Transcatheter Intralateral Shunt Device for the Treatment of Heart Failure

Rationale and Design of the Randomized Trial to REDUCE Elevated Left Atrial Pressure in Heart Failure (REDUCE LAP-HF I)


Background

Heart failure (HF) with preserved ejection fraction (HFpEF) is a major health concern and a thrombotic challenge. Elevated left atrial pressure (LAP) is believed to be a key contributor to diastolic dysfunction, exercise intolerance, morbidity, and mortality. Given the lack of success with pharmacological approaches, a device-based approach has been developed, in part based upon the observation that patients with Lutembacher syndrome (ASD + Mitral Stenosis) are less symptomatic than MS alone. It is hypothesized that the de-compression of the left atrium via a left to right, transcatheter, intralateral shunt may minimize symptoms in patients with HFpEF.

The Corvia Medical Inc. (Tewksbury, MA) Inter-atrial Shunt Device (IASD®) System II is the device being used in this first randomized trial to investigate reduction of LAP in HFpEF patients using a device-based therapy. It is self-expanding metal copolymer-covered nitinol wire based therapy. It is a self-expanding metal copolymer-covered nitinol wire delivery system, which allows for a stepwise release. It is radiopaque and echogenic for imaging purposes.

Primary Objective

The primary objective of this randomized controlled clinical study is to evaluate the peri-procedural safety and potential effectiveness (mechanistic effect) of implanting the IASD System II in heart failure patients with a LV ejection fraction ≥40%, elevated left sided filling pressures, and who remain symptomatic despite optimal Guideline Directed Medical Therapy (GDMT). Clinical outcomes will also be directed to examine the change in PCWP from baseline to one month post implantation.

Secondary Objectives

• Change in exercise PEAK PCWP from baseline at 1 month; • Cardiovascular death through 12 months; • Reduced morbidity (first unplanned) HF admissions/emergency clinic visits or acute care facilities for IV diuresis for HF through 12 months; • Change in QOL (EQ-5D, and KCQ score) at 12 months.

Key Safety Outcome Analysis: The percentage of patients with MACCRE will be compared between the treatment (IASD® System II) and control arm using chi-square test or Fisher’s exact test as appropriate. Cumulative event rates for MACCRE will be estimated for the 40 patients. The 2-sided 0.05 level of significance will be used.

Clinical Outcomes

40 patients ≥40 years of age with chronic heart failure and a LV ejection fraction ≥40% will be randomized from 22 U.S. and 6 sites outside of the U.S. Eligible patients are symptomatic despite optimal GDMT and meet invasive (and/or non-invasive) criteria for elevated LAP pressure (and exploratory PCWP) during routine exercise of ≥55mm Hg and greater than RAP by ≥25mm Hg. Patients also have to have site determined echocardiographic evidence of diastolic dysfunction.

Additionally, patients must be able to complete a 6 minute walk test and have no recent history of MI or percutaneous cardiac intervention, stroke, TIA, CABG, or cardiac neurostimulation therapy. Patients are also excluded if they have untreated atrial fibrillation, significant valve disease, a current indication for coronary revascularization, severe heart failure, or require dialysis.

Key Safety Outcome

Patients will be followed for 5 years after index procedure.

Statistical Considerations

The intent-to-treat population will be used for analysis purposes. Key Safety Outcome Analysis: The percentage of patients with MACCRE with a 2-sided exact confidence interval will be used. Also for each treatment group, Kaplan-Meier curves and estimates of cumulative MACCRE rates at 12 months will be calculated for the 40 patients.

Key Effectiveness Outcome: A mixed-models repeated measure ANOVA test with a two-sided 0.05 level of significance will be used to examine the change in PCWP from baseline to one month.

Discussion

This first randomized trial of a device-based therapy benefits from strict criteria for a HF diagnosis, detailed exercise hemodynamics, and a randomized design to reduce possible placebo effects. The small sample size and potential for unblinding of patients and investigators are limitations but this trial is not intended to be definitive.