First in Man CardiALLO NK1R+ MSC Phase I/II Trial in Ischemic NYHA II and III HFrEF

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BACKGROUND

PREVIOUS CLINICAL STUDIES OF BONE MARROW-DERIVED MESENCHYMAL STEM CELLS IN PATIENTS WITH ISCHEMIC HFrEF DELIVERED WITH EFFICIENT HELIX TRANSENDOCARDIAL DELIVERY CATHETER SYSTEM (4)

Study/ Identifier	N	Cell Delivery (Injection) Method	Cell Source & Type	Cell Dose (x 10^6)	Safety Results	Efficacy Results
1) POSEIDON NCT01087996 Hare 2012	30	Catheter-based IM (Helix) (IM=intra0myocardial)	Allogeneic vs Autologous BM MSCs	20 – 200	0% TE MACE in both groups. No perforation, arrhythmias, ischemic events. Some increased panel-reactive antibodies in response to therapy noted.	Improved 6-minute walk distance, improved quality of life, no change to MV02.
2) TACHFT NCT00768066 Heldman 2014	67	Catheter-based IM (Helix)	Autologous BM MSCs vs MNC	100 to 200	0% TE MACE. No increase in 1-year incidence of serious adverse events. No perforation, arrhythmias, ischemic events.	Improved 6-minute walk distance, improved quality of life, no change to MV02.
3) TRIDENT NCT02013674 Florea 2017	30	Catheter-based IM (Helix)	Allogeneic BM MSCs	20 – 100	0% TE MACE. 9% treatment related SAEs at 12 months. No perforation, arrhythmias, ischemic events.	Improved 6-minute walk distance, improved quality of life, reduced scar size, improved LVEF at high dose, improved NYHA class.

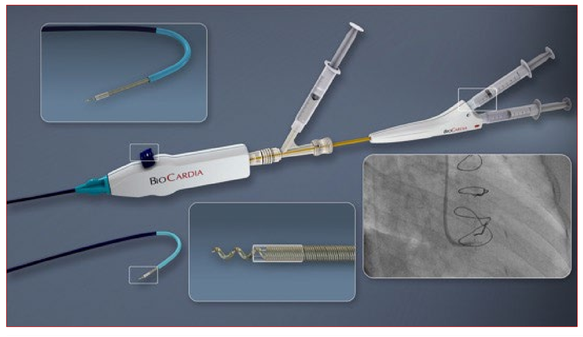
METHODS

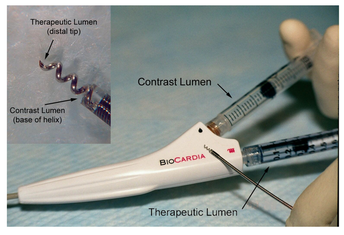
Phase I: Patients treated based on a traditional 3+3 dose escalation

1st dose	20 million cells*	N=3
2nd dose	100 million cells*	N=3
3rd dose	200 million cells*	N=3

*If no patients experience a dose limiting toxicity (DLT), the study will move to the next dosing level. A DLT is defined as any >Grade 3 adverse event (AE) or any Grade 2 toxicity not resolving within 14 days. From U S. Department of Health & Human Services (2017) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Publish Date: November 27, 2017.

Investigational Device and Therapy: CardiALLO™ Human Allogeneic Culture-expanded Bone marrow-derived human Mesenchymal Stem Cells (hMSCs) delivered with the Helix transendocardial delivery system.





Helical System consisting of the Helix biotherapeutic delivery catheter and Helix guide catheter. BioCardia, Inc., Sunnyvale, CA

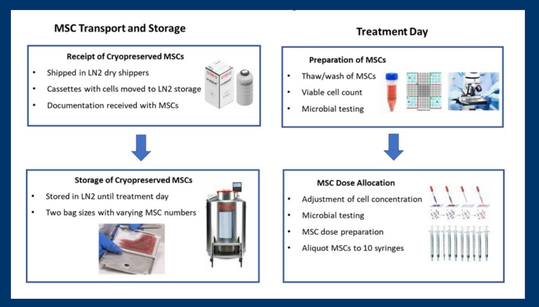
STUDY POPULATION AND KEY ELIGIBILITY CRITERIA

Using biomarkers indicative of cardiomyocyte stress (NT-proBNP) and inflammation (hsCRP), IHD patients (NYHA Cl II/III) selected and targeted earlier in disease course to confirm safety and obtain preliminary efficacy data.

- >21 and <80 years of age.
- NYHA Class II or III.
- Diagnosis of ischemic etiology heart failure with reduced ejection fraction (HFrEF)
- LVEF ≥ 20% and ≤ 40% by two-dimensional echocardiogram and not in the setting of a recent ischemic event, as assessed by echocardiography and not in the setting of a recent ischemic event (i.e., within 6 months).
- NTproBNP >500 pg/ml.
- Inflammation marked as high-sensitivity C-reactive protein (hs-CRP) > 2 mg/L.
- On stable evidence-based medical and device therapy for HFrEF, per the ACC/AHA Heart Failure guidelines, for at least three (3) months prior to randomization.

