

## Mesenchymal Precursor Cells as Adjunctive Therapy in Recipients of Contemporary Left Ventricular Assist Devices

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**Background**—Allogeneic mesenchymal precursor cells (MPCs) injected during left ventricular assist device (LVAD) implantation may contribute to myocardial recovery. This trial explores the safety and efficacy of this strategy.

**Methods and Results**—In this multicenter, double-blind, sham-procedure controlled trial, 30 patients were randomized (2:1) to intramyocardial injection of 25 million MPCs or medium during LVAD implantation. The primary safety end point was incidence of infectious myocarditis, myocardial rupture, neoplasm, hypersensitivity reaction, and immune sensitization (90 days after randomization). Key efficacy end points were functional status and ventricular function while temporarily weaned from LVAD support (90 days after randomization). Patients were followed up until transplant or 12 months after randomization, whichever came first. Mean age was 57.4 ( $\pm$ 13.6) years, mean left ventricular ejection fraction was 18.1%, and 66.7% were destination therapy LVADs. No safety events were observed. Successful temporary LVAD weaning was achieved in 50% of MPC and 20% of control patients at 90 days ( $P=0.24$ ); the posterior probability that MPCs increased the likelihood of successful weaning was 93%. At 90 days, 3 deaths (30%) occurred in control patients, and none occurred in MPC patients. Mean left ventricular ejection fraction after successful wean was 24.0% (MPC=10) and 22.5% (control=2;  $P=0.56$ ). At 12 months, 30% of MPC patients and 40% of control patients were successfully temporarily weaned from LVAD support ( $P=0.69$ ), and 6 deaths (30%) occurred in MPC patients. Donor-specific HLA sensitization developed in 2 MPC and 3 control patients and resolved by 12 months.

**Conclusions**—In this preliminary trial, administration of MPCs appeared to be safe, and there was a potential signal of efficacy. Future studies will evaluate the potential for higher or additional doses to enhance the ability to wean LVAD recipients off support.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01442129. (*Circulation*. 2014;129:2287-2296.)

**Key Words:** heart failure ■ left ventricular assist device ■ randomized controlled trial ■ stem cell

Left ventricular assist devices (LVADs) have well-documented survival and quality of life benefits in patients with advanced heart failure both as a bridge to cardiac transplantation and as a long-term therapy in patients who are not transplant candidates.<sup>1-4</sup> Reports of improved

myocardial function have motivated investigation of the use of LVADs as a bridge to recovery. Although most LVAD recipients show some indications of reverse remodeling of the left ventricle (LV), as evidenced by salutary changes in ventricular structure, myocyte contractile strength,<sup>5</sup> normalization of extracellular matrix and tissue and circulating neurohormones,<sup>6</sup> and programs of gene expression,<sup>7-10</sup> these

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improvements are rarely sufficient to allow removal of the device.<sup>11</sup> The disconnect between reverse remodeling and recovery of cardiac function has prompted efforts to investigate adjunctive therapies to LVAD support, including novel pharmacotherapies<sup>12</sup> and stem cells as potential interventions to augment ventricular recovery.

Recent preclinical and clinical evidence suggests that myocardial transplantation of allogeneic mesenchymal stem cells, in particular, can enhance cardiac performance in settings of acute and chronic functional impairment.<sup>13–15</sup> Unlike whole-organ transplantation or many other allogeneic cell transplants, mesenchymal stem cell transplants do not appear to cause rejection and instead may be associated with evidence of induced tolerance to the donor.<sup>16,17</sup>

We have therefore begun investigation of allogeneic mesenchymal precursor cell (MPC) transplantation concomitant with LVAD placement in patients with advanced heart disease. Although our ultimate goal is the achievement of robust bridging to recovery, allosensitization could adversely affect donor suitability in LVAD recipients who are transplant candidates. Accordingly, the primary goal of the initial trial reported here was exploration of the safety of intramyocardial implantation of a single low dose of allogeneic MPCs together with assessment of LV performance during short intervals of temporary reduction of LVAD support, over 1 year of observation after the implants, to assess safety and any impact on reverse remodeling.

