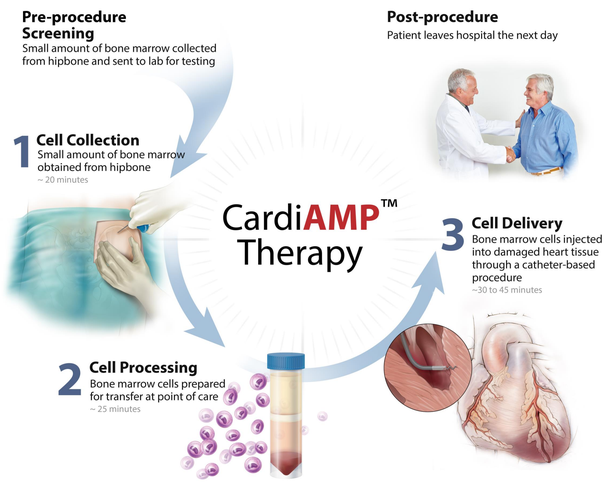
Autologous Bone Marrow Mononuclear Cells in HFrEF: Results of an Adaptive Trial Analysis

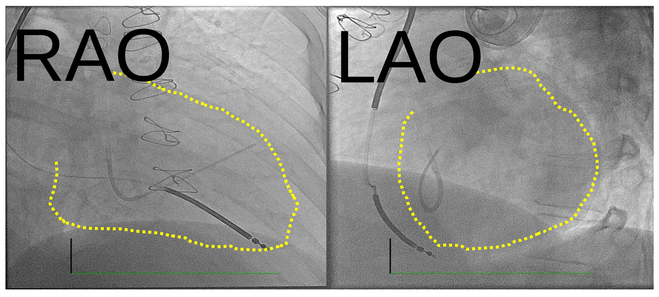
Amish N. Raval[1], Leslie W. Miller[2], R. David Anderson[3], Natasha Lipson Altman[4], Phillip C. Yang[5], Andreas Brieke[6], Peter Johnston[7], Jay H. Traverse[8], Duncan J. Stewart[9], Debby Holmes-Higgin[10], Sujith Shetty[10], Peter A. Altman[10], Carl J. Pepine[3], on behalf of the CardiAMP Heart Failure Trial Investigators

[1]University of Wisconsin—Madison; [2]BayCare HealthCare System, Clearwater, FL; [3]University of Florida—Gainesville, [4]Auckland City Hospital—New Zealand; [5]Stanford University—California; [6]University of Colorado—Denver; [7]Johns Hopkins Medicine, Baltimore; [8]Minneapolis Heart—Minnesota; [9]Ottawa Heart Institute—Ontario, Canada; [10]BioCardia, Inc., Sunnyvale, CA.

STUDY TREATMENT

CardiAMP Cell Therapy. Autologous cells are collected for ABMMNC analysis during screening. Bone marrow cells are aspirated & processed on procedure day at the point-of-care (cath lab). Cells are delivered using the Helix intra-myocardial injection catheter with a helical-shaped needle designed to increase intramyocardial retention compared to straight needle injections.





Representative biplane ventriculograms performed in RAO and LAO cine projections showing catheter injections at the level of the mid-ventricular antero-septum.

RESULTS

- Interim adaptive trial analysis implemented in this study
- Planned target n=260 and n=110 were available at the time of the interim adaptive analysis.

Demographics	Cell Therapy (n=72)	Control (n=38)
Age (mean ± SD)	65.4 ± 10.4	66.8 ± 7.9
Male Sex (%)	90	92
Race (%)		
White	90.3	94.7
Black/African American	4.2	0
Other	2.8	2.6
Unknown	2.8	2.6
Smoking Status (%)		
Never smoked	28.2	32.4
Former smoker	66.2	62.2
Current smoker	5.6	5.4
Implant (%)		
ICD,	59.7	55.3
CRT/ICD (CRT-D)	20.8	26.3
Pacemaker (single lead)	1.4	0
Diabetes mellitus (%) insulin- non-insulin-dep	40.3	47.4
6MWD test (meters ± SD)	346 ± 81	357 ± 68
NYHA (%) Classification		
II	72	79
III	28	21

DISCLOSURES

ANR and CJP are consultants to BioCardia as the study's co-Principal Investigators; PVJ, JHT, DJS serve on the study's Executive Steering Committee, SS is a consultant to BioCardia and DHH and PAA are BioCardia (study sponsor) employees.

