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The CardiAMP Cell Therapy for Heart Failure trial

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Introduction

Following advances in prevention and management, clinical outcomes for patients with ischemic heart disease—in particular, myocardial infarction—have substantially improved. There remains, however, an unmet need for novel therapies to better manage heart failure with reduced ejection fraction (HFrEF) in patients with a prior myocardial infarction beyond that afforded by current lifestyle modification and pharmacologic management. Cell-based therapies offer a promise to address this need.

Although limited in numbers and duration of follow-up, meta-analyses by the Cochrane Group[1] and others support the suggestion that, unlike trials on acute myocardial infarction, there is a signal of benefit after cell-based therapy for patients with more chronic ischemic heart disease who have HFrEF. These analyses suggest that autologous bone marrow cell-based treatment may reduce early mortality and rehospitalizations as a result of HF. These studies also showed evidence to support clinical health benefits, including improved left ventricular end-systolic volume, stroke volume, and ejection fraction, along with positive changes in New York Heart Association functional class and exercise capacity.

Recent developments, such as rapid, on-site cell processing and the ability to provide a high-dose cellular product[2-4] enriched in cells previously shown to be associated with a favorable response,[2,5,6] offer additional promise to address this need.

Study Design

The CardiAMP Cell Therapy for Heart Failure trial (ClinicalTrials.gov ID NCT02438306) is designed to test whether intramyocardial delivery of high-dose autologous bone marrow mononuclear cells (BM MNCs) in patients selected for the characteristics of their cells can improve clinical outcomes in ischemic HFrEF.[7] The trial is actively enrolling up to 260 patients in up to 40 centers in the United States and Canada, with a 10-patient, open-label, "roll-in" cohort. Trial design and outcomes are summarized in Figure 1.

Results to Date

The roll-in, open-label cohort has been completed at 3 US centers. All 10 patients received the autologous BM MNCs successfully, and no serious adverse events were observed related to any of the procedures performed.[8] Despite symptomatic ischemic HFrEF, 2-year survival was 100%, and all patients completed 24 months of follow-up. Changes in guideline-directed improvements in left ventricular ejection fraction and wall motion scores over the follow-up

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period (Fig. 2) were consistent with improvements in functional capacity, as measured by an increased median change in 6-minute walk distance of 37.5 meters at 12 months and an increase of 31 meters at 24 months, and in quality of life, as measured by the Minnesota Living with Heart Failure Questionnaire, in 7 of 10 patients at 12 months and 6 of 10 patients at 24 months.[9]

The randomized, double-blind cohort study continues to enroll patients with ischemic HFrEF at centers in the United States and Canada. To date, 110 patients have been enrolled and randomly assigned, with 10 of those patients randomly assigned to the control group having crossed over to receive the active cell treatment after 2 years of follow-up, as prespecified in the study protocol.

Future Directions

With the high CD34-positive effective dosage provided by the selected autologous BM MNCs, completion of the current trial is occurring in parallel with a different clinical trial program designed to evaluate the same autologous, personalized cell product for patients with refractory angina and chronic myocardial ischemia (ClinicalTrials.gov ID NCT03455725). To date, 3 patients have been enrolled in this study.

As a complementary adjunct to the ongoing phase 3 trial with autologous BM MNCs for patients with ischemic HFrEF, a trial to evaluate an allogeneic natural killer-1R–positive mesenchymal stem cell product for the same indication is beginning in 2023. This trial is intended to target patients who lack the optimal cells for personalized treatment using autologous BM MNCs.

On July 24, 2023, the sponsor announced a pause in enrollment based on an interim analysis and recommendations made by the independent data and safety monitoring board. Although there were no treatment-emergent safety concerns, the analysis indicated that the trial was unlikely to meet its primary 12-month, 3-tier hierarchical efficacy end point. Notably, available 24-month follow-up data suggest a 37% relative risk reduction in cardiac death equivalents and an 18% relative risk reduction in major adverse cardiac and cerebrovascular events. The sponsor, the principal investigators, and the executive steering committee are exploring a protocol redesign to better test whether this therapeutic approach is effective.

Abbreviations and Acronyms

BM MNC	bone marrow mononuclear cells
HFrEF	heart failure with reduced ejection fraction

