Autologous Cell Therapy for HFrEF: Efficacy Outcomes at Two Years for the Roll-in Cohort of a Phase III Pivotal Trial

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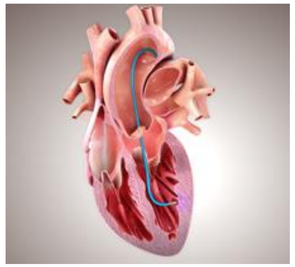
Study Background

The CardiAMP Cell Therapy Trial for Heart Failure (CardiAMP-HF, NCT02438306) is a prospective, multi-center, randomized, blinded sham-controlled trial that has recently been granted breakthrough designation by the FDA. The trial, which is currently enrolling, will include up to 260 patients with NYHA class II or III HFrEF due to ischemic cardiomyopathy (ICM). The final two-year results of the initial 10 patient open label roll-in cohort are presented here.

Methods

- Roll-in cohort patients (n=10) were enrolled at three U.S. study sites.
- Patients with HFrEF, LVEF 20-40%, due to ICM, on stable, guideline-directed medical (GDMT) +/- device therapy were eligible.
- All study subjects underwent a screening 5 ml bone marrow aspiration from the iliac crest to assess cell markers associated with a beneficial response to autologous cell therapy as indicated in previous trials.
- At the study procedure visit, a 60 ml bone marrow aspiration was performed with point of care (POC) isolation and transendocardial injection of bone marrow mononuclear cells (BM MNC; goal 200M cells; see **Figure 1**).
- Patients were followed for two years to assess safety and clinical outcomes; outcomes through one year were previously published.[1]

Figure 1. Point of Care BM MNC Isolation and Intramyocardial Delivery



(A) Bone marrow aspirate is obtained from the posterior iliac crest and transferred into the cell separation chamber (CardiAMP CS, BioCardia). (B) The device is centrifuged to separate cell poor plasma from nucleated cells (C). After the cell poor plasma layer is removed (D), the remaining nucleated product is drawn into a 10 mL syringe (E) and distributed into 1 mL syringes for transendocardial injections. All steps may be performed in the cath lab at the point of care in approximately 20 minutes. BM MNCs are delivered using a helical injection catheter ("Helix") with a novel delivery needle designed to optimize myocardial retention of cells and other products. The Helix catheter is telescoped within the steerable Morph guide. Both devices are positioned retrograde across the aortic valve into the left ventricle for transendocardial therapeutic injections under fluoroscopy (F).

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Results

Table 1. Demographics and Clinical Characteristics

Mean (SD) age, y	67 (12)		
Age range, y	46–81	Guideline-Directed Tx	
Male gender, n	9	Medications	
White race	10	ACEi	9
Tobacco smoking		ARNI (Entresto)	2
Never; Former	5; 5	Beta blocker	9
NYHA Class		MRA	9
II or III	8; 2	SGLT2i	0
Comorbidities		Implant	
Hypertension	8	ICD	7
VT/VF	7	CRT/ICD	3
Hypercholesterolemia	6	Previous Procedures	
AF	4	PCI	7
Diabetes	3	CABG	7
Renal dysfunction	2		

- Demographics at study start demonstrated characteristics typical of a ICM HFrEF cohort (**Table 1**).
- No serious adverse events (SAEs) were observed related to the bone marrow aspirations (screening and treatment) or transendocardial injection procedures.
- 2-year survival was 100%: all 10 patients completed 24 months of follow-up.
- Changes in GDMT and HF device therapy were minimal during the study period (**Table 2**).
- One patient had 4 hospital admissions; once for acute MI and three times for heart failure progression.
- 7/10 patients reported improved or stable quality of life over 24 months in the MLWHFQ.
- 4/10 were reported as NYHA class I at Month 24.
- 6-minute walk distance (%change from baseline) remained improved at Month 24 **(Figure 2**).
- LVEF (median value) was improved at Month 24 (**Figure 3**).
- Recruitment of previously akinetic left ventricular wall segments was observed at month 24 compared to baseline, consistent with LVEF and clinical results (**Figure 4**).

