

**Implantation of a Permanent Interatrial Shunt to
Reduce Left Atrial Filling Pressures Following MitraClip:
The V-Wave Shunt MitraClip Study**

Protocol Number: 3

National Clinical Trial (NCT) Identified Number: 04729933

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Version Number: v. 2

14 November 2022

Summary of Changes from Version 1.0 to 1.1:

Affected Section(s)	Summary of Revisions Made	Rationale
1.1, 1.2, 1.3, 2.3.1.1, 3.1.1, 4.1, 4.2.	Extended follow-up duration of the study to 5 years	Patients will be followed for 5 years after study device implantation to evaluate for late adverse events, including the risk of late paradoxical embolism
1.1, 2.1, 5.1	Revised Inclusion and Exclusion Criteria – MitraClip Eligibility	Inclusion and Exclusion criteria for commercial placement of MitraClip for the treatment of functional MR were included
1.1, 5.1	Revised Inclusion Criteria – Guideline Directed Medical Therapy	Added specifics as to what constitutes Guideline Directed Medical Therapy in the Inclusion Criteria
1.1, 5.2.1, 5.2.2	Revised Exclusion Criteria – Screening for Pulmonary Hypertension	Revised the definition of severe pulmonary hypertension in the Preliminary Exclusion Criteria, and screening for severe pulmonary hypertension by pulmonary artery catheterization to the Final Exclusion Criteria
1.1, 2.3.1, 2.3.3.3, 3.1.1, 3.4.1, 4.1, 4.2	Revised protocol to include discussion of risks and benefits of the combined MitraClip + V-Wave Shunt procedure	Added emphasis on the potential risk of paradoxical embolism, as well as a detailed discussion of the risks and benefits of the combined MitraClip + V-Wave Shunt procedure compared to alternatives.

Summary of Changes from Version 1.1 to 1.2:

Affected Section(s)	Summary of Revisions Made	Rationale
2.3.3.3	Extensive updates to the evidence and discussion of risks and benefits of concomitant MitraClip + V-Wave shunt placement	Added justification for the combined MitraClip + V-Wave shunt procedure at request of the FDA

1.1, 1.2, 2.3.3, 5.2.2	Changed the Exclusion Criteria to exclude patients with LAP $\leq$ 20 mmHg from the study	Increased the LAP threshold so that only patients with LAP > 20 mmHg are eligible for the study.
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Summary of Changes from Version 1.2 to 1.3:

Affected Section(s)	Summary of Revisions Made	Rationale
1.1, 1.2, 1.3, 4.1 5.4	Clarified that up to 50 patients may be enrolled after consent is signed and the Preliminary Screen passed, with the intent to implant the V-Wave device in the first 10 patients who pass the Final Screen based in invasive hemodynamics.	Change necessary to satisfy FDA regulations.
1.1, 5.1	Changed Inclusion Criteria to only include patients with NYHA Class III or ambulatory IV HF	Changed Inclusion Criteria at FDA request

Summary of Changes from Version 1.3 to 1.4:

Affected Section(s)	Summary of Revisions Made	Rationale
1.3	Typographical Error Corrected on Schedule of Activities	Typographical Error Correction
2.3.1.1, 2.3.2	Addition of language for unknown risks/benefits due to investigational state of the device added	To align with the ICF
4.2	Changed 'Executive Committee' to 'Sponsor', and Medical Monitor definition added	Due to the small size of the study, Executive Committee will not be utilized. Clarification provided for Medical Monitor's responsibility

6.1.3	Clarified database utilized for the study	Identified eCRF platform per FDA recommendation
9	Defined Statistical Analysis Plan	Described SAP per FDA recommendation

Summary of Changes from Version 1.4 to 1.5:

Affected Section(s)	Summary of Revisions Made	Rationale
1.3 (Schedule of Activities)	Screening/Baseline window expanded from -7 to -1 day to -30 to -1day, except echo studies. Cardiac Echo window is expanded to -90 to -1. NT pro BNP and electrolytes to be drawn on the day prior (Day -1) or day of the procedure.	To assure adequate time to screen and plan for the procedure, and to limit repeat imaging
1.3 (Schedule of Activities)	Screening/Baseline echo to include TEE if TTE was not performed.	To align with standard of care

Summary of Changes from Version 1.5 to 2:

Affected Section(s)	Summary of Revisions Made	Rationale
Protocol Summary Section , and 5.2.2 (Final Exclusion Criteria)	Additional Exclusion Criteria added to Final Screening: • Angle of placement of V-Wave shunt should be no more than 135 degrees to prevent slippage through the septum, and • Septal defect created by MitraClip devliery system must be 8mm or smaller, in any dimension, without evidence of a tear in the septum	To assure the V-WAVE shunt to be delivered and placed appropriately

INVESTIGATOR'S SIGNATURE PAGE

Protocol Number or Version: 3, Version 2

Protocol Date: 14 NOV 2022

Implantation of a Permanent Interatrial Shunt to Reduce Left Atrial Filling Pressures Following MitraClip: The V-Wave Shunt MitraClip Study

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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STATEMENT OF COMPLIANCE

1) The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) 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 before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-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: Implantation of a Permanent Interatrial Shunt to Reduce Left Atrial Filling Pressures Following MitraClip: The V-Wave Shunt MitraClip Study

Study Description: This is an investigator initiated, prospective study to demonstrate the safety and feasibility of implantation of the V-Wave Interatrial Shunt System (herein called the “V-Wave Shunt” or the “study device”) in patients immediately following percutaneous mitral valve repair using the MitraClip system.

The V-Wave Shunt is a device placed across the interatrial septum (IAS) by cardiac catheterization which allows for the transfer of blood from the left atrium (LA) to right atrium (RA). The intended effect is to reduce excessive left-sided cardiac filling pressures in patients with advanced heart failure (HF) and thus improve symptoms related to pulmonary congestion. All patients in the study must meet all anatomic and clinical eligibility in the FDA approved indications for use of the MitraClip in functional mitral regurgitation (MR). All patients must have persistence of New York Heart Association (NYHA) class III or ambulatory class IV HF symptoms despite maximally tolerated guideline directed medical therapy (GDMT) as assessed by a Cardiologist specialist in advanced heart failure (HF). All patients will have reduced left ventricular (LV) ejection fraction (EF) $\geq 20\%$ and $\leq 50\%$ and at least moderate to severe 3-4+ MR with a functional or combined functional and degenerative mechanism. Despite MitraClip treatment and maximum GDMT, these patients are at high risk for

recurrent HF events and readmission, and thus there is an unmet need for further therapies to improve outcomes in this patient population.

The existing transseptal puncture used for MitraClip placement will be used to place the V-Wave Shunt device after MitraClip placement.

Screening will take place in two steps: a Preliminary Screen at the baseline visit, and a Final Screen after assessing invasive hemodynamics after the MitraClip procedure. Patients will be considered enrolled after they sign consent and pass the Preliminary Screen. Up to 50 patients will be enrolled, with the intent to place the V-Wave shunt device in the first 10 patients who pass the Final Screen after invasive hemodynamics post-MitraClip are assessed. The primary analysis will be performed when the last enrolled patient has been followed for a minimum of 12 months, and all patients will be followed for safety events for 5 years. This study will be conducted at a single center to minimize interoperator variability.

Objectives:

The primary objective of this study is to provide reasonable assurance of the safety and feasibility of implantation of the V-Wave Shunt System (herein called “study device”) immediately after treatment with MitraClip therapy.

The secondary objective is to explore if there is a signal of improved efficacy in patients treated with the V-Wave shunt device compared to pre-study device implantation.

Endpoints:

Primary Endpoint (Safety):

Device-related Major Adverse Cardiovascular and Neurologic Events (MACNE), defined as the hierarchical composite rate of:

- All cause death
- Stroke and paradoxical embolism
- Myocardial infarction
- V-Wave shunt device embolization
- Cardiac tamponade
- Device related re-intervention or surgery

The primary analysis for the primary endpoint will be assessed at 1 month after study device implantation. Secondary analyses for the primary endpoint will be evaluated at 6 months, 1 year, 2 years, 3 years, and 5 years.

Secondary Endpoints (Efficacy - exploratory):

- 6 minute walk test (6MWT) distance / Borg scale
- Kansas City Cardiomyopathy Questionnaire (KCCQ) score
- NYHA HF class (I-IV)
- Echocardiographic parameters (measured by transthoracic and/or transesophageal echocardiogram [TTE or TEE, respectively])
 - o Degree of MR (none, trivial, 1-4+)

- Degree of tricuspid regurgitation (TR; none, trivial, 1-4+)
- Right ventricular systolic pressure (RVSP)
- Right atrial pressure (RAP)
- Right ventricular (RV) function (normal, mild-severe reduction)
- Left ventricular (LV) function (quantitative – LVEF %; qualitative – normal, mild-severe reduction)
- Incidence of loss of shunt flow across IAS by doppler and/or agitated saline study
- NT pro BNP
- Readmissions for HF (adjusted for all-cause mortality)
- Technical success (defined as successful delivery and deployment of the study device and removal of the delivery catheter)
- Device success
- Procedural success

The primary analysis for secondary endpoints will be baseline compared to 1 year. Secondary analyses for the secondary endpoint will be evaluated at 1 month, 6 months, 2 years, 3 years, and 5 years.

Study Population:

The study population will consist of patients aged ≥ 18 years, with moderate to severe (3+ or 4+) functional MR and reduced LVEF $\leq 50\%$, successfully treated with MitraClip therapy (residual MR $\leq 2+$). All patients will be on maximum tolerated GDMT prior to MitraClip placement, and must meet the inclusion and exclusion criteria as specified below.

Inclusion Criteria:

Inclusion criteria – to be assessed by the Preliminary Screen at the baseline visit:

1. All patients must meet clinical and anatomic eligibility for commercial placement of MitraClip for functional MR, as specified by the MitraClip Instructions for Use (IFU).
 - a. Clinical eligibility for MitraClip:
 - i. Symptomatic secondary MR (moderate-severe [3+ or 4+] or greater) due to ischemic or non-ischemic cardiomyopathy
 - ii. NYHA functional class III, or ambulatory IV
 - iii. Maximization of GDMT as directed by the “Heart Team”, including an interventional cardiologist (implanting physician), heart failure cardiologist, and cardiothoracic surgeon. This includes adequate treatment for systolic HF (LV dysfunction), rhythm disorders, and coronary disease, if applicable
 - (1) An inhibitor of the reninangiotensin 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)
 - (2) 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.
- (3) 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.
- (4) Drug intolerance, contraindications, or lack of indications must be attested to by the investigator.
- (5) Receiving Class I recommended cardiac rhythm management device therapy.
 - (a) 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 device implantation
 - (b) 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.
- iv. At least one hospitalization for heart failure in last year OR corrected BNP ≥ 300 pg/mL or corrected NTproBNP ≥ 1500 pg/mL
- v. Heart team has determined that mitral valve (MV) surgery will not be offered as a treatment option
- b. Anatomic eligibility for MitraClip:
 - i. LVEF $\geq 20\%$ and $\leq 50\%$
 - ii. LV end-systolic dimension ≤ 70 mm
 - iii. MV orifice area > 4.0 cm² by TEE
 - iv. Minimal calcification in the grasping area
 - v. No leaflet cleft in the grasping area
 - vi. In patients with a degenerative component to MR, the following additional criteria must be met:
 - (1) Flail width < 15 mm
 - (2) Flail gap < 10 mm
 - vii. The primary regurgitant jet is non-commissural, and in the opinion of the implanting investigator can be successfully be treated by the MitraClip (if a secondary jet exists, it must be considered clinically insignificant)
 - viii. Transseptal catheterization and femoral vein access is feasible per investigator
- 2. 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 (PEC) – to assessed by the Preliminary Screen at the baseline visit:

1. Severe pulmonary hypertension, defined as RV systolic pressure or PA systolic pressure > 70 mmHg, or PVR > 4 Woods units, measured by

- any modality (TTE, TEE, cardiac MRI, or pulmonary artery catheterization [if data available]).
2. Moderate or severe RV dysfunction defined as TAPSE <12mm or RVFAC ≤25% as assessed on Baseline TTE, or qualitative assessment of severe RV dysfunction on TTE, TEE, or cardiac MRI.
 3. Untreated severe (3+ to 4+) tricuspid or pulmonary regurgitation.
 4. Untreated clinically significant coronary disease requiring revascularization
 5. Coronary artery bypass grafting, percutaneous coronary intervention, transcatheter aortic valve implantation, or CRT-D implantation within 30 days
 6. Aortic or tricuspid valve requiring surgery or transcatheter intervention
 7. COPD requiring continuous home oxygen therapy or chronic outpatient steroid use
 8. Cerebrovascular accident within prior 30 days
 9. Known severe symptomatic carotid stenosis
 10. Carotid surgery or stenting within prior 30 days
 11. ACC/AHA Stage D heart failure
 12. Presence of any of the following:
 - a. Hypertrophy cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology
 - b. Infiltrative cardiomyopathy (e.g. amyloidosis, hemochromatosis, sarcoidosis)
 13. Leaflet anatomy which may preclude MitraClip implantation
 14. Hemodynamic instability defined as systolic pressure < 90 mmHg with or without afterload reduction, cardiogenic shock or the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device.
 15. Need for surgery within 12 months
 16. Life expectancy < 1 year due to non-cardiac conditions
 17. Status 1 for cardiac transplant or history of cardiac transplant
 18. Modified Rankin score ≥ 4 for disability
 19. Prior mitral valve leaflet surgery or any currently implanted prosthetic mitral valve, or any prior transcatheter mitral valve procedure
 20. Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
 21. Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e., noncompliant, perforated)
 22. Active infection requiring antibiotic therapy
 23. TEE is contraindicated or high risk
 24. Pregnant or planning pregnancy within 12 months
 25. Known hypersensitivity or contraindication to procedural medications that cannot be adequately treated
 26. Known allergy to nickel.