## Methods

### Study Design and Trial Oversight

This early-phase, randomized trial was designed to enroll 30 patients, and if safety is established, a larger follow-up trial will be conducted. Patients were randomly assigned in a 2:1 ratio to 25 million MPCs (Mesoblast, Inc) or control, comprised of cryoprotective medium alone (50% Alpha modified Eagle's medium/42.5% ProFreeze NAO freezing medium/7.5% dimethyl sulfoxide). Randomization was blocked to ensure equivalence of group size. All investigators and patients were masked to treatment intervention and overall outcomes data. End points were measured monthly until 90 days and every 60 days thereafter until 12 months after randomization. All patients were followed up until cardiac transplantation (for bridge to transplantation) or until 12 months after randomization (for bridge to transplantation and destination therapy), whichever came first.

The trial was conducted in 11 US centers with a Data and Clinical Coordinating Center (International Center for Health Outcomes and Innovation Research, Icahn School of Medicine at Mount Sinai) under an investigational new drug application. Interagency Registry for Mechanically Assisted Circulatory Support definitions were utilized for all relevant adverse events; bleeding events were defined by transfusion of  $\geq 4$  U of packed cells within any 24-hour period during the first 7 days after LVAD implantation and any transfusion of packed cells within any 24-hour period thereafter. An independent Clinical Events Committee adjudicated adverse events and causes of death. A National Institutes of Health-appointed protocol review committee reviewed the trial design and data, and a safety monitoring board reviewed the trial progress. Institutional review boards of participating centers and the Data and Clinical Coordinating Center approved the protocol, and all patients provided written informed consent.

### Patients and Interventions

The target population was adults with end-stage heart failure, of either ischemic or nonischemic etiology, who had a planned,

clinically indicated LVAD implantation for bridge to transplantation or destination therapy. Assist devices were required to be Food and Drug Administration-approved, contemporary, implantable, continuous-flow LVADs; selection of the specific device was left to the discretion of the surgeon. Patients were ineligible if percutaneous LVAD or biventricular mechanical support was anticipated and if they had cardiothoracic surgery or myocardial infarction within 30 days before randomization; had undergone prior cardiac transplantation, LV reduction surgery, or cardiomyoplasty; or were considered to have an acute reversible cause of heart failure. Other selected exclusion criteria included the presence of  $>10\%$  anti-HLA antibody titers with known specificity to MPC donor HLA antigens, active systemic infection within 48 hours before randomization, history of cancer before screening (excluding basal cell carcinoma), or stroke within 30 days before randomization. Patients were ineligible if they had received prior stem cell therapy for cardiac repair or any investigational cell-based therapy within 6 months before randomization. (The online-only Data Supplement includes complete eligibility criteria.)

The investigational agent was allogeneic MPCs, which are a STRO-3 immuno-selected, culture-expanded, immature subfraction of adult bone marrow-derived mononuclear cells.<sup>18</sup> The allogeneic MPCs are formulated and cryopreserved in 7.5% dimethyl sulfoxide/50% Alpha modified Eagle's medium/42.5% ProFreeze and stored in the vapor phase of liquid nitrogen until use. Cell procurement, processing, cryopreservation, and storage procedures were performed by a contract manufacturing facility under current Good Manufacturing Practice conditions. Donor and process testing were conducted for transmissible infectious diseases, karyotype, tumorigenicity, sterility, endotoxins, and mycoplasma. The product is characterized by cell count, viability, surface antigen expression of STRO-1, CC-9, and HLA class I and II. Cryopreserved products were shipped to sites for local storage, and cells were thawed and injected according to study procedures.

Intramyocardial injections of MPCs or control were performed at the time of LVAD implantation. Injection procedures were protocol defined, providing standardization of the intervention across sites and designed to maximize injections across as much of the LV myocardium as possible. LVAD implantation and management were performed in accordance with the directions for use, and the protocol provided guidance with respect to long-term management, including optimization of hemodynamic off-loading of the LV, reduction of mitral regurgitation when present, and optimization of mean blood pressure.

