BIOCARDIA®

CardiAMP™ Heart Failure Trial

Randomized Controlled Pivotal Trial of Autologous Bone Marrow Mononuclear Cells Using CardiAMP Cell Therapy in Patients with Post Myocardial Infarction Heart Failure

Hypothesis

Demonstrate treatment superiority in subjects treated using the CardiAMP cell therapy (Treatment Group) showing a statistically significant improvement in Six Minute Walk Distance (6MWD) compared to subjects undergoing a sham procedure, after 12M follow-up.

Secondary hierarchical endpoints include overall survival (non-inferiority), freedom from MACE (non-inferiority), Minnesota Living with Heart Failure Questionnaire, time to first MACE, and survival.

Study Design

Prospective, multi-center, randomized (3 Treatment:2 Sham Control), sham-controlled, patient and evaluator-blinded comparing treatment with the CardiAMP cell therapy to a sham treatment in 250 patients with post myocardial infarction heart failure.

Treatment Group: 150 Subjects treated with Autologous Bone Marrow Mononuclear Cells (ABM MNC) using the CardiAMP cell therapy

Sham Control Group: 100 Subjects treated with a Sham Control (no introduction of the Helix transendocardial delivery catheter and no administration of ABM MNC)

Optional Roll-in Phase: Maximum of 10 subjects

Total Number of Patients: Maximum of 260 subjects

Primary Endpoint

Comparison of change in distance walked in 6-minutes between the subjects treated with the CardiAMP cell therapy and subjects undergoing a sham control procedure, at 12-months follow-up

Secondary Hierarchical Endpoints

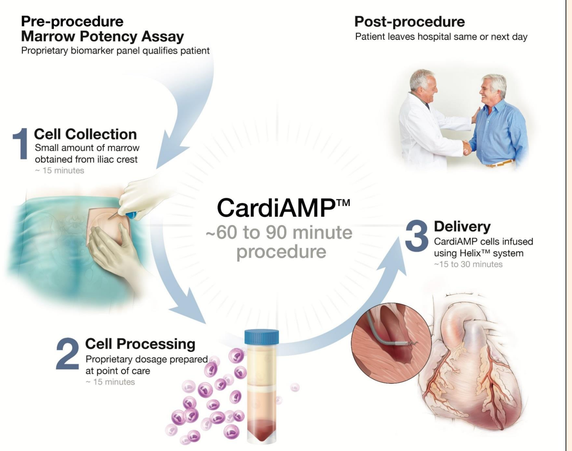
1. Overall survival at 12-months, as a non-inferiority outcome
2. Freedom from Major Adverse Cardiac Events at 12-months, as a non-inferiority outcome
3. Change in quality of life as measured by Minnesota Living with Heart Failure at 12-months, as a superiority outcome
4. Time to first MACE at 12-months, as a superiority outcome
5. Overall survival at 12-months, as a superiority outcome

Secondary Endpoints at 12M

1. Survival, at 2 years
2. Heart failure death
3. Treatment-emergent Serious Adverse Event, at 30-days
4. Heart failure hospitalization
5. All-cause hospitalization
6. Days alive out of hospital
7. Freedom from Serious Adverse Events
8. NYHA Functional Class
9. 6MWD repeated measure analysis
10. Echocardiographic measures of change in ejection fraction, left ventricular end systolic and end diastolic volumes, left ventricular end systolic and end diastolic dimensions, mitral regurgitation
11. Technical Success defined as successful delivery of ABM MNC, at the time of the procedure

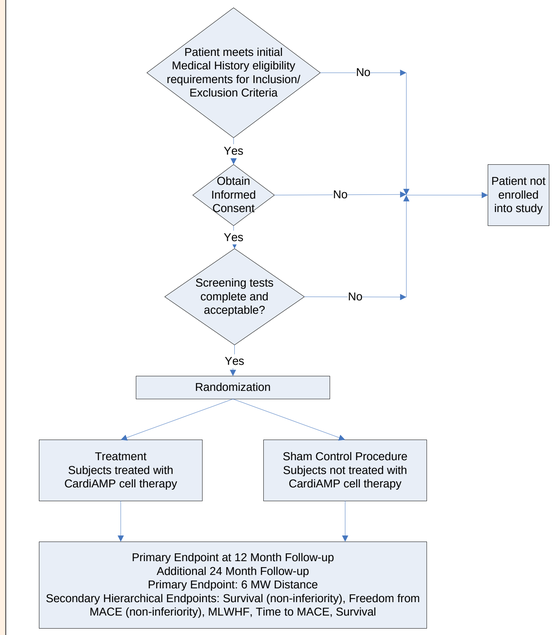
CardiAMP cell therapy

Point of care cell therapy delivered with the Helix™ transendocardial delivery catheter