27. Patient is otherwise not appropriate for the study as determined by the investigator or the Eligibility Committee, for which the reasons must be documented.
28. 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 by the Final Screening, performed at time of cardiac catheterization prior to device placement (Study Intervention Visit)

29. Presence of severe pulmonary hypertension assessed by invasive hemodynamic measurement with pulmonary artery catheterization prior to MitraClip placement, defined as PA systolic pressure > 70 mmHg or PVR > 4 Woods units.
30. Anatomical anomaly on TEE that precludes implantation of the study device across the interatrial communication created by the MitraClip procedure, including:
 - a. A posterior rim between the septum secundum and aorta (i.e. aortic rim) of < 5 mm.
 - b. 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.
31. Moderate or worse MR $\geq 2+$ at the end of MitraClip treatment (i.e. MR must be <2+ by TTE, TEE, invasive hemodynamics, or left ventriculography)
32. Key hemodynamic exclusions after MitraClip treatment:
 - a. Mean LAP ≤ 20 mmHg following final result from MitraClip placement (i.e. mean LAP must be elevated > 20 mmHg after completion of MitraClip).
 - b. Difference between mean LAP and mean RAP < 5mmHg after MitraClip placement (i.e. difference between LAP – RAP must be ≥ 5 mmHg).
 - c. If the patient meets these hemodynamic exclusion criteria and mean arterial pressure (MAP) is < 90 mmHg, the MAP may be increased to ≥ 90 mmHg and repeat pressure measurements obtained in order to evaluate eligibility.
 - i. IV fluids and medications may be given to support MAP to a goal ≥ 90 mmHg if necessary.
33. Angle of placement of V-Wave shunt should be no more than 135 degrees to prevent slippage through the septum.
34. Septal defect created by MitraClip delivery system must be 8mm or smaller, in any dimension, without evidence of a tear in the septum.
35. Patient is otherwise not appropriate for study as determined by the Investigator (reason must be documented).

Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	The current study will be performed at a single tertiary care center (Cleveland Clinic), by a limited team of operators, within the United States.
Description of Study Intervention:	All patients in the current study will be treated with the V-Wave Interatrial Shunt device, which allows the flow of blood from the LA to the RA in patients with elevated LA pressure > RA pressure. Please see text above, and protocol text for further details.
Study Duration:	The study duration from first patient enrolled until completion of the last follow-up is expected to take approximately 18 months.
Participant Duration:	Primary analysis will occur when the last patient enrolled completes 12 months of follow-up. Patients that are screen failures due to inability to pass the FEC will not be treated with the study device, and will be excluded from the study. Patients will be followed for the primary data analysis a minimum of 12 months from the Study Intervention Procedure. All patients will be followed for a total of 12 months from the procedure.

1.2 SCHEMA

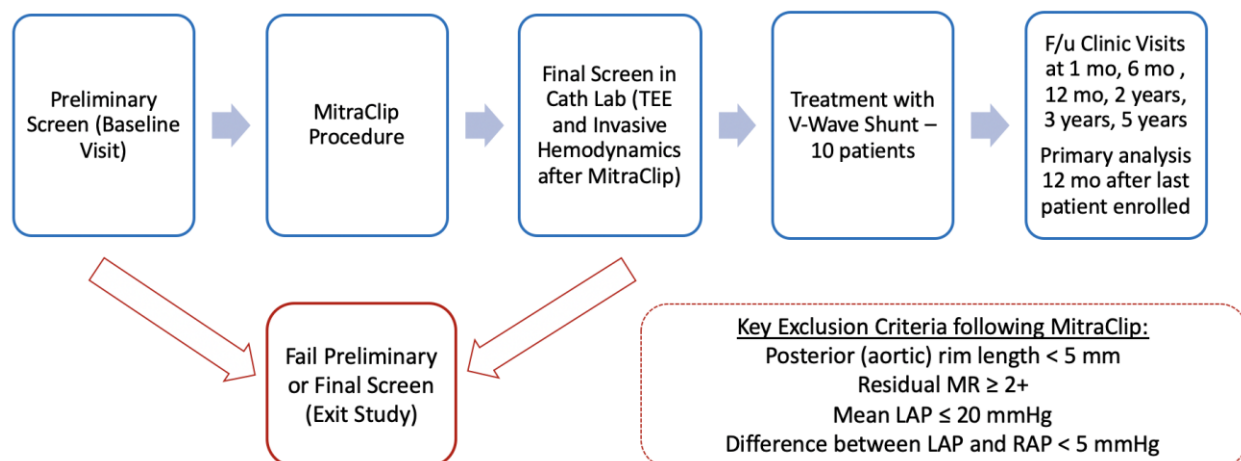


Figure 1. Patients are enrolled after successful two-phase screening: the Preliminary Screen will occur at the Baseline Visit, and the Final Screen will occur at time of catheterization prior to device placement. Up to 50 patients may be enrolled, with the device implanted in the first 10 patients who pass the Final Screen. This will be a single center study. Patients will be followed at 1 mo, 6 mo, 12 mo, 2 year, 3 year, and 5 year time intervals with clinic visits to record clinical status, laboratory work, ECG, and TTE. Patients who do not have the device implanted will not be followed longitudinally. Abbreviations as previously stated.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Visit Assessment	Preliminary Screen / Baseline Visit Day -30 to -1	Final Screen / Study Intervention Visit Day 1	Post-Intervention Prior to discharge	Follow-up Visit 1 (1 mo) Day 30 ±3 days	Follow-up Visit 2 (6 mo) Day 180 ± 7 days	Follow-up Visit 3 (12 mo) Day 365 ±14 days	Follow-up Visit 4 (2 years) Day 270 ±30 days	Follow-up Visit 5 (3 years) Day 1095 ±30 days	Follow-up Visit 6 (5 years) Day 1826 ±30 days
Informed consent	X								
Inclusion and Exclusion criteria review	X	X							
Demographics and medical history	X								
Vital signs, including weight and pulse oximetry	X ¹	X ¹	X ¹	X	X	X	X	X	X
Physical exam (including height and weight)	X	X	X	X	X	X	X	X	X
Implant study device (V-Wave Shunt)		X							
Medication review	X	X ²	X ²	X ²	X ²	X ²	X ²	X ²	X ²
Chemistry - Na, K, Hgb, HCT, PLTS, WBC, Cr, BUN, AST, ALT, T Bili, Alk phos	X ⁶		X ³	X ³	X ³	X ³	X ³	X ³	X ³
Pregnancy, PT, PTT, INR		X							
NT-proBNP	X ⁶		X	X	X	X	X	X	X
12 Lead ECG	X	X	X	X			X	X	X
Chest X-Ray (PA and lateral)	X		X						
Transthoracic echo (TTE)	X ⁵		X ⁴	X	X	X	X	X	X
Transesophageal echo (TEE)	X ⁵	X							
NYHA Functional Class assessment	X			X	X	X	X	X	X
KCCQ EQ-5D	X			X	X	X	X	X	X
6-minute Walk Test / Borg scale	X			X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X
Complete case report forms (CRFs)	X	X	X	X	X	X	X	X	X
¹ Temperature and pulse oximetry are only required at Baseline, Study Intervention ² Only cardiovascular, antiplatelet, and anticoagulant therapy medications will be collected during follow-up. ³ Limit to Cr, Hgb, HCT ⁴ If multiple TTEs are performed during the procedural hospitalization, the last TTE prior to discharge will be used. ⁵ If no TTE, TEE may substitute the baseline imaging if one is available. The baseline echo (TTE or TEE) should be within Day -90 to -1. ⁶ NT pro BNP and electrolytes to be drawn on the day prior (Day -1) or day of the procedure									

2 INTRODUCTION

2.1 STUDY RATIONALE

Congestive heart failure (HF) is a common medical condition that imposes a tremendous public health and economic burden on developed countries. It is estimated that over 6.2 million US adults currently have HF (2.2% of the US population ≥ 20 years old).¹ Despite HF affecting close to 1 in 50 US adults, HF is highly morbid, and causes reduced quality of life (QOL), increased likelihood of hospitalization, and high mortality – even with the best available medical and device therapies. The burden of HF on US health and healthcare expenditures is extraordinary, and is further expected to grow as the US population ages.^{1, 2}

The most common etiology of HF is left-sided heart failure due to ventricular (LV) systolic or diastolic dysfunction.¹⁻³ Patients with a reduced LV systolic ejection fraction (EF) are at particularly high risk of HF symptoms including respiratory distress, which is typically caused by elevated left atrial (LA) pressures, which in turn leads to pulmonary venous congestion and pulmonary edema.³ Pulmonary congestion is

reason for approximately 90% of acute CHF hospitalizations, and if not reversed can lead to respiratory failure, cardiogenic shock, cardiac arrhythmia, and death.

Mitral regurgitation (MR) is frequently encountered in patients with left-sided HF.⁴ MR further serves to increase LA pressures and symptoms of pulmonary congestion. The pathologic causes of MR may be due to an abnormality of the mitral valve (MV) or subvalvular apparatus itself, known as “degenerative” MR, or due to an enlargement in LV or LA size which causes the MV annulus to dilate and MV leaflets to become regurgitant, known as “functional” MR.⁴ Recently, the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial demonstrated that patients with reduced LVEF and functional MR treated with percutaneous mitral valve repair using MitraClip had reduced risk of hospitalization, improved QOL, and improved survival compared to medical therapy alone.⁵⁻⁹ Despite this, these patients often still have a significant burden of HF, and there remains an unmet need for innovative treatments in patients with reduced LVEF and functional MR after MitraClip.

Correcting LA pressure with diuretic therapy is the central tenant of treatment of acute CHF, and maintaining normal LA pressures is essential to avoiding respiratory distress and maintaining QOL. An implanted device that automatically decompresses the LA via a unilateral shunt that allows left-to-right flow between the LA and right atrium (RA) would lower LA pressures.¹⁰ The benefits of this could include reduced pulmonary congestion, reduced risk of hospitalization, improved exercise tolerance, and improved QOL in patients with left-sided CHF of any etiology. One such percutaneous interatrial shunt is the V-Wave shunt device.

With this realization, it is the goal of the current study to evaluate the feasibility and safety of implantation of the V-Wave Shunt device patients with reduced LVEF ≥ 20 and $\leq 50\%$ after successful MitraClip therapy. This shunt will be placed across the interatrial septum (IAS) immediately following MitraClip placement, across the interatrial shunt created by the MitraClip procedure. The timing of this will be ideal, as it will avoid the need for an additional transseptal puncture. Placement of the V-Wave shunt will serve as a mechanism for further reducing LA pressures in this high-risk patient population. Early experience with this device has demonstrated its safety in patients with both preserved and reduced LVEF, however patients with significant MR and those receiving MitraClip have been excluded from studies to date.¹⁰⁻¹³

It is hypothesized that the study will show that implantation of the V-Wave shunt device is feasible and safe in this patient population, and provide valuable information for conducting a larger study on the efficacy of this strategy in the future.

2.2 BACKGROUND

Please note that given overlap in subject matter, portions of the background were modified from the RELIEVE-HF protocol Version 5.0 (Protocol CL7018HF), with permission.

Congestive heart failure is 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. 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). Patients with HFpEF tend to be older, are more commonly female, hypertensive and diabetic.¹⁴

Mitral regurgitation is common in all subsets of patients with HF, and often complicates the management of patients with either HFrEF or HFpEF. MR may be the primary cause of HF in the case of HFpEF (i.e. degenerative MR), a consequence of reduced LV function, LV dilation, and altered MV annular geometry in the case of HFrEF (i.e. functional MR), or a mix of these etiologies.⁴

2.2.1 STANDARD OF CARE TREATMENT FOR HF

The mainstay therapy for patients with HFrEF are medications that regulate the renin-angiotensin-aldosterone system, encourage myocardial remodeling, reduce afterload, and control heart rate. The most commonly used drugs for HFrEF include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors—Entresto (ARNI), beta blockers, and mineralocorticoid receptor inhibitors (MRA). 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.¹⁴ Several devices also have evidence-based, Class I guideline indications for treating specific subsets of HFrEF patients including Implantable Cardioverter Defibrillator (ICD) devices to reduce risk of sudden cardiac death in patients with LVEF $\leq 35\%$, Cardiac Resynchronization Therapy (CRT) in patients with LBBB or RBBB and QRS duration ≥ 150 ms or dependence on chronic pacing, and Left Ventricular Assist Devices (LVAD) for patients with end-stage cardiomyopathy. Addressing atrial fibrillation with rhythm and rate control strategies, and valvular heart disease with surgical or percutaneous replacement or repair is also often indicated. 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. Decreasing pulmonary congestion with intravenous loop diuretics is the most common approach to relieving the worsening symptoms of ADHF.¹⁴

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. 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 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.¹⁵
 - The proposed mechanism of this is as such: 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.^{16, 17}
- There is a resting interatrial pressure gradient, where LAP exceeds RAP in ~98% of HF patients, nearly all of the time throughout the day.¹⁸
- HF patients with coexisting congenital atrial septal defects (ASD) or patent foramen ovale (PFO) have better than expected outcomes, and closure of ASD and PFO may unmask subclinical left ventricular dysfunction, provoking pulmonary edema.¹⁹⁻²¹
- 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.²²

The theory of operation for the V-Wave Shunt 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 across the interatrial septum, attenuating further elevation in left-sided pressure and pulmonary venous congestion. 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 RA 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.²³ 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. These benefits would be expected to be seen in patients regardless of presence or absence of left sided valvular heart disease, including moderate or severe MR. 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.