LVAD weaning was defined as a transient reduction in pump speed to minimize forward flow through the pump to assess native myocardial function. Protocol-specified guidelines for weaning were adopted from the Harefield Hospital protocol and included guidance for antithrombotic regimens, incremental speed reductions to a "low-speed" target of 6000 rpm, and monitoring of patients during the wean. The 6000-rpm target was chosen because this is the minimum speed necessary to prevent retrograde flow through the pump into the LV.<sup>19</sup> Weans were performed in patients deemed to be clinically stable by the clinical team and were terminated if patients developed signs or symptoms of low output or vascular congestion, such as light-headedness, dyspnea, fatigue, chest pain, or pulmonary edema. Patients who completed weaning but developed transient symptoms at any point during low speed were categorized as "wean failures" for that particular wean. A 6-minute walk (6MW) was performed after 20 minutes of low speed. A comprehensive echocardiogram was performed at full support before the wean, at 15 minutes of low speed, and again after the 6MW. The LVAD was reprogrammed to full support thereafter.

### End Points

The primary end point was safety, defined by the incidence of potential study intervention-related adverse events within 90 days after randomization, including infectious myocarditis, myocardial rupture, neoplasm, hypersensitivity reaction, and immune sensitization (defined as a clinical syndrome accompanied by detection of

donor-specific antibodies within 30 days of onset of the syndrome). The key efficacy end points were functional status, defined by the ability to tolerate wean from LVAD support for 30 minutes without signs or symptoms of hypoperfusion, and LV ejection fraction (LVEF) while weaned from LVAD support at 90 days after randomization. Ventricular function was quantified by LVEF assessed by transthoracic echocardiogram while weaned from LVAD support in those patients able to be weaned for 30 minutes.

Secondary end points for patients who tolerated weaning included echocardiographic assessments of myocardial size and function, 6MW, and duration of wean, all assessed while subjects were weaned from support, at multiple time points (30, 60, and 90 days after randomization and every 60 days thereafter until cardiac transplantation or 12 months, whichever came first) over the 12 months of the trial follow-up. Additional end points included the incidence of serious adverse events, anti-HLA antibody sensitization, neurocognitive outcomes, survival to transplantation, and exploratory mechanistic assessments including histological assessments of myocardium at explantation (at cardiac transplantation, LVAD replacement, or autopsy), peripheral blood cell phenotypic and functional analyses, and plasma chemokine/cytokine analyses at multiple time points over the 12 months of trial follow-up.

**Statistical Analysis**

**Safety**

A safety monitoring plan was based on prespecified rare events and mortality. Enrollment would be halted if any of the prespecified events associated with experimental treatment (infectious myocarditis, myocardial rupture, neoplasm, hypersensitivity reaction, or immune sensitization) were observed within 90 days after randomization. Similarly, randomization would be halted if, after 10 patients were randomized, the posterior probability that mortality on active therapy was increased compared with control exceeded 80%. Rates of adverse events were compared with the use of Poisson regression.

**Efficacy**

Superiority of MPC compared with control was assessed with a Bayesian approach. The posterior probability that the proportion of

successes (ability to tolerate LVAD wean for 30 minutes at 90 days after randomization) in the MPC group was greater than the proportion of successes in the control group was calculated on the basis of the observed proportions of successes in the 2 groups. A noninformative prior distribution,  $B(1,1)$ , was assumed for the true success probabilities in the 2 treatment groups.

Categorical variables were summarized as frequencies, and continuous variables were summarized as means and SDs. According to the protocol, LVEF was evaluated only in patients who tolerated the LVAD wean. The Fisher exact and Wilcoxon rank sum tests were used to compare the 2 groups when the sample size permitted. Kaplan-Meier curves and the log-rank test were used to assess survival in the 2 groups.