Inclusion Criteria

- Greater than (>) 21 and less than (<) 90 years of age
- New York Heart Association (NYHA) Class II or III
- Diagnosis of chronic ischemic left ventricular dysfunction secondary to myocardial infarction (MI) as defined by:
  - Previous MI (> 6M)
  - Treatment with thrombolytic therapy, coronary artery bypass surgery, or percutaneous coronary revascularization
- Ejection fraction ≥ 20% and ≤ 40% by 2D Echocardiogram and not in the setting of a recent ischemic event
- On stable evidence-based medical and device therapy for heart failure or post-infarction left ventricular dysfunction, per the 2013 ACC/AHA Heart Failure guidelines, for at least 3M prior to randomization
  - Pharmacological Therapy (as appropriate)
  - Cardiac Resynchronization Therapy (CRT), Cardiac Resynchronization Therapy-Defibrillator (CRT-D)
    - ➢ CRT or CRT-D implanted > 3M before randomization
    - ➢ Eligible or anticipated to be eligible for CRT or CRT-D > 6M
- Cell Potency Assay Score of 3, as determined by the Cell Analysis Core Lab results
- Provide written informed consent



References

De la Fuente LM, et al. Transendocardial autologous bone marrow in myocardial infarction induced heart failure, two-year follow-up in an open-label phase I safety study (the TABMMI study). *Eurointervention* 2011 Nov;7(7):805-12. doi: 10.4244/EIJV7I7A127.

Heldman AW, et al. Transendocardial Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells for Ischemic Cardiomyopathy: The TAC-HFT Randomized Trial. *JAMA*. 2014;311(1):62-73. doi:10.1001/jama.2013.282909.

Perin, E, et al. Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, Left ventricular function, and perfusion in chronic heart failure, The FOCUS-CCTRN Trial. JAMA. 2012;307(16).

Fisher, S, et al. Meta-analysis of cell therapy trials for patients with heart failure. Circ Research 2015.

Takehashi, et al. Cytokines produced by bone marrow cells can contribute to functional improvement of the infarcted heart by protecting cardiomyocytes from ischemic injury. Am J Physiol Heart Circ Physiol 291: H886–H893, 2006.

Loffredo FS, Bone marrow-derived cell therapy stimulates endogenous cardiomyocyte progenitors and promotes cardiac repair. Cell Stem Cell. 2011 April 8; 8(4): 389–398.

von Ramhorst J, et al. Intramyocardial Bone Marrow-Derived Mononuclear Cell Injection for Chronic Myocardial Ischemia: the Effect on Diastolic Function, Circ Cardiovasc Imaging, 2011.

Exclusion Criteria

- Acute coronary syndrome within 3M
- History of bronchospastic lung disease, orthopedic, muscular, or neurologic conditions that could limit the ability to perform the 6MWD Test
- Not a candidate for cardiac catheterization
- Require coronary artery revascularization. Patients who require or undergo revascularization procedures would undergo these procedures a minimum of 3M in advance of randomization in this study. Note that patients who later develop a need for revascularization following enrollment will be submitted for this therapy without delay
- Left ventricular thrombus, as detected by echocardiography
- Severe mitral regurgitation, as measured by echocardiography
- Severe mitral or tricuspid insufficiency or aortic insufficiency (>+ 2) as assessed by echocardiography
- Presence of aortic stenosis (> + 2 equivalent to an orifice area of 1.5cm2 or less)
- Have a mechanical aortic valve or heart constrictive device
- Have evidence of a life-threatening arrhythmia
- Have complete heart block or QTc interval >550 ms on screening 12-lead ECG
- AICD firing in the past 60 days prior to the procedure
- Have peripheral artery disease involving the aorta or iliofemoral system that impacts the feasibility or safety of the study intervention.
- Have a non-cardiac condition that limits lifespan to < 1 year
- Have a history of drug or alcohol abuse within the past 24M
- Be currently participating (or participated within the previous 30 days) in an investigational therapeutic or device trial or participated in the treatment arm of a gene or stem cell therapy trial within the previous 12M
- Unwilling or unable to comply with follow-up

Study Management

Sponsor

BioCardia, Inc., San Carlos, CA

Principal Investigators

Carl Pepine, MD (University of Florida, Gainesville, FL)
Amish Raval, MD (University of Wisconsin, Madison, WI)

Core Laboratories

Cell Analysis Core Laboratory (MD Anderson Cancer Center)
Echocardiographic Core Laboratory (Yale Cardiovascular Research Group)

Independent Data Review

Data Safety Monitoring Committee
Clinical Events Committee

Further Information

Please contact Cheryl Wong Po Foo at info@biocardia.com

Additional information is available at www.clinicaltrials.gov **(NCT02438306)**

Caution: Investigational device. Limited by United States law to investigational use

04491-B (MKT)