The location, the amount of flow, and the hemodynamic consequences of the V-Wave shunt device, are similar to what occurs with a hemodynamically insignificant congenital ostium secundum 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 ($Q_p:Q_s$) 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).

The earliest pre-clinical experience with the V-Wave Shunt was validated in a sheep model of ischemic dilated cardiomyopathy.²⁴ The Shunt in this study differed from the current version of the Study Device primarily in that it had a tissue valve disposed on its RA side to prevent right-to-left shunting that has since been removed to improve patency of the shunt device during follow-up, but was otherwise dimensionally similar. The animal HF model was induced with selective left circumflex coronary artery microembolization, which resulted in the development of LV dysfunction with LVEF falling to 36% within 2 weeks. Animals were then either treated with Shunts ($n=14$) or were Sham Controls ($n=7$). Control animals continued to deteriorate; after another 12 weeks, LVEF was markedly reduced to 18%, the septum further thinned, and LAP monotonically elevated to 25 mmHg. As a result, Control animals developed severe secondary pulmonary hypertension (PAP_{mean} 37 mmHg), and worsening RAP averaging 15 mmHg, consistent with right ventricular volume overload. Control animals had a 43% mortality.

Despite comparable LV function at baseline, there were marked contrasts in the evolution of objective HF indices between the control and shunted animals consistent with a device treatment effect. 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 RA 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 LV 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.²⁴

In summary, these early data demonstrated pre-clinical proof-of-concept. This study showed mechanistically how a small interatrial shunt device can selectively unload the heart, resulting in sustained reductions of LAP and improved LV 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.

2.2.3 CLINICAL DATA FOR THE V-WAVE SHUNT DEVICE

First-in-Man Experience

The first-in-man experience with the V-Wave shunt device was reported in 2015.¹¹ The device was implanted in a 70 year old male with chronic systolic HF due to ischemic cardiomyopathy, with LVEF 35%, and normal LV function. The patient had NYHA class III HF symptoms with significant orthopnea. The device was successfully implanted via transfemoral access, and the patient was successfully discharged 24 hours later. At 3 month follow-up, patency of the device was confirmed by echocardiogram, and the patient related an improvement in HF symptoms to NYHA class II, with resolution of orthopnea, improvement in KCC index from 39.1 to 77.6, and reduction in NT-proBNP from 502 ng/mL to 322 ng/mL. The Qp:Qs was 1.17, PCWP improved from 19 to 8 mmHg, without changes in pulmonary arterial pressure or RV function.¹¹ This study further fueled enthusiasm for an open-label registry to demonstrate the safety of the device in a larger group of patients.

Combined Open-Label Human Feasibility Studies

Study Methods

There have been two open-label human feasibility studies of the V-Wave shunt device run concurrently. Both have used a prior version of the V-Wave shunt device, which included a tissue valve located on the RA side to prevent early reversed (right-to-left) shunting, which has since been removed but is otherwise dimensionally the same.

The Canadian Special Access Program (CSAP) was a study conducted at a single site, while the First-in-Man (FIM) trial (NCT01965015) was performed at 5 sites in Spain and Israel.¹² The two studies had

similar major inclusion and 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.¹³

A peer-reviewed manuscript describing the experience of the first 10 patients with reduced LVEF was published in *The Lancet* in March 2016.¹² The data summarized below combines the CSAP and FIM studies and provides early and late results from this combined cohort, and was recently published in *JACC: Cardiovascular Interventions* in November 2018.¹³ Data from the control arm of the the CHAMPION study of the implantable CardioMEMS pulmonary artery pressure sensing device is provided as a comparison event rates for patients on maximal guideline directed medical therapy.^{16, 17}

The objectives for both the CSAP and FIM studies 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 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 (PAPsystolic >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. A medical monitor consisting of a heart failure cardiologist expertise in clinical trials and with access to statistical resources will adjudicate adverse events and monitor trial safety monthly.

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.^{16, 17} 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 CSAP/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 atrial 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.

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 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 SAEs 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: **Table 3** provides functional status and QOL results for the combined cohort. All patients were NYHA Class III/IV at enrollment. At 3-months, 78% improved to Class I or II; at 6 months 80% remained improved; and at 12 months 61% continued to be class I or II ($p < 0.001$ for all comparisons). For QOL, the proportions improved by ≥ 5 points in 74%, 59% and 73% at 3, 6, and 12 months, respectively ($p < 0.001$ for all comparisons). 6MWT increased by +51 m at 3 months ($p < 0.001$), +41 m at 6 months ($p = 0.01$), and to +34 m vs. baseline at 12 months ($p = 0.012$).

Table 3 similarly summarizes blood, echo, and hemodynamic parameters during follow-up. Shunt flow (Qp:Qs) 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 shunt placement.

TABLE 3 Functional, Echocardiographic, and Hemodynamic Parameters at Baseline and 3- and 12-Month Follow-Up

	Baseline (n = 38)	3 Months (n = 36)	12 Months (n = 36)	p Value*
Functional status/quality of life				
NYHA functional class III or IV	38 (100)	8 (22)	14 (39)	<0.001
NYHA functional class I or II	0 (0)	28 (78)	22 (61)	
KCCQ/MLHFQ (improvement ≥ 5 points)	—	27 (74)	26 (73)	<0.001
6-min walk distance (m)	290 $\pm$ 112	340 $\pm$ 94	324 $\pm$ 105	0.012
Laboratory parameters				
ln NT-pro BNP (pg/ml)	7.5 $\pm$ 0.9	7.4 $\pm$ 1.0	7.5 $\pm$ 0.9	0.83
eGFR (mL·min ⁻¹ ·1.73 m ⁻²)	54 $\pm$ 20	55 $\pm$ 23	53 $\pm$ 22	0.92
Echocardiographic variables				
LVEF, % (HFREF)	26 $\pm$ 7	27 $\pm$ 9	28 $\pm$ 8	0.54
LVEF, % (HFmrEF, HFpEF)	50 $\pm$ 9	52 $\pm$ 10	54 $\pm$ 9	0.74
MR grade†	3.9 $\pm$ 1.5	3.5 $\pm$ 1.2	3.5 $\pm$ 1.3	0.51
LAVI (mL/m ²)	42 $\pm$ 13	42 $\pm$ 13	41 $\pm$ 15	0.84
TAPSE (mm)	16 $\pm$ 4	17 $\pm$ 4	16 $\pm$ 4	0.94
Cardiac output (L/min)	1.9 $\pm$ 1.0	1.9 $\pm$ 0.5	1.9 $\pm$ 0.4	0.92
Q _p /Q _s	0.99 $\pm$ 0.11	1.17 $\pm$ 0.12	1.10 $\pm$ 0.13	0.005
Hemodynamic status				
PCWP, mm Hg	21 $\pm$ 5	20 $\pm$ 7	19 $\pm$ 7	0.49
RAP, mm Hg	8 $\pm$ 4	9 $\pm$ 5	9 $\pm$ 4	0.51
Mean PAP, mm Hg	30 $\pm$ 7	29 $\pm$ 8	30 $\pm$ 10	0.97

Values are n (%) or mean $\pm$ SD. *Kruskal-Wallis test and one-way analysis of variance for ordinal and interval data, respectively. †MR grade: 1 = none to 7 = severe. KCCQ = Kansas City Cardiomyopathy Questionnaire; LAVI = left atrial volume index; MLHFQ = Minnesota Living With Heart Failure Questionnaire; PAP = pulmonary artery pressure; TAPSE 1/4 tricuspid annular plane systolic excursion; other abbreviations as previously described. Table credit: Rodés-Cabau et al., JACC: Cardiovascular Interventions. 2018;11(22):2300-10.

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 remaining patients with flow across their shunts, TEE showed that by 12 months, an additional 13 of 36 patients (36%) had developed in-shunt stenosis, consistent with the location of the bioprosthetic leaflets. Stenosis severity was assessed as subtotal in 7 cases, and the jets were measured to be skewed (range 9 to 26) from the long axis of the shunt in 5 of 6 remaining cases (Figure 2). Stenotic shunt cases were objectively differentiated from patients with widely patent shunts by measured vena contracta diameters (stenotic: 0.0 mm (IQR: 0 to 2.5 mm) vs. patent: 3.1 mm (IQR: 3.0 to 3.8 mm); $p < 0.001$) and Q_p/Q_s (stenotic: 1.05 $\pm$ 0.12 vs. patent: 1.17 $\pm$ 0.12; $p = 0.023$). There was no thrombus seen in or near the shunts, no migration of shunts from the site of deployment, and no erosion into adjacent cardiac structures. Shunt stenosis or occlusion was not associated with pre-cipitation of acute adverse clinical events, including thromboembolic events. The root cause of stenosis or occlusion was suggested from a stenotic shunt that was explanted during cardiac transplantation at 27-month follow-up (Figure 3). The bioprosthetic leaflets were thickened and stenotic with neoendocardial hyperplasia (pannus).

Medication Changes: Baseline drug therapy with standard HF 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 HF 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.

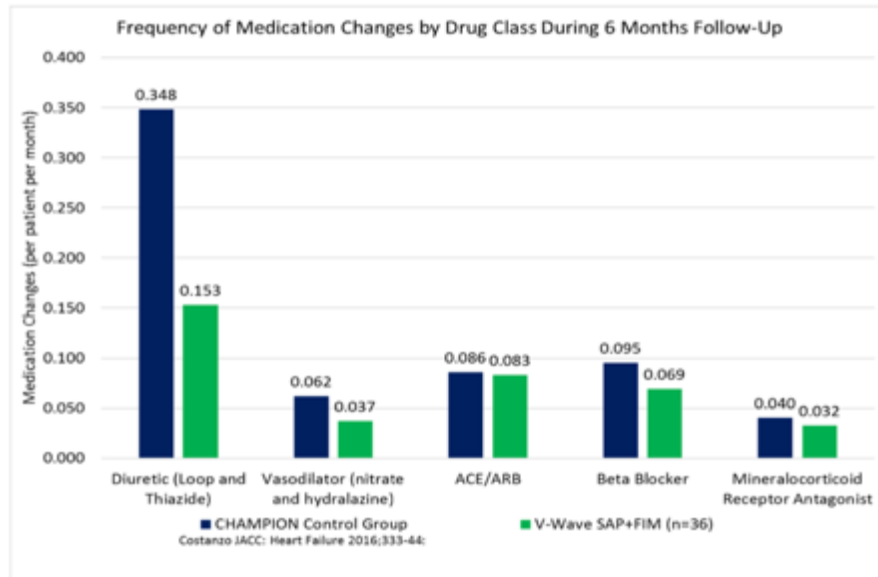


Figure 2. Medication Changes by Drug Class in CSAP+FIM vs. Champion Dataset

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.