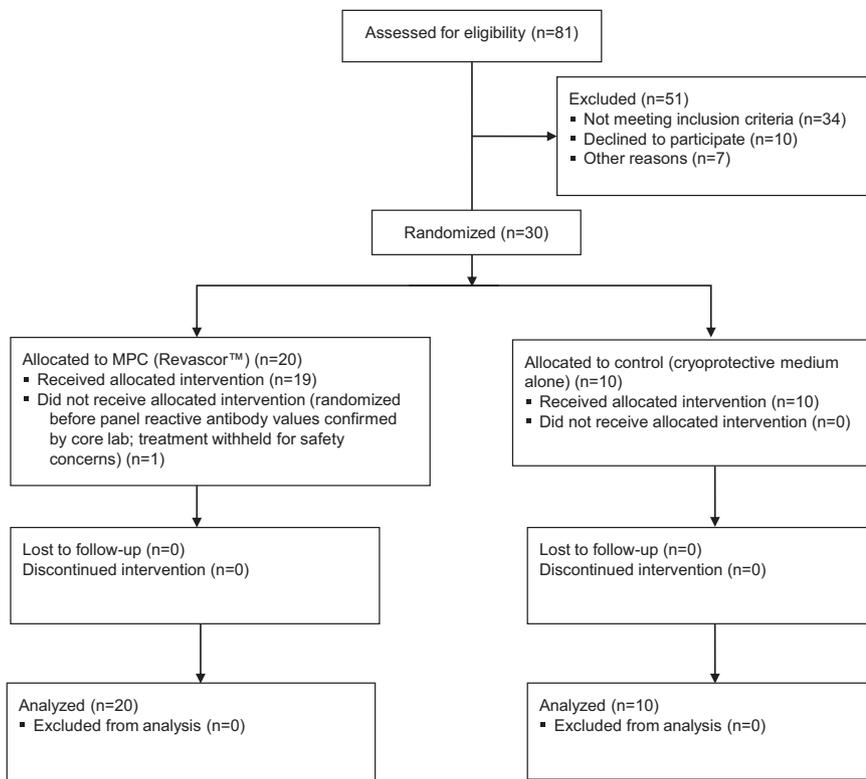
Sample size was determined on the basis of simulations. A sample size of 30 patients was chosen to allow us to detect an approximate tripling of the odds that active therapy is superior (ie, from 50% probability of superiority of active therapy, or 1:1 odds, to 75%, or 3:1 odds) with probability  $\geq 75\%$  if the absolute probability of a successful outcome with active therapy is  $\approx 10\%$  to 15% higher than for control.

**Results**

**Patients**

Eighty-one patients were screened, 47 were eligible, and 30 were randomized (Figure 1): 20 patients to intramyocardial MPC administration and 10 to intramyocardial injection of cryoprotective medium (control). Treatment intervention was withheld from 1 MPC patient who was randomized before we obtained core laboratory results of the panel of reactive antibodies to exclude preexisting donor-specific antibodies.

The treatment groups were similar with respect to baseline characteristics (Table 1). The mean age was 57.4 years ( $\pm 13.6$ ), and 83% were male. The mean LVEF was 18% ( $\pm 4.3$ ), 37% had ischemic cardiomyopathy, and all patients



**Figure 1.** Consort diagram. MPC indicates mesenchymal precursor cell.

**Table 1. Baseline Characteristics of Patients**

Characteristic	MPC (n=20)	Control (n=10)
Male	17 (85)	8 (80)
Age, y	55.1±15.4	62.2±7.8
Race		
White	14 (70)	8 (80)
Black or African American	6 (30)	2 (20)
Cardiomyopathy		
Ischemic	7 (35)	4 (40)
Nonischemic	13 (65)	6 (60)
Biventricular pacemaker	11 (55)	7 (70)
Preoperative IABP	3 (15)	0 (0)
Creatinine, mg/dL	1.3±0.4	1.2±0.3
Cardiac index, L/(min·m <sup>2</sup> )	1.8±0.6	1.8±0.5
PVR, Wood units	2.7±2.0	3.2±1.8
LVEF, %	17.5±3.9	19.3±5.1
NYHA classification		
I and II*	0 (0)	1 (10)
III	3 (15)	2 (20)
IV	17 (85)	7 (70)
Medications		
β-Blocker	14 (70)	5 (50)
Aldosterone receptor antagonist	11 (55)	5 (50)
ACEi/ARB	7 (35)	7 (70)
Inotropic therapy		
1 Agent	10 (50)	7 (70)
>1 Agent	4 (20)	2 (20)
Vasoactive therapy	4 (20)	0 (0)
Indication for LVAD		
Bridge to transplantation	7 (35)	3 (30)
Destination therapy	13 (65)	7 (70)

Plus-minus values are mean±SD; categorical values are n (%). ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MPC, mesenchymal precursor cell; NYHA, New York Heart Association; and PVR, pulmonary vascular resistance.