Article Information

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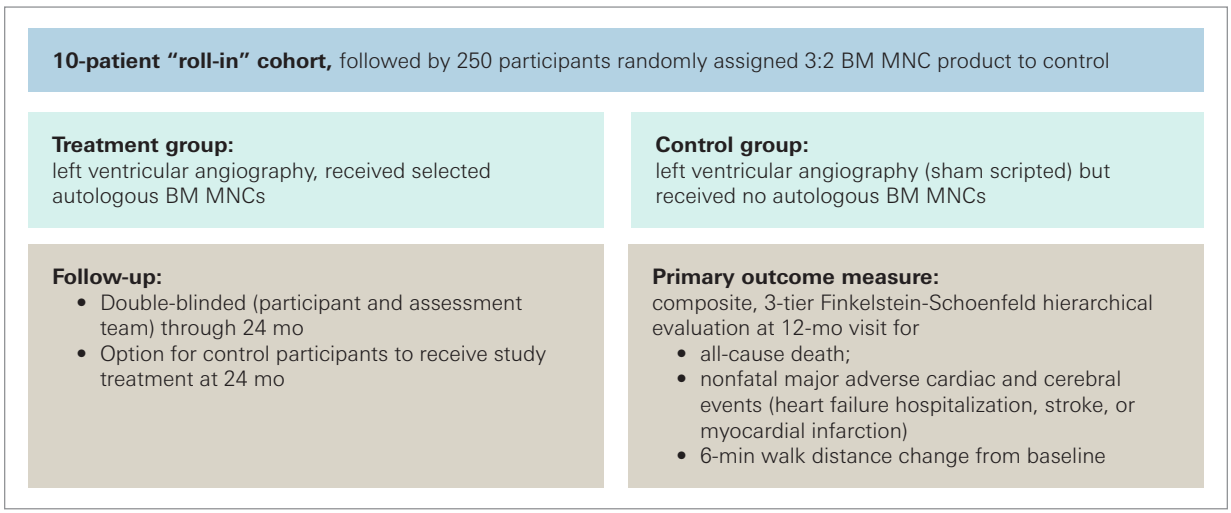
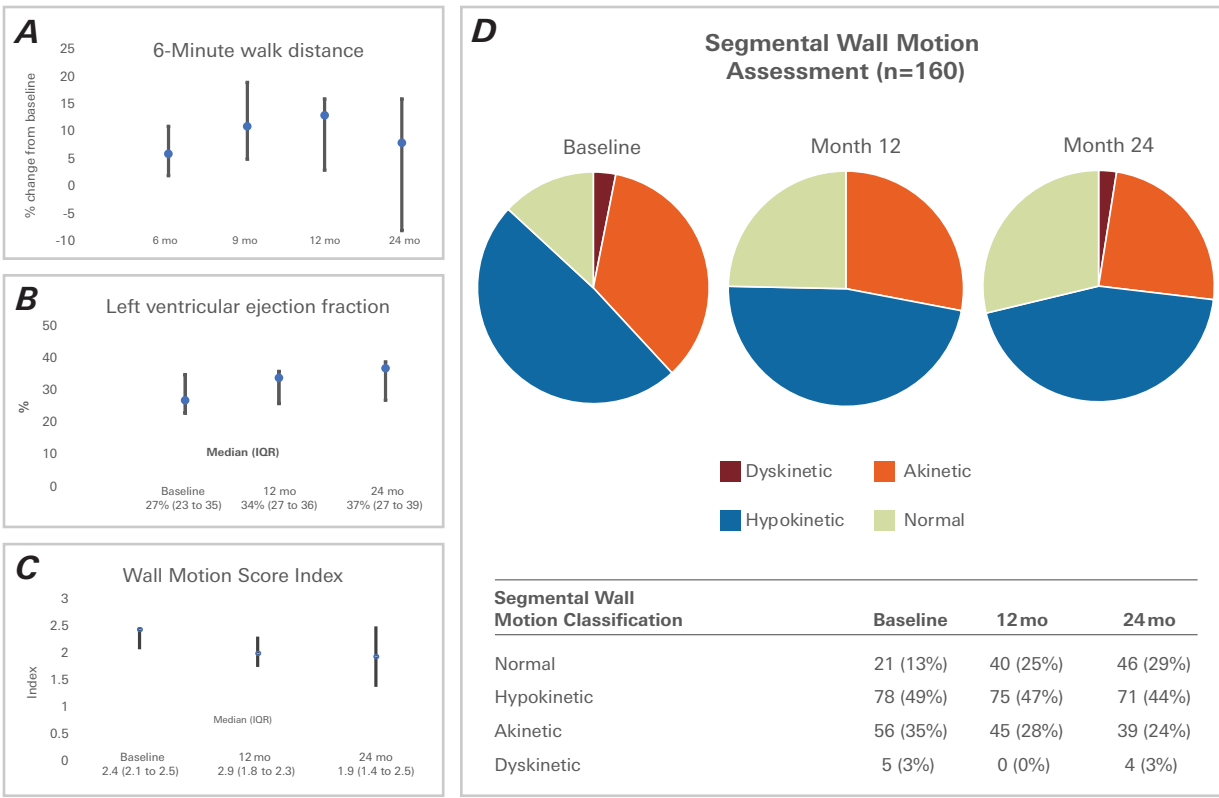


Fig. 1 CardiAMP Cell Therapy for Heart Failure trial in ischemic HFrEF: a summary

BM MNC, bone marrow mononuclear cell.



Segmental Wall Motion Classification	Baseline	12 mo	24 mo
Normal	21 (13%)	40 (25%)	46 (29%)
Hypokinetic	78 (49%)	75 (47%)	71 (44%)
Akinetic	56 (35%)	45 (28%)	39 (24%)
Dyskinetic	5 (3%)	0 (0%)	4 (3%)

Fig. 2 Roll-in cohort findings (all 10 participants received active bone marrow cell product). At 2 years after treatment, **A**) 6-minute walk distance, **B**) left ventricular ejection fraction, and **C**) left ventricular wall motion score improved. **D**) Details of the segmental left ventricular wall motion classification are summarized at baseline, 12 months, and 24 months. Note **B**) the improvements in LVEF and **D**) the increase in normal segments. These improvements were documented from the echocardiography lab, which was masked to patient information.

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Acknowledgment: This trial is currently paused (not for safety issues) and undergoing protocol revisions.

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