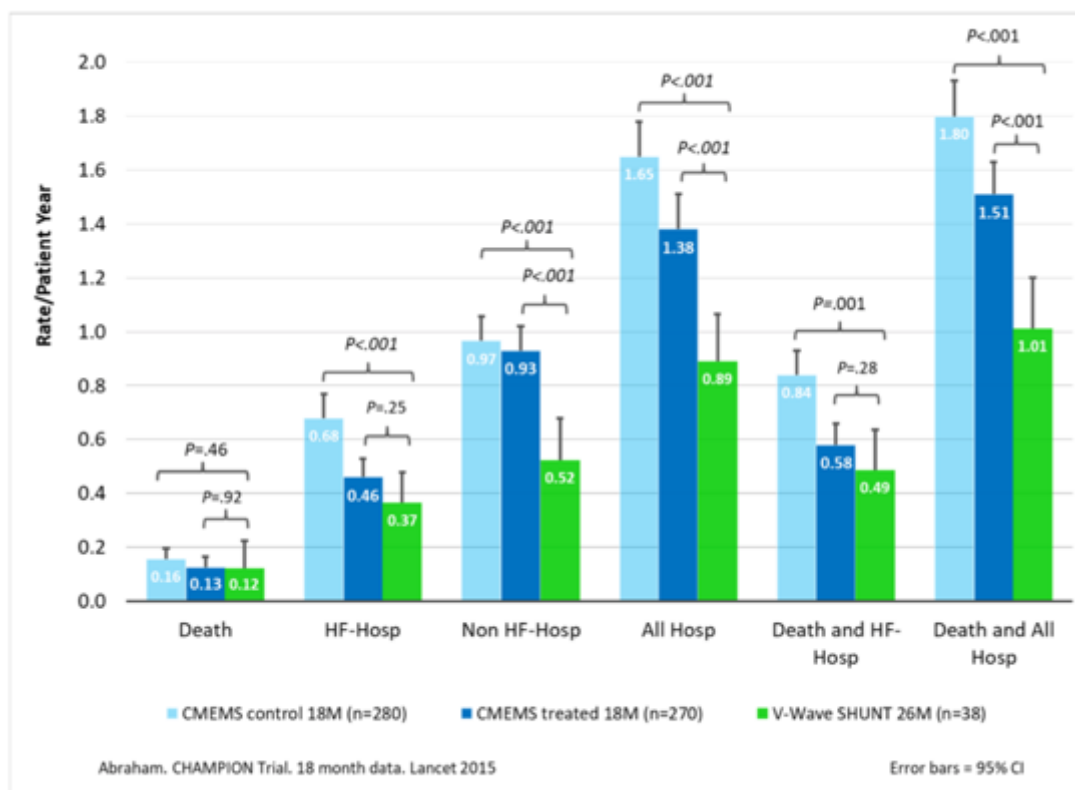


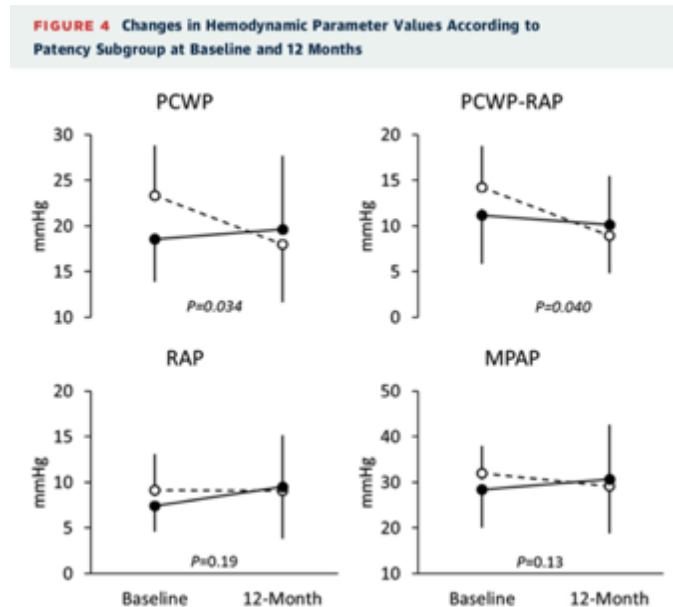
Figure 3. Hospitalization and Mortality of V-Wave Shunt vs. CHAMPION dataset

Shunt Patency

In the combined CSAP/FIM study, left-to-right flow through the shunt was confirmed in all patients at 3 months. At 12-month follow-up, there were 5 of 36 cases (14%) with total occlusions. In the remaining 31 patients (86%) with flow across their shunts, TEE showed that by 12 months, an additional 13 of 36 patients (36%) had developed in-shunt stenosis, consistent with the location of the bioprosthetic leaflets. Stenosis severity was assessed as subtotal in 7 cases, and the jets were measured to be skewed (range 9 to 26) from the long axis of the shunt in 5 of 6 remaining cases. Stenotic shunt cases were objectively differentiated from patients with widely patent shunts by measured vena contracta diameters (stenotic: 0.0 mm (IQR: 0 to 2.5 mm) vs. patent: 3.1 mm (IQR: 3.0 to 3.8 mm); $p < 0.001$) and Q_p/Q_s (stenotic: 1.05 0.12 vs. patent: 1.17 0.12; $p = 0.023$). There was no thrombus seen in or near the shunts, no migration of shunts from the site of deployment, and no erosion into adjacent cardiac structures in patients with occluded or stenotic shunts. Shunt stenosis or occlusion was not associated with precipitation of acute adverse clinical events, including thromboembolic events. The root cause of stenosis or occlusion was suggested from a stenotic shunt that was explanted during cardiac transplantation at 27-month follow-up. The bioprosthetic leaflets were thickened and stenotic with neoendocardial hyperplasia (pannus).

Compared with patients who developed shunt stenosis or occlusion, those who maintained patent shunts had baseline features with trends generally consistent with a poorer prognosis, including older age, more severe underlying heart disease and comorbidities, reduced exercise capacity, poorer systolic function, and worse hemodynamic status.

Figure 4 shows baseline and 12-month hemodynamic status according to shunt patency status at 12 months (n=18 stenotic or occluded and n=18 patent). Notwithstanding starting with generally poorer baseline hemodynamic status, by 1 year, patients with patent shunts exhibited improvements in PCWP (from 23.3 ± 5.4 mm Hg at baseline to 18.0 ± 4.0 mm Hg at 12 months, $p=0.011$), without worsening of RA or pulmonary artery pressures. These improvements were also significant relative to a lack of change in the stenotic or occluded subgroup. Patent shunt patients with reduced systolic function (n=14) exhibited a rise in LVEF from $23 \pm 7\%$ to $26 \pm 8\%$ ($p=0.007$) compared with a nonsignificant increase in LVEF (from $29 \pm 6\%$ at baseline to $32 \pm 8\%$ at 12 months, $p=0.066$) among those patients with HFrEF and occluded or stenotic shunts (n=16).



Patent shunt patients (open circles) and stenotic or occluded shunt patients (solid circles). P values are for comparisons between subgroups of the differences between baseline and 12 months. MPAP 1/4 mean pulmonary artery pressure. Abbreviations as previously stated. Figure credit: Rodés-Cabau et al., JACC: Cardiovascular Interventions. 2018;11(22);2300-10.

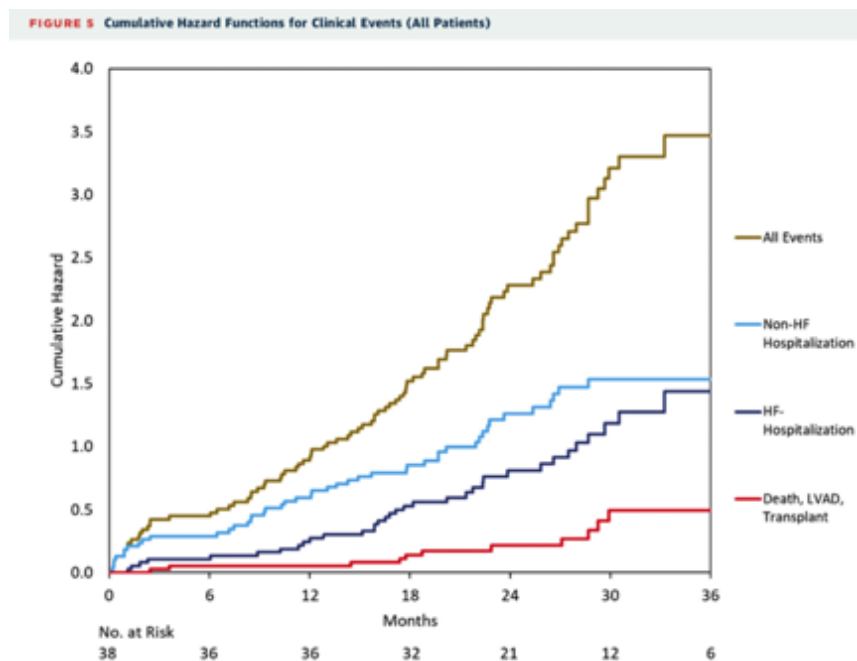
Regarding echocardiographic parameters of right ventricular structure and function, patients had moderate baseline right ventricular dilation, with systolic and diastolic dysfunction, mild to moderate tricuspid regurgitation, and pulmonary hypertension. Both patency subgroups maintained stable right ventricular function at 1 year.

Late Clinical Outcomes and Influence of Shunt Patency on Outcomes

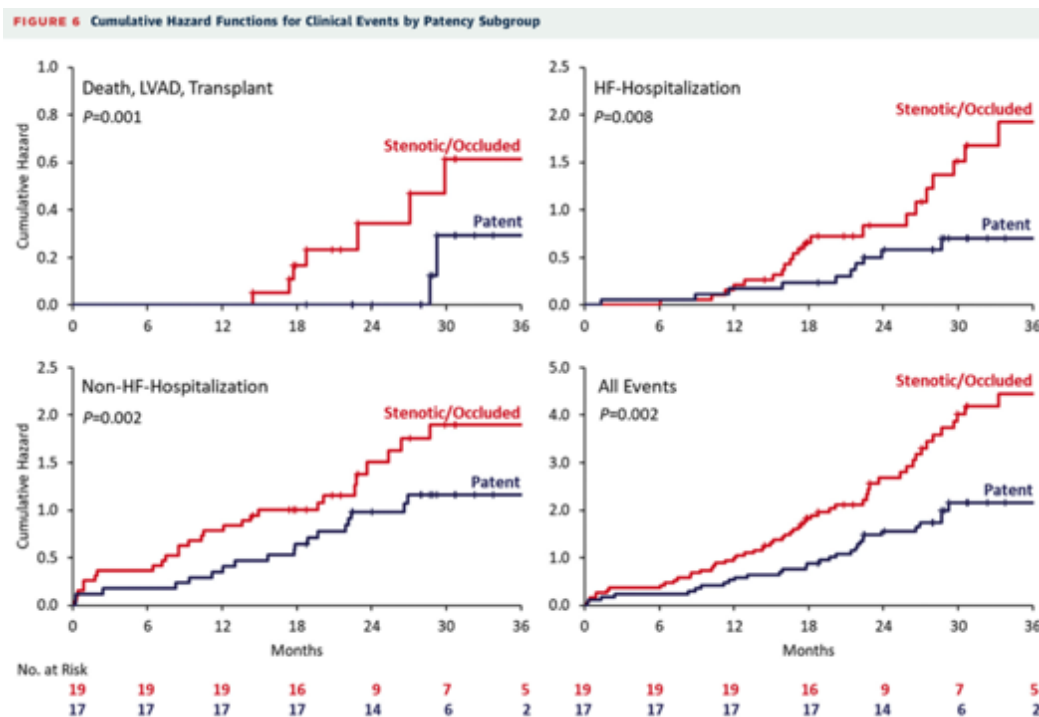
Throughout the total follow-up duration, there were 10 deaths (8 cardiovascular and 2 of non-cardiovascular causes). One patient received a left ventricular assist device as destination therapy at 15 months, and another underwent heart transplantation at 27 months. There were 30 HF hospitalization events in 11 patients (29%), and 45 non-HF hospitalizations in 19 patients (50%). Of the non-HF hospitalizations, 14 (31%) had coexisting worsening of HF.

Beyond the 12-month follow-up data, 10 patients with patent shunts surviving to their 24-month anniversary underwent TTE. One patient was found to have no flow, which was confirmed to be occluded on TEE. For the purposes of associating shunt patency with long-term clinical events, there were 17 and 19 patent and stenotic or occluded shunts, respectively.

Figure 5 shows the cumulative hazard functions of event types for all patients, and Figure 6 compares cumulative events according to shunt patency subgroup.



LVAD, left ventricular assist device. Other abbreviations as previously stated. Figure credit: Rodés-Cabau et al., JACC: Cardiovascular Interventions. 2018;11(22);2300-10.



Numbers at risk apply to upper and lower panels. Figure credit: Rodés-Cabau et al., JACC: Cardiovascular Interventions. 2018;11(22);2300-10.

Patients with patent shunts had a significantly lower risk for the combination of death, transplantation, or left ventricular assist device placement ($p=0.001$), of HF hospitalization ($p=0.008$), of non-HF hospitalization ($p=0.002$), and of all combined events ($p=0.002$), compared with those with stenotic or occluded shunts. Patients who would lose shunt patency tended to have low event rates during the first year, but then event rates increased corresponding to the period after documented shunt stenosis or occlusion. For example, the rate of HF hospitalization was 0.21 per patient-year during the first 12 months, increasing to 0.65 per patient-year thereafter ($p=0.035$). The increased rate of non-HF hospitalization seen in stenotic or occluded patients was in part associated with a larger number of cases with coexisting worsening HF during the hospital admission (10 of 27 events vs. 4 of 17 events in stenotic or occluded and patent patients, respectively).

In response to these data, the design of the V-Wave shunt has been modified and no longer includes the tissue valve, which should significantly reduce the incidence of shunt occlusion and stenosis.

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.

2.2.4 PERCUTANEOUS MITRAL VALVE REPAIR AND CLINICAL BENEFITS

As previously stated, MR may be due to a primary valve pathology such as mitral valve prolapse, MV perforation, or disruption of the subvalvular apparatus causing “flail” of the MV leaflet(s), known as degenerative MR. Degenerative MR can be the underlying etiology of HFpEF due to valvular heart disease, and significant MR may result in LV volume overload and subsequent LV dilation and reduced LV function. While afterload reduction and control of volume status (i.e. LA pressure and LVEDP) with diuretic therapy are key to the management of degenerative MR, surgical mitral valve repair or replacement has long been considered the gold standard for patients with degenerative MR. However, in patients at high-surgical risk, transcatheter mitral valve repair with the MitraClip device has been shown to be a safe and nearly as effective alternative (data summarized below).