\*One patient was classified as NYHA II heart failure.

were implanted with HeartMate II LVADs (Thoratec Corp); 67% were implanted for destination therapy indication.

### Safety and Mortality

No patients developed a primary safety event within 90 days after randomization (the primary end point) or during the 12-month follow-up period. At 90 days, there were 3 deaths (30%) in the control group and none in the MPC group. In a post hoc analysis, the posterior probability that mortality at 90 days is reduced in the MPC group exceeded 80%. Six MPC patients (30%) died over the 12 months, with no additional deaths occurring in the control group. Figure 2 depicts the Kaplan-Meier survival curves. The most frequent primary causes of death in this patient population were LVAD failure (22.2%) and multisystem organ failure (22.2%); the most frequent underlying causes of death were pump thrombus (33.3%) and sepsis (22.2%). Causes of death were similar

between the groups, and no deaths were classified as related to the study intervention.

Serious adverse event rates were similar between the 2 groups (Table 2). At 90 days, the serious adverse event rate was 1.30 per patient-month in the treatment group and 1.16 in the control group. The overall rate was 6.95 per patient-year in the treatment group and 6.89 in the control group. The most prevalent serious adverse events over the course of the trial were major bleeding, respiratory failure, right heart failure, and localized nondevice infection. The major bleeding event rate per patient-year at 12 months was 3.88 in the treatment group and 3.97 in the control group; major bleeding requiring surgery or rehospitalization is depicted in Table 2. Of note, 1 trial patient, who did not receive intramyocardial injections at the time of LVAD implantation (described above), had multiple bleeding events and received 32 U of packed red blood cells over the course of the trial. Donor-specific HLA sensitization developed after randomization in 2 MPC and 3 control patients. By 1 year, 1 sensitized patient in each arm died, and all donor-specific antibodies had resolved in surviving patients.

### Efficacy

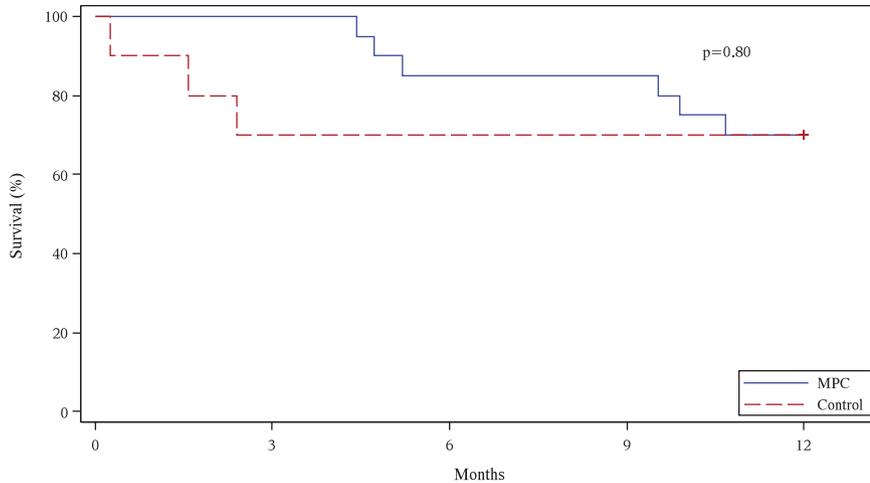
In the MPC group, 50% of patients were able to successfully tolerate the weaning from LVAD support for 30 minutes at 90 days compared with 20% in the control group ( $P=0.24$ ). On the basis of these results, the posterior probability that MPCs increase the likelihood of successful weaning is 93% (Figure 3). The duration of temporary LVAD wean, for those who tolerated it, was greater in MPC than in control patients at each time point (Figure 4). None of the control patients and 4 (20%) of the MPC-treated patients were able to tolerate the LVAD wean at the 30-day time point.