CardiALLO MSC Trial (NCT05925608)

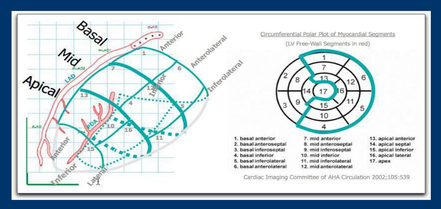
Cell Preparation & Delivery to the Cath Lab



Study Procedure Planning

Pre-procedure treatment planning for injection sites:

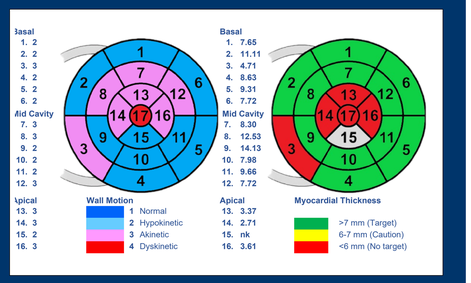
- A pre-procedure echo or MRI enables targeting of cell delivery relative to infarct zones.
- Bullseye target map is made:
  - Echo data reviewed: wall thickness and contractility
  - Map created to target peri-infarct regions

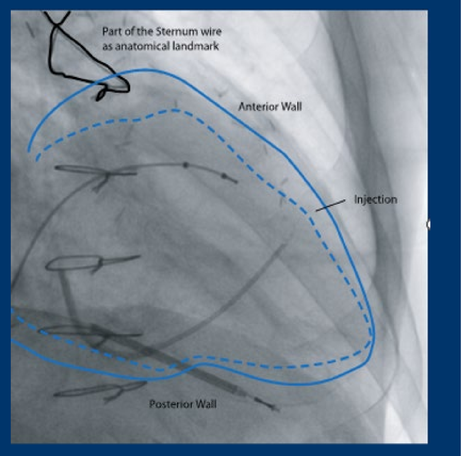


Circumferential polar plot of myocardial segments and study procedure planning polar maps

Study Injection Procedure

- Helix delivery catheter maneuvered to engage LV endocardium at target zone.
- Delivery catheter advanced and rotated clockwise three turns into endocardium.
- Contrast solution discharges at the base of the delivery catheter Helix to confirm engagement.
- At targeted site, therapeutic product is injected (over ~30 sec).
  - Catheter held in place (~15 sec)
  - Catheter disengaged and repositioned.
  - 10 injections (0.5 ml) to complete study procedure
  - Fluoroscopy overlay in RAO view for patient with biventricular pacing, previous open chest procedure (image at right).





ABSTRACT. Background: Despite enormous effort in clinical and basic cardiovascular disease research, a persisting unmet need is a disease modifying therapy for heart failure (HF) with reduced ejection fraction (HFrEF) due to ischemic heart disease (IHD). Current evidence supports the notion that HF progression is a result of paracrine effects on cardiovascular tissue, largely via inflammation. Allogeneic bone marrow human mesenchymal stem cells (hMSCs) dampen inflammation. With hMSCs, neurokinin-1 receptor (NK-1R) upregulation may enhance immune modulatory impact. When delivered utilizing a transendocardial approach, hMSCs offer promise as a therapy for ischemic HFrEF, based on previous experience (1-3) **Methods:** The CardiALLO MSC trial is a Phase I/II trial, with 9 patients being treated in the Phase I dose escalation (3x3, 20M, 100M, 200M MSCs) in preparation for a 60-patient randomized, sham controlled, double blind Phase II study. CardiALLO MSC will deliver high effective dosage of hMSC intramyocardially to ten delivery sites using a minimally invasive Helix 5.2Fr helical needle tipped transendocardial delivery catheter advanced through a bidirectional Morph "DNA" 5.5 French sheath equivalent "whipless guide". Using biomarkers for cardiomyocyte stress (NT-proBNP) and inflammation (hsCRP), IHD patients (NYHA Cl II/III) are selected and targeted earlier in the disease course to confirm safety and obtain preliminary effectiveness data. **Results:** The first patient has been enrolled and treated in the low dose group and a second patient has been scheduled for treatment. By the time of presentation, the entire low dose cohort is scheduled to be completed in time for the full low dose experience to be presented. **Conclusions:** The study procedure appears feasible, with no treatment emergent MACCE, post procedure evidence of rejection or allergic reaction to the transplanted allograft cells.

RESULTS AND STUDY STATUS

- The first patient has been enrolled and treated in the low dose group and is doing well clinically.
- Grant funding or partner sought to enable this trial to advance significantly.

CONCLUSIONS AND CLINICAL IMPLICATIONS

- This trial is the first prospective trial to be conducted in patients selected for elevated inflammation (hsCRP) and heart stress (NTproBNP) levels and builds on previous clinical experience (1,2,3).
- The study procedure is feasible, with no treatment emergent MACCE observed. There has been no post procedure evidence of rejection or allergic reaction to the transplanted allograft cells.

REFERENCES

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DISCLOSURES

CJP is a consultant to BioCardia as the study's Principal Investigator; RDA, is the study site Principal Investigator, and AJ, JP, SS, DHH and PAA are BioCardia employees.