MR may also be due to a secondary mechanism and not due to valvular pathology itself, termed functional MR. The most common causes of functional MR are due to LV enlargement, reduced systolic function / HFrEF, focal regional wall motion abnormality causing restriction of the posterior mitral valve leaflet, and/or LA dilation. Ischemic heart disease is a common cause of HFrEF and restricted LV wall motion, and is thus a common cause of functional MR as well. While the key tenants of GDMT for chronic systolic HF, afterload reduction and control of volume status apply similarly to functional MR, the benefits of surgical mitral valve repair or replacement have not translated to this patient population. The reasons for this are unclear, however a potential explanation is that prior studies of MV surgery in patients with functional MR included patients with very severe LV dysfunction less likely to benefit, and patients with functional MR are often sicker with advanced medical co-morbidities compared to patients with degenerative MR.

Despite a lack of benefit to surgical MV repair or replacement, transcatheter mitral valve repair with MitraClip was recently shown to significantly improve HF symptoms, reduce hospitalization, improve QOL, and improve survival

in patients with functional MR considered disproportionate (or worse) than the magnitude of LV dilation and LV dysfunction.

The MitraClip device is placed via a sheath placed in the femoral vein, commonly under transesophageal echo (TEE) guidance. The sheath provides access to the RA, and subsequently the interatrial septum is crossed with a transseptal puncture in standard fashion. The MitraClip delivery catheter is then advanced across the interatrial septum to the LA, and the MitraClip device is placed. The device clips the anterior and posterior mitral valve leaflets, improving apposition of the leaflets and altering annular geometry, which reduces MR. After MitraClip placement, the delivery catheter is removed and access site closed in usual fashion. The result of MitraClip placement is a reduction in MR, which leads to a reduction in LA pressures, reduced transmission to the pulmonary veins, and less pulmonary venous congestion. The MitraClip device is the only device currently FDA approved for treatment of both degenerative and functional MR.

Data from recent studies and trials of percutaneous MV repair are summarized below.

2.2.5 CLINICAL DATA ON PERCUTANEOUS MITRAL VALVE REPAIR

Degenerative MR

EVEREST II

There are a large number of observational studies reporting outcomes for MitraClip for degenerative MR, supporting its safety and efficacy in this patient population. The highest-quality data on MitraClip for degenerative MR is Endovascular Valve Edge-to-Edge Repair Study (EVEREST II).²⁵ In this study, 279 patients with moderate to severe (at least 3-4+) MR were randomized 2:1 to MitraClip or surgery for MR. Most (73%) had degenerative MR, while a minority (27%) had functional MR. Most patients had at least NYHA class II or III HF symptoms, and most (86%) underwent mitral valve repair. The primary endpoint of freedom from death, freedom from surgery for MV dysfunction, and freedom from 3-4+ MR was more common with surgery compared to MitraClip (73% vs 55%, $P=0.007$). This was driven by a more need for subsequent surgery in the MitraClip group, however there were no differences in the grade of residual MR or death. Importantly, MitraClip was safer than surgery, as surgery caused more major adverse events (48% vs 15%, $P<0.001$), driven predominantly by more patients that had ≥ 2 units blood transfused (45% vs 13%, $P<0.001$). There were no differences in other major safety events.

In the high-risk and continued access registry of the EVEREST II trial, 16.4% of patients had residual grade 3-4+ MR at 12 months. This is consistent with other registries which suggest the prevalence of residual 3-4+ MR is approximately 16-21% after MitraClip. Although MitraClip did not always completely eliminate MR, reduction in MR to 2+ or less was associated with LV reverse remodeling measured by improvements in LV end-diastolic volume and LA volume.^{26, 27}

These results indicate that while MitraClip for degenerative MR is not quite as effective as surgery, it is a reasonable alternative in high-risk patients, and is safer than surgery as it is not associated with as much major bleeding or need for blood product transfusion as surgery.

Functional MR

Key Registry Studies

Observational data from several studies likewise supports the safety of MitraClip for functional MR.²⁸ Illustrating this, in the large 2011-2012 Pilot European Sentinel Registry of 628 patients treated with MitraClip (72% had functional MR, 85.5% NYHA class III or IV), procedural success was very high (95.4%), and 1-year mortality was 15.3%. There were no differences in rates of 1-year mortality and HF

rehospitalization between patients with functional or degenerative MR (Log-rank $P=0.103$). While there was a significant improvement in MR grade in most patients, residual moderate or severe MR was observed in a 41.4% of patients at 1-year follow-up.²⁸ This relatively high prevalence of residual MR likely reflects that this was the early experience with MitraClip, as this has improved in more recent studies.

MITRA-FR

The Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trial was a trial of 304 patients with moderate to severe (2+ to 4+) functional MR randomized 1:1 to MitraClip or standard care.²⁹ All patients had reduced LVEF 15-40% (average LVEF 31%, LV EDV 135 ml), and NYHA class II-IV HF symptoms. While MR was reduced to 1+ or less in 75.6% of patients treated with MitraClip, there were no differences in the primary outcome of composite all-cause mortality or unplanned hospitalization between the intervention and control groups (54.6% vs 51.3%, Odds Ratio [OR] 1.16, 95% confidence interval (CI) 0.73-1.84, $P=0.53$), or components of the composite.³⁰ Results out to 2-years similarly showed no difference in the primary outcome or components of the composite, however in a repeat-event analysis, there was a significant reduction in HF hospitalization with MitraClip therapy observed between years 1 and 2, indicative of a late treatment effect of MitraClip. While the results of MITRA-HF support the safety of MitraClip, there was a higher-than-expected procedural complication rate in MITRA-FR than observed in other studies (14.6%), which may also be a reason for reduced efficacy in this trial.

COAPT

The COAPT trial is the definitive trial of percutaneous MV repair with the MitraClip system for degenerative MR.⁶ In COAPT, 614 patients with functional MR were randomized 1:1 to MitraClip + GDMT or GDMT alone. All patients had 3-4+ MR, with severe 4+ MR present in 48% of patients, and mean LVEF was 31%. The mean number of clips implanted/patient was 1.7 (slightly higher than earlier studies), and MR was 1+ or less in 85% of implanted patients at DC.

The primary efficacy endpoint of hospitalization for HF within 24 months was significantly lower in patients treated with MitraClip vs GDMT alone (35.8% vs 67.9%; HR 0.53, 95% CI 0.40-0.70, $P<0.001$), as was the secondary endpoint of death from any cause within 24 months (29.1% vs 46.1%; HR 0.62, 95% CI 0.46-0.82, $P<0.001$) (**Figure 7**). All secondary endpoints were likewise in favor of MitraClip over GDMT alone (**Table 5**). There was also a high freedom from device complications at 12 months (96.6%, lower confidence limit 94.8%).

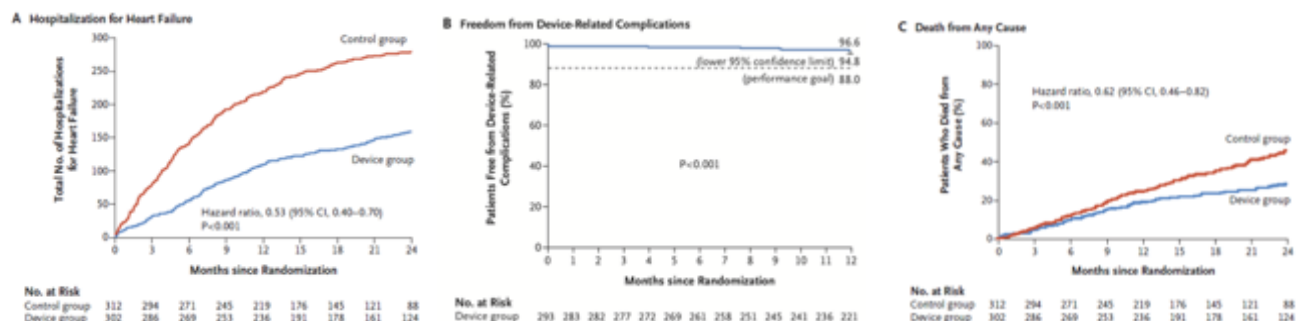


Figure 7. Key results from the COAPT trial. MitraClip significantly reduced hospitalization for HF, death from any cause, and there was a 96.6% freedom from device complications at 12 months. Adapted from Stone GW, et al. COAPT Trial. N Engl J Med 2018;379:2307-18.

Secondary, listed in hierarchical order				
Mitral regurgitation grade of 2+ or lower at 12 mo — no./total no. (%)	199/210 (94.8)	82/175 (46.9)	—	<0.001**
Death from any cause at 12 mo — no. of events (Kaplan–Meier estimate of event rate)	57 (19.1)	70 (23.2)	0.81 (0.57 to 1.15)††	<0.001 for noninferiority‡‡
Death or hospitalization for heart failure within 24 mo	—	—	—	<0.001§§
Change in KCCQ score from baseline to 12 mo — points¶¶	12.5±1.8	-3.6±1.9	16.1 (11.0 to 21.2)	<0.001***
Change in distance on 6-min walk test from baseline to 12 mo — m†††	-2.2±9.1	-60.2±9.0	57.9 (32.7 to 83.1)	<0.001***
All hospitalizations for any cause within 24 mo — no. of events/total no. of patient-yr (annualized rate)	474/446.5 (106.2)	610/416.8 (146.4)	0.76 (0.60 to 0.96)	0.02§
NYHA functional class of I or II at 12 mo — no./total no. (%)	171/237 (72.2)	115/232 (49.6)	—	<0.001**
Change in left ventricular end-diastolic volume from baseline to 12 mo — ml	-3.7±5.1	17.1±5.1	-20.8 (-34.9 to -6.6)	0.004***
Death from any cause within 24 mo — no. of events (Kaplan–Meier estimate of event rate)	80 (29.1)	121 (46.1)	0.62 (0.46 to 0.82)	<0.001‡‡‡
Freedom from death from any cause, stroke, myocardial infarction, and nonelective cardiovascular surgery for a device-related complication at 30 days — % (lower 95% confidence limit)	96.9 (94.7)	—	—	<0.001 for comparison with goal of 80.0%**

Table 5. Key secondary endpoints of the COAPT Trial.

The primary efficacy endpoint was shown to favor MitraClip across all patient subgroups. Further, analysis demonstrated no clear echocardiographic parameters predictive of favorable results. Recently presented 3-year results from COAPT indicate that 38% of eligible patients crossed over from medical therapy to MitraClip between years 2 and 3, and that the benefit for patients who crossed over was similar to patients randomized thereafter.³¹ Further, dedicated QOL studies indicate a sustained improvement in QOL in patients treated with MitraClip compared to medical therapy alone,⁷ and that MitraClip is cost effective compared to accepted standards (\$55,600/QALY).³² These results indicate that MitraClip improves outcomes across a broad range of patients, as there was a near universal benefit from MitraClip among treated patients in the COAPT trial.

Reconciliation of Mitra-FR and COAPT studies

The results of the COAPT trial were the main determinant leading to FDA approval of MitraClip for patients with functional MR. There are several plausible explanations for the positive findings from COAPT and negative findings from MITRA-FR. First, the COAPT trial was a larger trial, with longer follow-up, and thus has higher power to detect a difference in event rates. Second, on closer inspection COAPT and MITRA-FR studied different patient populations. Patients in MITRA-FR had slightly less severe MR with an effective regurgitant orifice area (EROA) of 0.31 mm², compared to an EROA of 0.41 mm² in COAPT. Further, patients in COAPT had higher NT pro BNP levels (1043 vs 800 ng/L). These findings suggest that patients in COAPT had MR that was worse than may be expected were LV dysfunction to be the predominant cause. This concept has been termed “disproportionate MR”, or MR that is out of proportion for the degree of LV dysfunction. Thus, the results of COAPT and MITRA-FR may be viewed as complementary. Patients with disproportionate MR similar to those enrolled in COAPT may be expected to benefit more from MitraClip therapy, whereas patients with more severe LV dysfunction and dilation and less severe MR similar to those in MITRA-FR may not achieve the same results.

With this realization, all patients enrolled in the current study will be treated with MitraClip per current FDA guidelines, which follow similar screening criteria as COAPT.

Potential Benefits of V-Wave Shunt Placement after MitraClip

The potential benefits of V-Wave Shunt placement after MitraClip are follows:

- 1- The V-Wave shunt will allow for shunting of blood from left to right atrium in patients with residual elevation in LA pressure after MitraClip. This will further serve to decrease LA pressure, pulmonary venous pressure, pulmonary venous congestion, and pulmonary edema. This benefit would be expected for patients regardless of their level of residual MR (whether present or not).