The mean LVEF at the conclusion of the temporary wean, for those who tolerated LVAD turnaround, was 24% (MPC;  $n=10$ ) and 22.5% (control;  $n=2$ ) at 90 days ( $P=0.56$ ), and the median 6MW was 883 (first and third quartiles, 750 and 1042) feet in the treatment arm and 1080 (first and third quartiles, 871 and 1289) feet in the control arm ( $P=0.35$ ).

At 12 months, there was no difference between groups in the ability to tolerate temporary weaning: 30% of MPC and 40% of control patients ( $P=0.69$ ) were weaned from LVAD support. Eighty-five percent of MPC patients tolerated 1 or more temporary LVAD weans over the 12-month follow-up period compared with 40% of control patients ( $P=0.03$ ; Figure 5). Importantly, heart failure therapy, including angiotensin receptor and aldosterone antagonists, β-blockers, diuretics, and inotropic therapy, was similar between the 2 groups at 90 days. At 1 year, the regimens remained similar across groups with the exception of angiotensin antagonists (MPC:  $n=14$  [100%]; control:  $n=4$  [57%]).

### Hospitalizations

There was no difference between groups with respect to hospitalizations. The median length of stay of index hospitalization was 29.5 days in the MPC group and 35.0 days in the control group ( $P=0.91$ ). By 90 days after randomization, 26 patients had been discharged from the index hospitalization; of those, 22% (4/18) of MPC patients and 38% (3/8) of control patients



**Figure 2.** Survival. Crosses depict censored patients. MPC indicates mesenchymal precursor cell.

MPC	20	20	17	17	14
Control	10	7	7	7	7

were readmitted. The rate of rehospitalization per person-year was 2.15 (MPC) and 2.14 (control). The median time to first readmission was 91 days (first and third quartiles, 44 and 263) in the MPC group and 51 days (first and third quartiles, 10 and 150) in the control group. The most frequent reasons for readmission were noncardiovascular in both groups, driven by infection (8.8%) and bleeding (70.6%); 96% of the latter were gastrointestinal in origin (Table 3).

### Discussion

This is the first randomized trial of allogeneic MPCs in patients undergoing LVAD implantation for the management of advanced heart failure.<sup>20–22</sup> Early experience with mesenchymal stem cells, or their subpopulations, suggests that they may be more effective than unfractionated bone marrow mononuclear cells in clinical applications. MPCs are multipotent cells with extensive proliferative potential that secrete numerous antiapoptotic, angiogenic factors and growth factors.<sup>23,24</sup> Because MPCs are immune privileged, they can be transplanted into unrelated recipients without the need for HLA matching or immunosuppression, thereby creating the possibility of an allogeneic, off-the-shelf cell product, readily available for administration.<sup>13,15,25</sup> The predominant mechanism of MPC therapy in cardiovascular disease is generally considered to be mediated by the paracrine effects of the cells because both long-term engraftment and transdifferentiation into cardiomyocytes are unlikely on the basis of previous studies; neither mechanism can account for the biological activity demonstrated in numerous studies.<sup>15,26–28</sup> Indeed, MPCs are known to secrete significant amounts of potentially relevant growth and angiogenic factors, such as stromal cell-derived factor-1, hepatocyte growth factor-1, insulin-like growth factor-1, vascular endothelial growth factor, and interleukin-6.<sup>25,28</sup> Mechanistic effects of the MPCs used in this trial will be examined in further biospecimen analyses.

