox PH model. If the predictor representing treatment group is found to violate the PH assumption, then treatment effect cannot be represented by a single HR value and can only be expressed as a function of time. In that case, the time-to-event analysis of comparing treatment group outcomes will default to a standard Kaplan-Meier survival analysis evaluated using the logrank test statistic.

References

KLEINAUM, D. G. (1996). Survival Analysis: A Self-Learning Text, Springer

THERNEAU, T. M. AND GRAMBSCH, P.M. (2000). Modeling Survival Data: Extending the Cox Model, Springer

8.0 VERSION HISTORY

This Statistical Analysis Plan (SAP) for study RELIEVE-HF is based on protocol version 7.0 dated 27-Sept- 2021.

Table 5. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1.0	Original	Submitted to FDA under Pre-sub
2.0	Internally signed off document	Internal working document updated with the release of Clinical Study protocols Rev. 4.0 and 5.0.
3.0	Updates to address questions from FDA received during presub review of SAP. Updated to point to RELIEVE-HF Protocol Rev. 6.0 and adjust site expansion	Added additional effectiveness endpoint analysis for outpatient clinic HF visit. Added definition for Heart Failure Clinic ADHF Visit. Added randomization plan according to study protocol. Clarified when KCCQ component of primary effectiveness endpoint will be assessed. Clarified that primary safety analysis endpoint will include any randomized patients for which the device implant was attempted but did not succeed. Updated description of hypothesis for composite primary effectiveness endpoint. Clarified which covariates will be used for multiple imputation associated with sensitivity analysis for composite primary effectiveness endpoint. Clarified secondary endpoint for heart failure hospitalizations adjusted for all-cause mortality. Clarified interim analysis recommendation from DSMB to Sponsor to match DSMB Charter. Added description of joint frailty analysis model. Pointed to latest version of the RELIEVE-HF protocol Rev. 6.0. Adjusted number of worldwide sites to 120. Adjusted number of roll-in patients per site from 3 to 2.

4.0	Updates to address recommendations from FDA for SAP 3.0	**Redlines accepted by FDA in September 2020**: Clarify methods used for secondary endpoints in Section 5.3 Add details in the interim analysis. **Additional Redlines accepted by FDA in July 2021**: Address FDA recommendations from the SAP draft Rev 4.0 approval letter dated September 18, 2020. Increase randomized cohort sample size from 600 to 1000. Add supplemental Worsening Heart Failure component as an Outpatient event to the primary effectiveness endpoint. Reranked hierarchical tested secondary effectiveness endpoints; 6MWT is now ranked last. Add analyses to examine the impact of COVID-19 on the components of the primary effectiveness endpoint over the duration of the study. Add option to increase from 120 sites up to 150 sites, with the majority of sites located in the US, if the recommendation from the interim analysis results in an increase in the original maximum total sample size of 600 subjects.
	Updates to include the DSMB Recommendation for the modified primary effectiveness endpoint	**Additional Redlines accepted by FDA in September 2021:** Primary effectiveness endpoint to add Worsening HF treated as an Outpatient as the 4th component of the primary effectiveness endpoint. The WIN ratio (R_w) for the primary effectiveness endpoint will use the same pre-specified weight in the two phase (interim and post-interim analysis). Include a supplemental analysis of the primary effectiveness endpoint without the component of the worsening HF.
5.0	Updates to address recommendations from FDA for SAP 4.0	Correct editing errors in Section 5.3, #1, #3, and #8, when the hierarchical ranking of the secondary endpoints was changed in revision 4.0.

		Add Section 7.4, Appendix 4: Secondary Endpoint 3, 4 and 6 – Cox Regressions, to provide details on how the proportional hazard assumptions will be assessed and the analysis method that will be used if the assumptions are not met for one or more of the model predictors.
5.1	Updates to specify per-protocol population	List the specific major protocol deviations lead to per-protocol exclusion. Correct the errors in the endpoints to analyze from step 3 to step 4 in Section 5.2.2.1.