- 2- While most patients will be left with 2+ residual MR after MitraClip, the procedure does not often completely eliminate MR. Patients with residual MR at rest or exercise-induced MR may be less likely to enter pulmonary edema, as instead of the V-wave from MR becoming worse during exercise and being transmitted to the pulmonary veins, this would at least in part be transmitted across the interatrial shunt. This could result in reduced pulmonary venous congestion during exercise, and increased exercise tolerance.
- 3- Importantly, **V-Wave shunt placement would use the existing transeptal puncture location that the MitraClip sheath was advanced across.** This would be a tremendous benefit of placing the V-Wave shunt after MitraClip, as an additional transeptal puncture would not be needed. This would reduce the risk and time needed to complete of the V-Wave shunt procedure significantly.

2.2.6 OTHER ONGOING STUDIES ON INTERATRIAL SHUNT PLACEMENT

The proposed study is unique among all completed and ongoing studies of interatrial shunt placement. Importantly, although the CSAP/FIM study included both patients with HFrEF and HFpEF, patients with moderate to severe or severe MR were excluded from these studies. Thus, it is the goal of the current study to evaluate the feasibility and safety of placement of the V-Wave shunt device after successful percutaneous mitral valve repair with MitraClip in patients with reduced LVEF $\leq 50\%$ and residual elevation in LAP after the procedure, using the existing transeptal communication created during MitraClip placement to deploy the device. As this has not yet been studied, and minimizes procedural risk to the patient, this represents a significant opportunity to improve care in this high-risk patient population.

Regarding the other ongoing studies of interatrial shunt placement, the REducing Lung congestion symptoms using the v-wave shunt in adVancEd Heart Failure (RELIEVE-HF) trial (NCT03499236) is a large, prospective, multicenter, patient and observer blinded randomized control trial of 400 patients with either HFrEF or HFpEF randomized 1:1 to V-Wave shunt or medical therapy alone. Importantly, although V-Wave Ltd has provided permission for the RELIEVE-HF protocol to serve as a foundation for this study protocol, the current study is investigator initiated. V-Wave Ltd does not sponsor the current study, and the current study has no formal relationship to the RELIEVE-HF trial.

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 $\geq 40\%$.

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.^{33, 34} Key inclusion criteria included: LVEF $\geq 40\%$, 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 reported November 2017.³⁵ 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 $\geq 40\%$, IASD treatment unloads the LA 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 LA 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.
- 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 | • Failure to deliver interatrial shunt to its intended site | • Psychological intolerance |
| • Allergy, anaphylactic reaction, drug reaction, to contrast medium, anesthesia reaction, device components | • Failure to retrieve delivery system components | • Pulmonary thromboembolism |
| • Arrhythmia | • Fever or hyperthermia | • Radiation induced skin or tissue injury |
| • Atrial septal defect (iatrogenic) | • Gastrointestinal disturbance (tear of bleeding of esophagus, peritonitis, infarction, ileus, nausea, vomiting, diarrhea) | • Reintervention/closure of shunt due to excessive shunting |
| • Bleeding | • Hematuria | • Removal of shunt due to infection |
| • Cardiac arrest | • Hemolysis | • Renal insufficiency |
| • Cardiac or great vessel perforation | • Hemoptysis | • Respiratory failure, atelectasis, pneumonia |
| • Cardiac tamponade | • Hemorrhage requiring transfusion | • Seizure |
| • Coagulopathy | • Hypertension | • Shock (cardiogenic or anaphylactic) |
| • Damage to adjacent cardiac structures | • Hypotension | • Skin irritation or inflammation |
| • Death | • Hypoxemia | • Stridor |
| • Deep venous thrombosis (DVT) | • Infection (including septicemia and endocarditis) | • Stroke or transient ischemic attack (TIA) |
| • Device migration, embolization or erosion | • Interference with other implanted devices | • Syncope |
| • Device thrombosis | • Loss of limb | • Thrombosis |
| • Dislodgement of other previously implanted devices | • Myocardial infarction | • Urinary retention |
| • Effusion (e.g., pericardial, pleural, ascites) | • Nerve damage | • Urinary tract infection |
| • Emboli (air, thrombus, device) | • Pain | • Vascular trauma (dissection, occlusion, hematoma, arteriovenous fistula, pseudoaneurysm, perforation, spasm) |
| • Emergency cardiac or vascular surgery | • Permanent disability | • Worsening right ventricular heart failure and pulmonary hypertension |
| | • Pneumothorax | |

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 CREATION OF AN INTERATRIAL SHUNT

Risk of Transseptal Puncture

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. In the case of the current protocol, the V-Wave Shunt device will be placed after the MitraClip procedure. A transseptal puncture is performed for the MitraClip procedure, and the MitraClip sheath is advanced across the interatrial septum for the MitraClip procedure. V-Wave Shunt placement will thus use the existing transseptal puncture / interatrial communication created by the MitraClip procedure, and will not require an additional transseptal puncture. This should significantly reduce the risk of V-Wave shunt placement, and eliminate risk from this part of the procedure were V-Wave shunt placement to be performed on its own independent of MitraClip.

In the event that the transeptal puncture used for MitraClip placement is not in an anatomical location suitable for V-Wave shunt placement, the patient will be excluded from the study. While performing a new transseptal puncture in an appropriate anatomical location for V-Wave shunt placement could be considered, there are no data on the safety of this and thus these patients will be excluded from the

current study. Data will be collected on the percentage of patients who are excluded from the study based on this criteria.

Transseptal catheterization and catheter manipulation within the LA 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 LA 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.^{25, 36, 37} 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., published survey data from 5,520 transseptal catheterizations performed in 33 Italian centers spanning 12 years through 2004.³⁸ 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 trans-septal 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 and structural heart intervention on structures in the LA or interatrial septum are generally known and appears to be acceptable relative to the natural history of the underlying disorders being treated.

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 LA chamber and the outlet side in the RA 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 to the V-Wave shunt 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.

The incidence of embolization, maldeployment, and inadvertent deployment are not expected to be increased in patients undergoing V-Wave shunt placement after MitraClip therapy if they are good anatomical candidates for device placement, as determined as satisfying the anatomical criteria specified in this protocol.

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. It has been asserted that for VTE to enter the systemic circulation, the prevailing LA to RA pressure gradient seen in HF 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. 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. These circumstances may theoretically increase the risk of paradoxical embolism across the V-Wave shunt device.

Any risk of stroke from paradoxical embolization must be weighed against the background rate of stroke in HF patients. HF patients are known to 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.³⁹ To this point, in a long-term follow-up cohorts of the CORONA and GISSI-HF studies totaling 9,585 patients, 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.⁴⁰ These and other data suggest that although paradoxical embolic stroke may be associated with atrial shunting, stroke is more likely due to AF and non-cardioembolic causes. An increased risk of stroke is unlikely given the already elevated underlying rate of stroke in patients with advanced HF.

Another potential concern is thromboemboli originating from the surfaces of the shunt device itself. In a review of 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).⁴¹ Risk factors for device thrombosis include AF, 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.

Given the plausible mechanism for an increase in the risk of paradoxical embolism and device-related thromboembolism, patients will be followed long-term out to 5 years. This will allow for the assessment of late paradoxical embolism after V-Wave shunt placement.

Risk of Creating Too Large of 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.⁴²⁻⁴⁵ 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.⁴⁶⁻⁴⁸ 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.^{49, 50} 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.^{46, 51} 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.

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. The V-Wave shunt device creates a shunt of 5 mm, and thus the adverse effects sometimes observed with larger shunts would not be anticipated.

Possible Interaction with Concomitant Medical Treatments

The V-Wave Shunt may interfere with catheter-based or surgical procedures which require access to the LA. These include but are not limited to: future repeat mitral valve repair or replacement, LA 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.

Additional Risks

Due to the investigational status of the interatrial shunt, there may be additional risks that are not yet known.

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

Due to the investigational status of the interatrial shunt, risk/benefits are not yet known.

Studies with the MitraClip suggest that many patients who receive the MitraClip may be minimally symptomatic after the procedure, and therefore may not benefit from the V-Wave interatrial shunt. The selection process at the time of MitraClip implant in our study is designed to identify patients who are more likely to remain symptomatic; this selection process is not yet fully validated.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

2.3.3.1 STEPS TO MITIGATE RISK

According to the manufacturer of the V-Wave shunt (V-Wave, Ltd.), 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, severe pulmonary hypertension, and residual moderate or worse MR ($\geq 2+$) 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.

To minimize variability in patient selection and implantation technique, only a single center will be used for this study (Cleveland Clinic). This site is highly experienced with advanced HF services, and two physician expert investigators will be allowed on the study 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.

All 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 be 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 medical monitor will adjudicate all SAEs for device or procedure-relatedness. However, given the small nature of this study, a formal data safety monitoring board (DSMB) will not be required.

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

Table 6 lists the anticipated device and procedure-related major risks as well as expected event frequencies with respect to background rates in a representative control group of patients with HF.

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%	-

Table 6. Anticipated Device and Procedure-Related Risks

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.

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 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.

2.3.3.3 COMPARISON OF POTENTIAL RISKS AND BENEFITS OF MITRACLIP ALONE, THE COMBINED MITRACLIP + V-WAVE SHUNT PROCEDURE, AND MITRACLIP FOLLOWED BY STAGED V-WAVE SHUNT PLACEMENT

Comparison of Risk of Paradoxical Embolism Based on Treatment Strategy

As discussed in Section 2.3.1, there is a theoretical risk of paradoxical embolism in patients with an intraatrial shunt. MitraClip placement alone requires a transseptal puncture and placement of the MitraClip sheath across the septum, creating a small iatrogenic ASD, which is typically 2-3 mm diameter. In the majority of patients, this iatrogenic ASD closes spontaneously. In a minority of patients (up to 40% of patients), this ASD persists, but is rarely hemodynamically significant.^{6, 49, 52} Though there is similarly a theoretical risk of paradoxical embolism in patients following MitraClip with persistent iatrogenic ASD, there have been no reports to date of increased risk of paradoxical embolism in patients following MitraClip placement with persistent ASD to date.

To this point, the MITHRAS-trial (Closure of Iatrogenic Atrial Septal Defects following Transcatheter Mitral Valve Repair) was recently presented at the Transcatheter Therapeutics (TCT) 2020 annual meeting (NCT03024268). In this study, 80 patients with iatrogenic ASD present 30 days after transcatheter mitral valve repair were randomized 1:1 to percutaneous closure of the ASD (n=40) or conservative therapy (n=40), and followed for an additional 5 months (6 months total). All patients had Qp:Qs ≥ 1.3 and a predominantly left-to-right shunt. Compared to patients who underwent ASD closure, a persistent ASD was not associated any adverse events, including a difference in 6MWT distance, NYHA functional class, NT-proBNP values, or death or hospitalization for heart failure. While this is a small trial underpowered for clinical events, these results suggest that there will be low risk of adverse events from creation of an iatrogenic ASD in V-Wave MitraClip study.

That said, the V-Wave shunt device creates a larger, permanent ASD of 5.1 mm diameter. Given this, the risk of paradoxical embolism may be higher in patients after V-Wave shunt device placement, whether or not combined with MitraClip placement. As described in Section 2.3.1, this is a theoretical risk, as the risk of stroke is more likely attributable to other risk factors present in this patient population with advanced HF rather than the ASD – principally, atrial fibrillation.³⁹

It is believed that the risk of paradoxical embolism is highest in patients with right to left shunting such as patients with RAP > LAP, and those with bidirectional shunting. To minimize this risk, patients with moderate-severe RV dysfunction, severe pulmonary hypertension, and moderate-severe tricuspid valve disease will be excluded.

The study's selection of only including patients with LAP > 20 mmHg and LAP – RAP > 5 mmHg at the end of MitraClip placement is for this very reason – to maximize the likelihood of a small but consistent left to right atrial shunt, which may in turn reduce the risk of paradoxical embolism (see Exclusion Criteria).

Association of LAP with Outcomes After MitraClip Therapy

Though the current study is designed to demonstrate the safety of V-Wave shunt placement in this patient population, including the hemodynamic eligibility criteria above may also select patients who would benefit most, as an elevation in LAP post-MitraClip may reflect residual LV or diastolic dysfunction not addressed with correction of MR.

Supporting the use of these hemodynamic criteria for V-Wave Shunt placement, there is evidence that elevated LAP and persistent V-Waves following MitraClip therapy associates with worse outcomes during follow-up. In a study of 50 patients who had MitraClip therapy, improvements in LA hemodynamics correlated with improvement in exercise capacity as documented by 6MWT at 30-days.⁵³ In this study, lower post-MitraClip final mean LAP was associated with an improvement in 6MWT above median (25 m) (OR 0.87; 95% CI 0.77-0.99, P=0.03). In multivariable analysis, each 5 mmHg decrease in V-wave was independently associated with a 49% increased likelihood for improvement in 6MWT above median (OR 1.49, 95% CI 1.01-2.18, P=0.04). Based on the results of this study, it is reasonable to infer that placement of the V-Wave shunt device in patients with residual elevation in LAP could potentially improve 6MWT, especially if the elevation in LAP is due to significant residual V-Wave.