The majority of patients enrolled in this trial had non-ischemic cardiomyopathy, which, although atypical for the epidemiology of the broader heart failure population, is

representative of the breakdown by etiology of the advanced heart failure LVAD subgroup.<sup>4,29</sup> Nearly 70% of trial patients received an LVAD for long-term use, with approximately a third of the patients receiving LVAD support for bridge to transplantation. The bridge to transplantation population in particular influenced the dose selection for this trial because these patients are in general younger and may be more likely to experience myocardial recovery but also are at unique risk of jeopardizing their transplant eligibility if they become immune sensitized. For this reason, we selected a dose of 25 million cells, a comparatively low dose relative to other trials of cell-based therapies.

This early trial demonstrates that MPCs are safe; no primary safety end point adverse events occurred within 90 days after randomization or over the course of the 12-month follow-up. As observed, 1 of the major safety concerns in the bridge to transplantation LVAD population is HLA sensitization. Interestingly, more control patients developed donor-specific antibodies within the first 90 days after randomization than those who received MPCs, and by 1 year all donor-specific sensitization had resolved. All 3 control patients who developed donor-specific antibodies received transfusions after randomization, perhaps contributing to the sensitization. No sensitization that developed during the trial was associated with any clinical findings. These data provide sufficient safety experience to explore higher doses of MPCs in this vulnerable patient population.

Serious adverse event rates at 90 days and over 1 year were similar between MPC and control groups. Furthermore, adverse event rates, except for bleeding, generally were similar to those previously reported for the LVAD population.<sup>2,4,30</sup> Major bleeding was adjudicated more conservatively in this trial than is current practice. In this trial, bleeding events were defined by transfusion requirements at 24-hour increments, regardless of the presence of a clinical bleeding episode, and an ongoing bleed over time was captured as multiple events on the basis of transfusions per time period. This categorization may have contributed to the higher rate of major bleeding observed in this trial relative

**Table 2. Serious Adverse Events**

	90 Days			12 Months		
	MPC (n=20) (Patient-Month=59.2)	Control (n=10) (Patient-Month=25)	P Value	MPC (n=20) (Patient-Year=18.3)	Control (n=10) (Patient-Year=7.6)	P Value
	No. of Events (Rate/Patient-Month)			No. of Events (Rate/Patient-Year)		
<b>Bleeding</b>						
Intraoperative bleeding	2 (0.03)	1 (0.04)		2 (0.11)	1 (0.13)	
Major bleeding requiring surgery	7 (0.12)	1 (0.04)		7 (0.38)	1 (0.13)	
Major bleeding requiring rehospitalization	0 (0.00)	4 (0.16)		10 (0.55)	7 (0.93)	
<b>Cardiac arrhythmias</b>						
Cardiac arrest	0 (0.00)	0 (0.00)		1 (0.05)	0 (0.00)	
Sustained ventricular arrhythmia*	2 (0.03)	2 (0.08)		2 (0.11)	2 (0.26)	
Sustained supraventricular arrhythmia†	1 (0.02)	2 (0.08)		2 (0.11)	2 (0.26)	
Pericardial effusion‡	3 (0.05)	0 (0.00)		3 (0.16)	0 (0.00)	
<b>Device malfunction</b>						
Pump failure	0 (0.00)	0 (0.00)		1 (0.05)	0 (0.00)	
Non-pump failure	0 (0.00)	0 (0.00)		3 (0.16)	0 (0.00)	
Pump thrombus suspected	0 (0.00)	1 (0.04)		1 (0.05)	1 (0.13)	
Pump thrombus confirmed	2 (0.03)	1 (0.04)		4 (0.22)	1 (0.13)	
Hemolysis	1 (0.02)	1 (0.04)		1 (0.05)	2 (0.26)	
Hepatic dysfunction	0 (0.00)	0 (0.00)		1 (0.05)	0 (0.00)	
<b>Major infection</b>						
Localized nondevice infection	3 (0.05)	2 (0.08)		4 (0.22)	2 (0.26)	
Internal pump component inflow or outflow tract infection	0 (0.00)	0 (0.00)		1 (0.05)	0 (0.00)	
Sepsis	2 (0.03)	0 (0.00)		3 (0.16)	1 (0.13)	
Unspecified	0 (0.00)	0 (0.00)		1 (0.05)	0 (0.00)	
<b>Neurological dysfunction</b>						
Transient ischemic attack	0 (0.00)	0 (0.00)		1 (0.05)	0 (0.00)	
Ischemic stroke	0 (0.00)	0 (0.00)		1 (0.05)	0 (0.00)	
Hemorrhagic stroke	0 (0.00)	1 (0.04)		0 (0.00)	1 (0.13)	
Toxic metabolic encephalopathy	2 (0.03)	0 (0.00)		2 (0.11)	0 (0.00)	
Other	0 (0.00)	0 (0.00)		1 (0.05)	0 (0.00)	
<b>Renal dysfunction</b>						
Acute	4 (0.07)	1 (0.04)		4 (0.22)	1 (0.13)	
Chronic	1 (0.02)	0 (0.00)		1 (0.05)	0 (0.00)	
Respiratory failure	5 (0.08)	2 (0.08)		5 (0.27)	2 (0.26)	
Right heart failure	3 (0.05)	1 (0.04)		3 (0.16)	3 (0.40)	
Venous thromboembolism	1 (0.02)	1 (0.04)		1 (0.05)	1 (0.13)	
Other	38 (0.64)	8 (0.32)		61 (3.34)	24 (3.18)	
<b>Total</b>	<b>77 (1.30)</b>	<b>29 (1.16)</b>	<b>0.60</b>	<b>127 (6.95)</b>	<b>52 (6.89)</b>	<b>0.96</b>

