The CardiAMP™ Heart Failure Clinical Trial
First Results from the Unblinded Roll-In Phase

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Background
Stem cell therapy shows promise in experimental ischemic cardiomyopathy (ICM), although results in clinical trials are variable. Growing data suggests that marked differences in stem cell regenerative potential contribute to differential effects. The CardiAMP Heart Failure Trial (CardiAMP-HF) is the first to prospectively assess stem cell therapeutic potency as part of enrollment criteria. Here we report first results from the CardiAMP-HF Roll-In Phase.

Study Purpose
To determine the safety and efficacy of the CardiAMP cell therapy system in patients with post-infarct heart failure. The CardiAMP cell therapy system consists of the CardiAMP Cell Separator (CIS), the Helix® transendocardial delivery catheter and the Morph® deflatable guide catheter (BioCardia, San Carlos, CA).

Study Design
• Prospective, multi-center, 2:1 randomized, sham-controlled patient- and evaluator-blind EED trial comparing treatment with the CardiAMP cell therapy to a sham treatment in 250 patients with post-infarct heart failure NYHA functional class II-III
• Patients with chronic ICM, ejection fraction 20-40%, on optimal medical therapy with NYHA Class 2-3 heart failure symptoms were screened; all underwent screening bone marrow aspiration (BMA). Ten patients who met criteria were enrolled in the unblinded “Roll-In” phase and received intramyocardial injections of high dose autologous bone marrow mononuclear cells (target of 200 M_MNC). Briefly, BMA, autologous BM-MNCs were isolated and processed with the point-of-care CardiAMP Cell Separator (see figure 3).
• Intramyocardial delivery of BM-MNCs at the infarct border was performed using the BioCardia Helix transendocardial delivery catheter. To date, Roll-In patients have been followed for 9 months with a primary outcome of 6-minute walk distance (6MWD) and secondary outcomes, including NYHA Class and MLWHFQ score.

Primary Endpoint
Composite of six-minute walk distance, death and major adverse event that precludes the assessment of six-minute walk test performance at 12 months follow-up.

Secondary Hierarchical Endpoints
1. Overall survival at 12 months (non-inferiority outcome)
2. Freedom from Major Adverse Cardiac Events (MACE) (defined as the composite of all-cause death, hospitalization for worsening heart failure, recurrent myocardial infarction, placement of a ventricular assist device (LVAD), or heart transplantation, at 12-months (non-inferiority outcome)
3. Change in quality of life as measured by the MLWHFQ (Minnesota Living with Heart Failure Questionnaire) at 12 months follow-up (superiority outcome)
4. Time to first MACE at 12 months follow-up (superiority outcome)
5. Overall survival at 12 months (superiority outcome)

Other Secondary Endpoints at 12 Months
Treatment-emergent serious adverse events at 30 days. Days alive out of hospital, NYHA heart failure functional class, Echocardiographic measures of change in ejec tion fraction, Left ventricle end systolic and end diastolic volumes as determined by an independent Core Laboratory (Yale University, New Haven, CT).

Cell Potency Assay
All subjects underwent a 5 mL bone marrow aspiration from the iliac crest during screening for the study. The cell aspirate is tested for predefined stem cell markers capturing their proangiogenic and regenerative properties of bone marrow cells in prior studies.1,4

Study Flow

Figure 1. CardiAMP-HF ‘Roll-in’ Phase. Autologous cells are collected and cell potency is analyzed in a screening phase. If the patient’s test study eligible/clear, the patient may receive bone marrow cells harvested and processed at the point-of-care. (C) The separation chamber is centrifuged, resulting in the separation of plasma, nucleated cells and buffy coat. (D) The remaining nucleated BM MNCs are isolated (Cellics) and injected using the Helix catheter. This catheter has a funnel-shaped needle with a distal lumen to deliver the catheter and a more proximal lumen for injection of cell solution, which is used to verify transendocardial delivery.

Study Procedure
• Patients undergo aspiration of 15 mL bone marrow from the iliac crest under local anesthesia / conscious sedation.
• The bone marrow aspirate is immediately processed in the cardiac catheterization laboratory using a point-of-care system, the CardiAMP Cell Therapy system (see fig 3).
• The CardiAMP Cell Therapy device uses density-tuned dual buoy separation to isolate the BM-MNC and typically takes ~25 minutes.
• Patients randomized to active treatment then undergo 10 transendocardial injections of 0.5 mL high-dose BM MNC in the peri-infarct myocardial segments using the Helix and Morph catheters.
• The target dose is ~200 million autologous BM MNCs.
• All patients receive clinical follow-up for 2 years.

Statistics
Missing values due to clinical events (e.g., hospitalization. MACE) are assigned a score that is less than or equal to the average score of the 30-day follow-up visit. Since rank-based tests will be applied the specific value used for the missing value is immaterial. Subjects with observations missing for unknown reasons or because they have not yet had a given follow-up visit, are removed from the analysis for that visit. Second, all observations from baseline and a given follow-up visit are pooled and a rank assigned to each observation independent of visit. Each subject will then have a rank at baseline and follow-up. Change in rank from baseline to the follow-up visit is calculated, and the p-value is calculated using an one-sample t-test applied to the change in rank.

Results
All patients had successful BMA, BM-MNC isolation, and delivery with no peri-procedural SAE. At 9 months, there was improvement in 6MWD (8.1±2.4 m, p=0.36 [mean ± sem]), MLHQ (−8.6 ± 6.1, p=0.93 [mean ± sem]), and NYHA class (p=0.19). One patient was not available at 9 months follow-up due to hospitalization.

Discussion
Clinically meaningful improvements were seen across the three endpoints presented and were statistically significant at 6 months, although not at 9 months relative to baseline. This difference was in part to lack of 9 month follow-up in one patient due to a MACE event, as well as due to small sample size. These results are preliminary, however, the improvements seen in 6MWD and MLHQ were greater in magnitude than those observed in the previous Phase II randomized placebo-controlled trial, which reached statistical significance in both endpoints when compared to control.

Conclusion
CardiAMP-HF is the first multicenter clinical cell therapy trial to prospectively screen stem cell therapeutic potency. Early results from the unblinded “Roll-In” phase of the study suggest improvement in 6MWD and NYHA class and support continued investigation in the 250 patient randomized, double-blinded, sham-controlled phase of CardiAMP-HF, which is actively enrolling.

References

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