Building on this, in a separate study of 50 patients who had continuous LAP measurement during MitraClip placement, patients who had an improvement in LA mean pressure after MitraClip therapy had less risk of rehospitalization for HF, and were less likely to have NYHA class III or IV HF at follow-up (median 112 days). In this study, intraprocedural mean LA pressure was independently associated with

NYHA class III-IV status at follow-up (HR 1.612, 95% CI 1.109-2.345, $P=0.012$), as was LA mean pressure indexed to LV systolic pressure (afterload) (HR 1.497, 95% CI 1.006-2.102, $P=0.005$). Further, LA mean pressure indexed to LV systolic pressure remained independently associated with rehospitalization due to heart failure during follow-up (HR 3.377, 95% CI 3.180-3.585, $P=0.007$).^{54, 55} Similar results were obtained by Kaplan-Meier analysis:

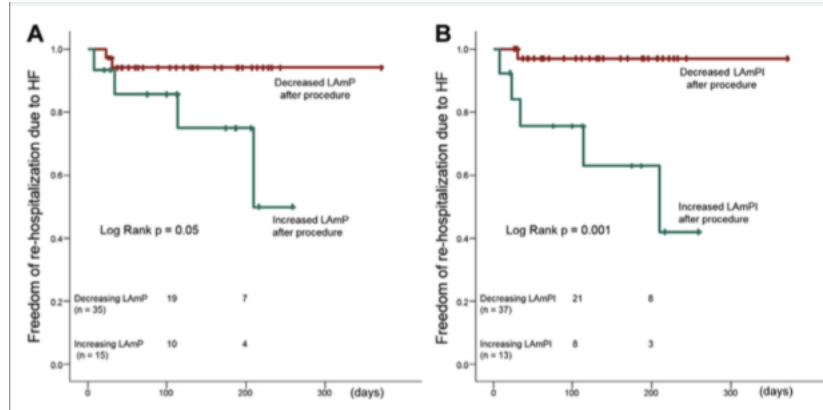


Figure 8. Association between LA mean pressure (LAmP) (Panel A) and LA mean pressure indexed to LV systolic pressure (LAmPI) (Panel B) at the end of the MitraClip procedure and freedom from re-hospitalization from HF.⁵⁴

In another study, improvement in pulmonary venous waveform morphology (i.e. restoration of normal pulmonary venous flow into the LA) at the time of MitraClip placement was independently associated with a survival at 24 months, and less risk for cardiac rehospitalization at 1 year.⁵⁶

Given these data, it is the hypothesis that implantation of the V-Wave shunt will be safe, and may further reduce LAP and improve PV waveforms, which have been shown to be associated with less risk for rehospitalization and improved NYHA functional class during longitudinal follow-up.

Comparison of Net Risk-Benefit Ratio Based on Treatment Strategy

It is expected that certain patients will improve from MitraClip placement alone. However, a substantial number of patients have NYHA class III-IV HF symptoms even after MitraClip therapy. While a comparison of MitraClip alone, combined MitraClip + V-Wave Shunt placement during the same procedure, and MitraClip followed by V-Wave placement if necessary may be one possible strategy to demonstrate the efficacy of the V-Wave device in this patient population, demonstrating efficacy is not the goal of the current early feasibility study. Further, as previously described, elevations in LAP and lack of an improvement in pulmonary venous waveform morphology are associated with poorer outcomes after MitraClip therapy. Thus, it is likely that patients with persistently elevated LAP > 20 mmHg and LAP – RAP > 5 mmHg after MitraClip therapy will benefit from V-Wave Shunt placement, making sequential implantation not necessary, and adding to increased patient risk from having to undergo a separate procedure.

To this point, there may be specific benefits of undergoing both MitraClip and the V-Wave shunt in a combined, single procedure. As the combined procedure will eliminate the need for two separate procedures, additional vascular access will be not needed, saving the need for repeat femoral access and potentially reducing the risk for major bleeding and vascular access complications. Further, the transseptal puncture used for the MitraClip procedure will be used for V-Wave shunt placement, eliminating the need for another transseptal puncture in patients without a persistent ASD. As this is

one of the major risks of the procedure, the combined procedure is expected to carry significantly less risk. Further, the need for another transesophageal echocardiogram, repeat general anesthesia, and repeat endotracheal intubation will be eliminated, also significantly reducing risks compared to doing separate procedures. In addition, performing the combined procedure would minimize inconvenience to the patient, as it combines two procedures into one. It is believed that these important considerations will tip the risk-benefit balance in favor of performing the combined procedure.

Importantly, the V-Wave shunt is not FDA approved, and cannot be offered as a stand-alone treatment after MitraClip placement currently. As such, there is no option for standalone V-Wave shunt placement after MitraClip as a separate procedure at this time, and thus this comparison cannot be made outside of a clinical study. A study powered for efficacy would require a much larger sample size. Thus, it is important to demonstrate early feasibility and safety of the combined MitraClip + V-Wave shunt procedure prior to performing an efficacy study and subjecting a much larger number of patients to the procedure.

3 OBJECTIVES AND ENDPOINTS

The objective of the current study is to provide reasonable assurance of safety and feasibility of implantation for the V-Wave Interatrial Shunt System immediately after MitraClip placement.

3.1 PRIMARY SAFETY ENDPOINT

3.1.1 PRIMARY SAFETY ENDPOINT

The Primary Endpoint of the study will be to demonstrate device safety. 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. MACNE is defined as all-cause death, stroke, myocardial infarction, V-wave shunt device embolization, cardiac tamponade, or device related re-intervention or surgery.

Specifically, 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.

Patients will be followed out to 5 years for the assessment of adverse events, including late paradoxical embolism.

3.2 SECONDARY EFFICACY ENDPOINTS

3.2.1 SECONDARY EFFECTIVENESS ENDPOINTS (EXPLORATORY)

Several efficacy outcomes will be assessed as secondary endpoints. The goal of including these endpoints is to detect a signal of efficacy, as the study will not be powered for these outcomes. Outcomes will be compared in individual patients before and after study device placement (paired analyses), as well as in all patients pre- compared to after study device placement (where applicable).

- 6 minute walk test (6MWT) distance / Borg scale
- Kansas City Cardiomyopathy Questionnaire (KCCQ) score
- New York Heart Association (NYHA) HF class (I-IV)
- Echocardiographic parameters (measured by transthoracic and/or transesophageal echocardiogram [TTE or TEE, respectively])
 - Degree of MR (none, trivial, 1-4+)
 - Degree of tricuspid regurgitation (TR; none, trivial, 1-4+)
 - Right ventricular systolic pressure (RVSP)
 - Right atrial pressure (RAP)
 - Right ventricular (RV) function (normal, mild-severe reduction)
 - Left ventricular (LV) function (quantitative – LVEF %; qualitative – normal, mild-severe reduction)
 - Incidence of loss of shunt flow across IAS by doppler and/or agitated saline study
- NT pro BNP
- Readmissions for HF (adjusted for all-cause mortality)
- Technical success (defined as successful delivery and deployment of the study device and removal of the delivery catheter)
- Device success
- Procedural success

The primary analysis for secondary endpoints will be baseline compared to 12 months, however will be evaluated at 1 month, and 6 months as well.

3.3 EFFECTIVENESS QUALIFYING ENDPOINT AND ELIGIBILITY EVENT DEFINITIONS

3.3.1 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, hepatjugular 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, as adjudicated by the independent medical monitor 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.

3.3.2 TECHNICAL SUCCESS

Technical success will be measured at exit from cath lab and is defined as alive, with successful 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.

3.3.3 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.

3.3.4 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 $\geq$ 48 hours).

3.4 OTHER ENDPOINT DEFINITIONS

3.4.1 STROKE

Stroke will be classified according to Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative (NeuroARC).⁵⁷ Events will be classified as CNS injury (Type 1) including ischemic stroke, with or without hemorrhagic conversion, along with other Type 1 subtypes.

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.

Patients will be followed out to 5 years to assess for the risk of late paradoxical embolism from placement of the V-Wave shunt device and creation of an intraatrial shunt.

4 4 STUDY DESIGN

4.1 OVERALL DESIGN

The V-Wave Shunt / MitraClip study hypothesis is that implantation of the V-Wave Shunt System immediately following MitraClip placement is feasible and safe. This will be demonstrated by achieving the Primary Safety Endpoint, demonstrating an acceptably low level of device-related MACNE. While the study will not be powered to demonstrate efficacy, we will collect data on study device efficacy to assess if a signal of efficacy exists.

The current study is a prospective study with the intent to implant the V-Wave shunt device after MitraClip in 10 patients (Schema Figure 1). The study will be performed in a single center (Cleveland Clinic, Cleveland, OH). The study device will be implanted by a team of 3 operators, all of which are skilled in structural heart procedures including transseptal puncture, MitraClip placement, and interventions involving the left side of the heart (LA, left atrial appendage, and MV).

Patients will be screened for eligibility in a 2-step process. Patients will undergo a Preliminary Screen at the Baseline Visit at which time Inclusion Criteria and Preliminary Exclusion Criteria will be assessed. All patients must be considered clinical and anatomic candidates for commercial MitraClip placement, for the indication of functional MR or mixed functional and degenerative MR. Screening assessments should be completed with the patient in stable condition as an outpatient. Consenting a patient pre-

discharge or at discharge is acceptable. Final eligibility for V-Wave device implantation is subsequently assessed at the Final Screen assessed by the *Implanter-Investigator* at the time of MitraClip placement, at which time invasive hemodynamics will be measured with right heart catheterization, and TEE performed to assess whether final hemodynamic and anatomic exclusion criteria are absent. In recognition that a proportion of patients that pass the Preliminary Screen at the Baseline Visit will not pass the Final Screen after MitraClip, the study will allow for up to 50 patients to be enrolled, with the intent to place the V-Wave shunt in the first 10 patients who pass the Final Screen. Patients will be considered enrolled in the study once they sign consent and pass the Preliminary Screen, but will only be followed longitudinally if the V-Wave shunt is placed or attempted to be placed.

The enrolling site will undergo proctoring by the Company prior to study initiation. All patients will have the same in clinic follow-up schedule as described in the Schedule of Activities (SoA, Section 1.3) and be treated with Guideline-Directed Medical Therapy as per commercial MitraClip guidelines. After shunt placement, patients will 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.

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). Patients will be followed out to 5 years for the determination of late adverse events, including paradoxical embolism. Standard trial governance procedures including event endpoint adjudication by a Clinical Events Committee will also help assure patient safety.

4.2 END OF STUDY DEFINITION

It is anticipated that the study will require approximately 6 months to enroll patients. The study primary endpoint will be reported approximately 12 months from the date of the last patient enrolled. The study will continue for 5 years from the date of the last patient enrolled to detect late safety events, including paradoxical embolism.

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).

An independent Medical Monitor will be appointed to monitor the study by reviewing the case report forms, SAE and AE forms at specified intervals throughout the study and will be responsible for the oversight of safety.

After each scheduled review of the accumulating safety data, medical monitor will provide 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. Given the small size of the study, the medical monitor will serve the purpose typically performed by a clinical events committee (CEC) and DSMB. The medical monitor recommendations will be reviewed by the Sponsor and also sent to the FDA, and if suspension or termination is recommended for the safety of the patient, the FDA can

then suspend the trial. If a decision is made to terminate the study early, a modified protocol for follow-up of implanted patients will be created by the sponsor, which will be submitted to the FDA. The Sponsor reserves the right to terminate the clinical investigation at any time and for any reason.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Inclusion criteria – to be assessed at Baseline Visit:

1. All patients must meet criteria for commercial placement of MitraClip for functional MR, as specified by the MitraClip IFU.
2. Clinical eligibility for Mitraclip:
 - a. Symptomatic secondary MR (moderate-severe [3+ or 4+] or greater) due to ischemic or non-ischemic cardiomyopathy
 - b. NYHA functional class III, or ambulatory IV
 - c. Maximization of GDMT as directed by the “Heart Team”, including an interventional cardiologist (implanting physician), heart failure cardiologist, and cardiothoracic surgeon. This includes adequate treatment for systolic HF (LV dysfunction), rhythm disorders, and coronary disease, if applicable
 - i. An inhibitor of the reninangiotensin 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)
 - ii. 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.
 - iii. 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.
 - iv. Drug intolerance, contraindications, or lack of indications must be attested to by the investigator.
 - v. Receiving Class I recommended cardiac rhythm management device therapy.
 - (1) 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 device implantation
 - (2) 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.
 - d. At least one hospitalization for heart failure in last year OR corrected BNP ≥ 300 pg/mL or corrected NTproBNP ≥ 1500 pg/mL
 - e. Heart team has determined that mitral valve (MV) surgery will not be offered as a treatment option
3. Anatomic eligibility for MitraClip:
 - a. LVEF $\geq 20\%$ and $\leq 50\%$
 - b. LV end-systolic dimension ≤ 70 mm

- c. MV orifice area > 4.0 cm² by TEE
 - d. Minimal calcification in the grasping area
 - e. No leaflet cleft in the grasping area
 - f. In patients with a degenerative component to MR, the following additional criteria must be met:
 - i. Flail width <15 mm
 - ii. Flail gap <10 mm
 - g. The primary regurgitant jet is non-commissural, and in the opinion of the implanting investigator can be successfully be treated by the MitraClip (if a secondary jet exists, it must be considered clinically insignificant)
 - h. Transseptal catheterization and femoral vein access is feasible per investigator
4. 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)