Table 2. Clinical Outcomes for Patients Listed Chronologically by Age at Month 24

Age	NYHA-Baseline	NYHA-Month 24	MLwHFQ change from baseline	Changes in HF meds	# CHF Hospitalizations through 24 Months
47	II	II	-16	no changes	none
48	II	I	-24	no changes	none
64	II	I	1	no changes	none
64	III	II	-38	reduced B-B; reduced ARNI	none
70	II	I	-12	no changes	none
73	II	III	-40	no changes	none
79	II	II	-5	started B-B	none
81	II	III	64	removed ARNI; MRA titrated; added ARNI	4; acute MI; HF progression; HF progression; HF progression
81	II	III	30	no changes	none
83	III	I	35	no changes	none

Figure 2. Six Minute Walk Distance (median +/- 25th, 75th quartiles)

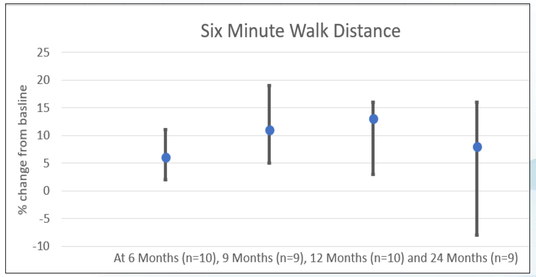


Figure 3. Left Ventricular Ejection Fraction (median +/- 25th, 75th quartiles)

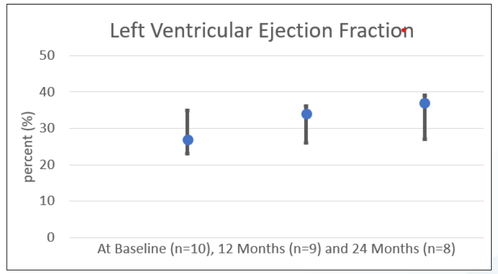
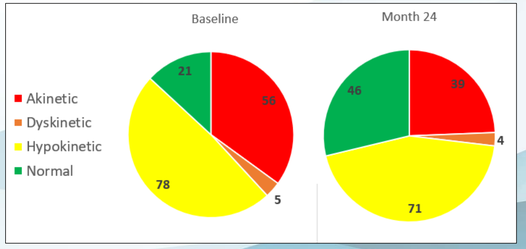


Figure 4. Myocardial Wall Segments as Assessed by Core Echocardiography Lab



Discussion

The results of prior clinical trials of autologous BM MNCs in HF patients suggest that intramyocardial delivery is safe and potentially efficacious,[1-10] although efficacy results are limited by variable clinical responses both between and within trials. For instance, a Cochrane meta-analysis of RCTs in which BM MNCs were tested in HF patients with ischemic heart disease found that compared to control, BM MNC treatment significantly reduced all-cause mortality, nonfatal MI, and arrhythmias at 12 months follow-up, although the heterogeneity among the trials limited robustness of the analysis.[2] There are multiple potential causes for the heterogenous response of HF patients to BM MNCs, including variability in BM MNC abundance, regenerative capacity, and quality of cell preparation.[10] CardiAMP-HF (NCT02438306) was designed to select participants most likely to respond to BM MNC delivery based on patient-specific cell characteristics and using a state-of-the art cell isolation and delivery system that maximizes BM MNC yield and retention. The 24-month follow-up results from the CardiAMP-HF Roll In Cohort presented here confirm that isolation and intramyocardial delivery of BM MNCs using the CardiAMP Cell Therapy system is safe with evidence of efficacy in important clinical outcomes. While limited by the small number of patients and open label nature of the study, the final results of the Roll In cohort support the on-going pivotal, randomized, sham-controlled portion of the trial now enrolling at centers in the US and Canada.

Conclusion

At the final two-year follow-up of the 10-patient open label CardiAMP-HF roll-in cohort, CardiAMP cell therapy was well tolerated and safe with no treatment-related adverse events and no observed mortality. In addition, 6-minute walk distance, quality of life, and LVEF all remained stable or improved. These results support the safety and potential efficacy of this autologous cell therapy currently under investigation in the pivotal, multicenter randomized and sham-controlled CardiAMP-HF Trial.

References

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Author Disclosures & Acknowledgements

PVJ: Site principal investigator (PI), Member Executive Steering Committee (ESC); RDA: Site PI; AR: study co-PI, site PI, Member ESC; DHH: BioCardia employee; CJP: study co-PI, Member ESC.

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