INTERIM ADAPTIVE TRIAL ANALYSIS

12-Month F-S Hierarchical Analysis (p=0.64, n=110 total enrolled at time of analysis)

	Cardiac Death Equivalents	Non-fatal MACCE	6MWD change from baseline, M
Cell Therapy	5.6%	12.5%	36 ± 71
Control	5.3%	10.5%	33 ± 75

Through Month 24 (p>0.05; n=92 at Month 24 at time of analysis)

	Cardiac Death Equivalents	Non-fatal MACCE	6MWD change from baseline, M
Cell Therapy	8.3%	16.7%	2 ± 76
Control	13.2%	18.4%	17 ± 96

NTproBNP is a well-recognized heart failure marker and is commonly included as a study inclusion eligibility criterion in contemporary studies evaluating treatments for heart failure. It was not considered in the CardiAMP HF Trial as an eligibility criterion but has been added to CardiAMP HF Trial II, NCT06258447, recently approved by FDA to start enrolling. The CardiAMP HF Trial II study protocol was developed based on the results of this adaptive interim data analyses.

SUBGROUP ANALYSES: NTproBNP >500 pg/ml at Screening/Baseline (n=54 at time of analysis)

Through Month 24 (3-tiers include 6MWD change from baseline, p=0.073)

	Cardiac Death Equivalents	Non-fatal MACCE	6MWD change from baseline, M
Cell Therapy	2.9%	20.0%	19 ± 63
Control	21.1%	26.3%	-3 ± 113

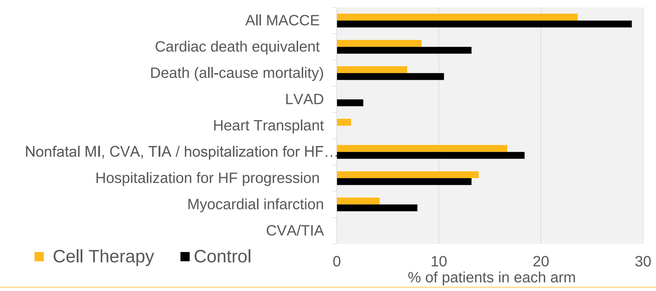
Through Month 24 (3-tiers include QoL (MLwHFQ) change from baseline, p=0.026)

	Cardiac Death Equivalents	Non-fatal MACCE	QOL change from baseline, pts*
Cell Therapy	2.9%	20.0%	-10 ± 23
Control	21.1%	26.3%	6.5 ± 21

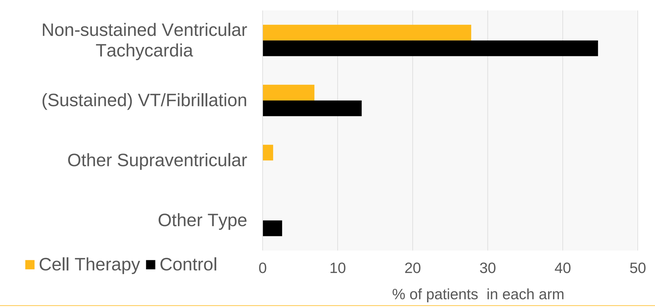
*Minnesota Living with Heart Failure Questionnaire, change toward negative or lower number is better