Preliminary Exclusion Criteria (PEC) – to be assessed at Screening Visit:

1. Severe pulmonary hypertension, defined as RV systolic pressure or PA systolic pressure > 70 mmHg, or PVR > 4 Woods units, measured by any modality (TTE, TEE, cardiac MRI, or pulmonary artery catheterization [if data available]).
2. Moderate or severe RV dysfunction defined as TAPSE <12mm or RVFAC ≤25% as assessed on Baseline TTE, or qualitative assessment of severe RV dysfunction on TTE, TEE, or cardiac MRI.
3. Untreated severe (3+ to 4+) tricuspid or pulmonary regurgitation.
4. Untreated clinically significant coronary disease requiring revascularization
5. Coronary artery bypass grafting, percutaneous coronary intervention, transcatheter aortic valve implantation, or CRT-D implantation within 30 days
6. Aortic or tricuspid valve requiring surgery or transcatheter intervention
7. COPD requiring continuous home oxygen therapy or chronic outpatient steroid use
8. Cerebrovascular accident within prior 30 days
9. Known severe symptomatic carotid stenosis
10. Carotid surgery or stenting within prior 30 days
11. ACC/AHA Stage D heart failure

12. Presence of any of the following:
 - a. Hypertrophy cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology
 - b. Infiltrative cardiomyopathy (e.g. amyloidosis, hemochromatosis, sarcoidosis)
13. Leaflet anatomy which may preclude MitraClip implantation
14. Hemodynamic instability defined as systolic pressure < 90 mmHg with or without afterload reduction, cardiogenic shock or the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device.
15. Need for surgery within 12 months
16. Life expectancy < 1 year due to non-cardiac conditions
17. Status 1 for cardiac transplant or history of cardiac transplant
18. Modified Rankin score ≥ 4 for disability
19. Prior mitral valve leaflet surgery or any currently implanted prosthetic mitral valve, or any prior transcatheter mitral valve procedure
20. Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
21. Active endocarditis or active rheumatic heart disease or leaflets degenerated from rheumatic disease (i.e., noncompliant, perforated)
22. Active infection requiring antibiotic therapy
23. TEE is contraindicated or high risk
24. Pregnant or planning pregnancy within 12 months
25. Known hypersensitivity or contraindication to procedural medications that cannot be adequately treated
26. Known allergy to nickel.
27. Patient is otherwise not appropriate for the study as determined by the investigator or the Eligibility Committee, for which the reasons must be documented.
28. 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)

Final Exclusion Criteria (FEC) - Assessed at time of cardiac catheterization (Study Intervention Visit), just prior to device placement

1. Presence of severe pulmonary hypertension assessed by invasive hemodynamic measurement with pulmonary artery catheterization prior to MitraClip placement, defined as PA systolic pressure > 70 mmHg or PVR > 4 Woods units.
2. Anatomical anomaly on TEE that precludes implantation of the study device across the interatrial communication created by the MitraClip procedure, including:
 - a. A posterior rim between the septum secundum and aorta (i.e. aortic rim) of < 5 mm.
 - b. 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.
3. Moderate or worse MR $\geq 2+$ at the end of MitraClip treatment (i.e. MR must be <2+ by TTE, TEE, invasive hemodynamics, or left ventriculography)
4. Key hemodynamic exclusions after MitraClip treatment:
 - a. Mean LAP ≤ 20 mmHg following final result from MitraClip placement (i.e. mean LAP must be elevated > 20 mmHg after completion of MitraClip).
 - b. Difference between mean LAP and mean RAP < 5mmHg after MitraClip placement (i.e. difference between LAP – RAP must be ≥ 5 mmHg).
 - c. Mean arterial pressure (MAP) must be normal (i.e. ≥ 60 mmHg) at time of this assessment.
 - i. IV fluids and medications may be given to support MAP to a goal ≥ 60 mmHg if needed.
5. Characteristics of septal defect:
 - a. Angle of placement of V-Wave shunt should be no more than 135 degrees to prevent slippage through the septum, and
 - b. Septal defect created by MitraClip delivery system must be 8mm or smaller, in any dimension, without evidence of a tear in the septum
6. Patient is otherwise not appropriate for study as determined by the Investigator (reason must be documented).

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 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.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

The study is expected to implant the V-Wave device in 10 patients. Up to 50 patients may be enrolled at the Baseline Visit after passing the Preliminary Screen, however, the V-Wave device will only be implanted in the first 10 patients who pass the Final Screen. This is in recognition that a number of patients may not qualify for V-Wave placement after hemodynamic and anatomic assessment post-MitraClip placement.

The target population includes adult male and female patients irrespective of age, race, and ethnicity. 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.

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. The placement of the V-Wave Shunt in patients after MitraClip has yet to be studied. Demonstrating the safety and feasibility of V-Wave Shunt placement in this patient population is the goal of the current study.

6.1.2 V-WAVE INTERATRIAL 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. In this case, the MitraClip procedure will be performed, and the existing transseptal communication created by the MitraClip procedure will be used for V-Wave Shunt placement.

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

The single study site (Cleveland Clinic, Cleveland, OH, USA) has experienced HF services and numerous physician expert investigators who are experienced in participating in randomized trials. This study calls for 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.

All Investigators and trial personnel are required to attend Sponsor training sessions. Training of 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 benchtop model and then proctored during the first 3 cases at a minimum, per the protocol requirements.

Data collection will be performed via electronic database, Cleveland Clinic REDCap Cloud, which is a 21 CFR Part 11 compliant database.

6.1.4 PROCTORING

The current study involves the use of new device implantation techniques and post implantation patient management. As such, resources will be available for proctoring device implantation. The Company will assign an experienced proctor for each V-Wave Interatrial Shunt implantation, for at least the first 3 cases. The proctor may be an employee of the Company 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* document contained within the *Manual of Operations* (MOP) for at least 3 cases, or 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 add additional proctoring cases must be agreed to in written communications between the Investigators.

7 PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 SUBJECT WITHDRAWAL FROM THE STUDY

A subject may withdraw from the study at any time and should notify the investigator in this event. The investigator may also withdraw the subject from the clinical study at any time based on his medical judgment.

7.2 SUBJECT LOST TO FOLLOW-UP

A subject will be considered lost to follow-up and terminated from the study once they have missed two consecutive appointments without contacts and three attempted contacts are unanswered (it must include a contact with certified letter).

8 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.1 ADVERSE EVENTS

Definition of Adverse Events (AE): An adverse event is an untoward medical occurrence or exacerbation of an existing medical condition subsequent to the experimental therapy. Adverse events are rated in several ways:

- Expected (expected, not expected)
- Device and procedure relationships
 - Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
 - Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.2 SERIOUS ADVERSE EVENTS

Definition of Serious Adverse Events (SAE): AEs that resulted in any of the following:

- Death
- A life-threatening experience that places the patient, in view of the investigator, at immediate risk of death from the adverse event

- Hospitalization or prolongation of an inpatient hospitalization
- Persistent or significant disability/incapacity. This criterion applies if the disability caused by the reported adverse event results in a substantial disruption of a person's ability to conduct normal life functions
- Any congenital anomaly/birth defect
- Other medically significant event that required intervention to prevent one of the outcomes listed above

8.3 UNANTICIPATED ADVERSE EVENTS

Definition of an Unanticipated Adverse Device Effect (UADE):

Any serious adverse 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 application), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

The study investigator shall notify the study sponsor and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

9 STATISTICAL CONSIDERATIONS

This is not a hypothesis driven study. Descriptive analysis will be performed. Categorical data will be summarized as frequency (number) and percent of total and continuous data will be summarized as mean, standard deviation, median, interquartile range and minimum/maximum values.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

All subjects must provide informed consent prior to any study related procedures being performed. If they meet the initial inclusion criteria, the possibility of a V-WAVE Shunt will be discussed in outpatient clinic or hospital exam rooms.

The investigator will review the subject's history, physical examination, and imaging studies prior to obtaining informed consent. An IRB approved informed consent form will be obtained from the subject after the purposes of the study, the risks, expected discomforts, and potential benefits have been explained. 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. Copies of the informed consent will be included in the study records. Another copy will be given to the subject for their records. The informed consent process will be conducted and documented in each subject's medical record (including the date), 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.

10.1.2 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. If the study is prematurely terminated or suspended, the Sponsor-Principal Investigator will promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- 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).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. 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), and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical 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 per FDA regulations and reviewing IRB policy.

10.1.4 MONITORING

Study monitoring will be performed by experienced and appropriately trained personnel appointed by the sponsor-investigator to ensure that the investigation is conducted accordance with the FDA IDE regulations. Monitoring will be conducted by the independent monitor in CCF HVI Research Department.

HVI (Heart and Vascular Institute) Research Department
Cleveland Clinic Foundation
9500 Euclid Ave.
Cleveland, OH 44195

On-site monitoring will occur at regular intervals throughout the duration of the trial, and monitor visit with summary of findings will be outlined in monitoring report.

Monitoring activities will include:

- Study Initiation visit
- Review of training and delegation of authority log
- Review of FDA/IRB approval letters and correspondences
- Review of informed consent to ensure:
 - That the subject signed and dated the informed consent form for him/herself
 - A valid and effective version (reviewed and approved by the IRB) of the consent form was used
 - That the informed consent process was appropriately documented
- Confirmation that the study staff is conducting the study in compliance with the protocol approved by the IRB.
- Source Document Verification (i.e., review all subjects' charts for: study eligibility, primary and secondary endpoints data, and that the protocol specific source documents are on file)
- Ensuring the data reported on the eCRF is consistent with the source documentation
- Review of outstanding queries on the eCRF
- Review of all subject research records to ensure the following:
 - All AEs and SAEs have been reported including any abnormal exam findings determined to be clinically significant;
 - AEs have been reviewed, attribution has been assigned and signed by investigator in a timely manner;
 - EAEs and SAEs have been submitted to the IRB and FDA per IRB/FDA reporting criteria; and
 - All deaths have been reported appropriately
- Ensuring any protocol deviation that meets reporting requirements has been reported to the IRB as well as reported in eCRF
- Ensuring investigational products have been properly handled
- Verification of device used
- Study termination/closure visit

10.1.5 INSTITUTIONAL REVIEW BOARD

The protocol shall be evaluated and approved by the Institutional Review Board at the Cleveland Clinic Foundation prior to proceeding with the study.

Institutional Review Board
Alan Lichtin, MD – IRB Chairman
Cleveland Clinic Foundation
9500 Euclid Avenue, OS 1
Cleveland, OH 44195
(216) 444-2924

10.1.6 INVESTIGATOR AGREEMENT

Dr. Samir Kapadia, as a study Sponsor and P.I. will certify all participating investigators will sign the investigator agreement and no investigator will be added until the investigator agreement is signed in accordance with 21 CFR 812.43.

Investigator responsibilities include, but not limited to:

- Conducting the study in accordance with the investigational plan, signed agreement and applicable regulations protecting the rights and safety of study subjects
- Informing all subjects that the device being utilized is for investigational purposes, and ensuring that the requirements relating to obtaining informed consent and IRB approval are met
- Ensuring that IRB approval is secured prior to starting the study and ensuring continuing review and approval as required throughout the investigation
- Ensuring and supervise all associates, colleagues, and employees assisting the conduct of the study are informed about their obligations, are adequately qualified and trained, and meet their commitments
- Maintaining adequate and accurate records and ensuring those records are available for inspection at any time
- Ensuring that conducting the study does not give rise to conflict of interest
- Controlling of all investigational devices

10.1.7 REPORTING

Deviation from the Investigational Plan: The sponsor-investigator will notify the reviewing IRB and FDA of any deviation from the investigational plan to protect the life of physical well-being of a subject in an emergency. The notice will be provided as soon as possible but no later than 5 working days after the emergency occurred. If the change or deviation may affect the scientific soundness of the investigational plan or the rights, safety or welfare of the subject, the sponsor will obtain prior IRB and FDA approval for deviation by submitting an IDE supplement.

UADE: The sponsor-investigator will report the results of an evaluation of an unanticipated adverse device effect to FDA and IRB within 10 working days after the sponsor-investigator first receives notice of the device adverse effect.

Withdrawal of IRB approval: The sponsor-investigator will notify FDA of the withdrawal of IRB approval or any part of the investigation within 5 working days of receipt of withdrawal of approval.

Progress report or annual reports: The sponsor will provide progress reports to the reviewing IRB and to the FDA.

Recall and device dispositions: The sponsor-investigator will notify FDA and reviewing IRB of any request that a sponsor-investigator return, repair, or dispose of any unit of an investigational device. The notice will be made within 30 days after the request is made and will state why the request was made.

Final report: The sponsor-investigator will notify FDA and reviewing IRB within 30 working days of the completion or termination of the study. The sponsor-investigator will also submit a final report to FDA and reviewing IRB within 6 months after the completion or termination of the study.

Failure to obtain informed consent: The sponsor-investigator will submit a report of the use of a device without first obtaining informed consent. The report will be made to the FDA within 5 working days after receipt of notice of such use.

Other reports: The sponsor-investigator will provide accurate, complete, and current information about any aspect of the investigation upon request from the reviewing IRB or FDA.

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