ABSTRACT. **Background**: In a Cochrane meta-analysis, myocardial injection of autologous bone marrow mononuclear cells (ABM MNC) showed improved cardiovascular outcomes including reduced mortality in HFrEF. The CardiAMP HF study (NCT02438306) was designed to test the safety and efficacy of ABM MNC treatment in HFrEF patients selected based on favorable bone marrow cell characteristics. Due to slow enrollment during COVID 19, an adaptive trial analysis was implemented. **Methods**: Patients with chronic HFrEF (EF 20-40%; NYHA II/III) secondary to MI were randomized to cardiac catheterization with or without transendocardial ABM MNC treatment. The primary outcome, a 3-tier composite of cardiac death equivalents (all-cause death, LVAD, heart transplant), major adverse cardiac / cerebrovascular events (MACCE) and 6-minute walk distance (6MWD) at 12 months, was evaluated using a Finkelstein-Schoenfeld hierarchical analysis. Secondary outcomes included quality of life as measured by the Minnesota Living with Heart Failure questionnaire (MLwHFQ) and echocardiographic measures. Study subjects were followed-up through 24 months. **Results**: At 12 months, there was an unexpectedly low rate of tier 1 and 2 events and a similar improvement in 6MWD for both groups (Table). The 24-month data showed trends for reduced Tier 1 and 2 events with cell therapy. These trends were supported by study outcome measures other than 6MWD, including MLwHFQ scores (-9.1+/-24 vs -2.5+/-17), measures of LV function and reduction in sustained ventricular tachyarrhythmias for patients (7% vs 13%). **Conclusion**: Adaptive interim analysis of this study in Ischemic HFrEF patients selected for bone marrow cell characteristics tended to have reduced cardiac death equivalents and MACCE at 24 months with ABM MNC therapy. Quality of life, echocardiography measures, and reduced ventricular tachyarrhythmias supported these observations but 6-minute walk distance testing did not.

Overview of MACCE Events through 24 Months



Ventricular Arrhythmias through 24 Months



DISCUSSION AND CONCLUSIONS

- Following adaptive interim analysis, DSMB recommended pausing enrollment pending outcomes of patients currently completing 1-year follow-up.
- Reason for pause was low likelihood of meeting primary endpoint using the 6MWD test at 12 months and slow enrollment related to COVID-19.
- Notably, prespecified futility threshold for efficacy was not met and there were no safety-related concerns.
- Sponsor has redesigned the protocol to address lower than expected event rate by selecting patients with elevated NTproBNP (CardiAMP HF II)
- Double-blind will be maintained for CardiAMP HF until all follow-up completed.
- At 2 years follow-up in the interim analysis, the **Cell Therapy Group** had:
  - 37% relative risk reduction in cardiac death equivalents
  - 9% relative risk reduction in non-fatal MACCE
  - Fewer sustained ventricular arrhythmias (p<0.073)
  - Improved LVEF and decreased NTproBNP
  - A subgroup with baseline NTproBNP >500 pg/mg that had significant improvements in the primary outcome
- 6MWD test potentially confounded by inclusion criterion of walk distance threshold (150 - 450 meters)
- Screening bone marrow cell "potency" criterion likely contributed to selection of healthier pts with fewer than anticipated MACCE

ACKNOWLEDGEMENTS

The authors wish to acknowledge the following for their support of the study: The Maryland Stem Cell research Foundation and Centers for Medicare and Medicaid (CMS) for financial support, the Statistical Data Analysis Center (SDAC) at the University of Wisconsin, Madison, for data analyses, the Center for Cell and Gene Therapy at Baylor University, Regenerative Medicine Research and Biorepository Center at Texas Heart Institute, and Yale Echocardiography Core Laboratory at Yale University for core lab services and the CardiAMP HF Trial Investigators including those listed above and: Peter V. Johnston, Johns Hopkins Hospital, R. David Anderson, Univ. of Florida, Gainesville, Zachary M. Gertz, VCU Health, Gregory K. Kumkumian, Suburban Hospital-Bethesda, Zakir H. Sahul, Michigan Heart, Abhishek Singh, Atlantic Health, Mark A. Tannenbaum, Iowa Heart Center, Gerald Koenig, Henry Ford Health, David H. Chang, Cedars-Sinai, Kamran I. Muhammad, Oklahoma Heart Institute, Michael X. Pham, California Pacific Medical Center, F. David Fortuin, Mayo Clinic – AZ, Safwan Kassas, Ascension St. Mary's, Saginaw, MI, Stuart Katz, NYU Langone for enrolling patients in the study.