MPC indicates mesenchymal precursor cell.

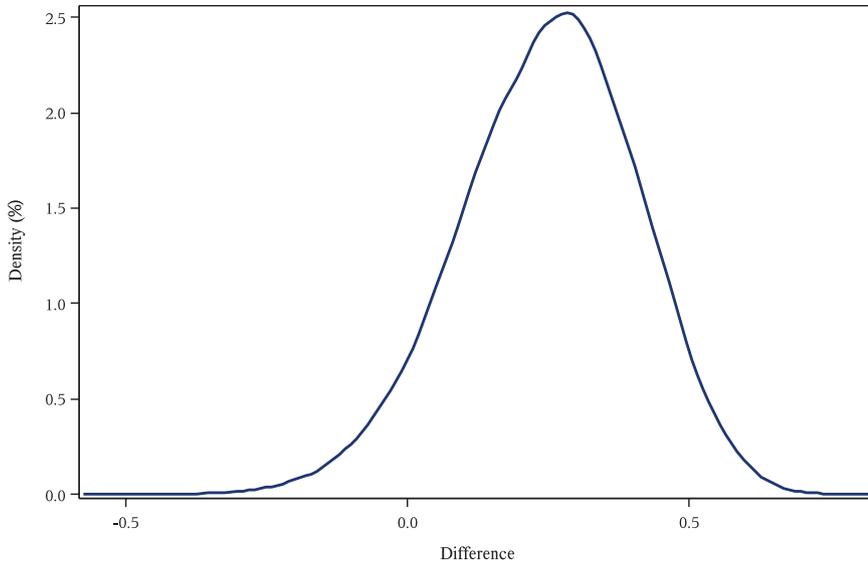
\*Sustained ventricular arrhythmia requiring defibrillation or cardioversion.

†Sustained supraventricular arrhythmia requiring drug treatment or cardioversion.

‡Fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage.

to the published literature. Nearly 75% of bleeding events occurred >30 days after LVAD surgery and intramyocardial injections. Respiratory failure, although theorized to be associated with trapping of cells in the lungs in the setting of cell-based therapies, was experienced at similar rates across the treatment groups in this trial and was consistent with

existing benchmarks in LVAD patients.<sup>30,31</sup> Direct comparison of suspected and confirmed device thrombus rates seen in this small population with those in the literature is challenged by differences in definitions and duration of LVAD support. However, the 90-day and 12-month rates observed in the trial population are not dissimilar to those recently



**Figure 3.** Posterior distribution analysis curve. Difference indicates difference in response rates (mesenchymal precursor cell vs placebo); 93% of the area under the curve is between 0 and 1, corresponding to the probability that mesenchymal precursor cells provide better response than placebo.

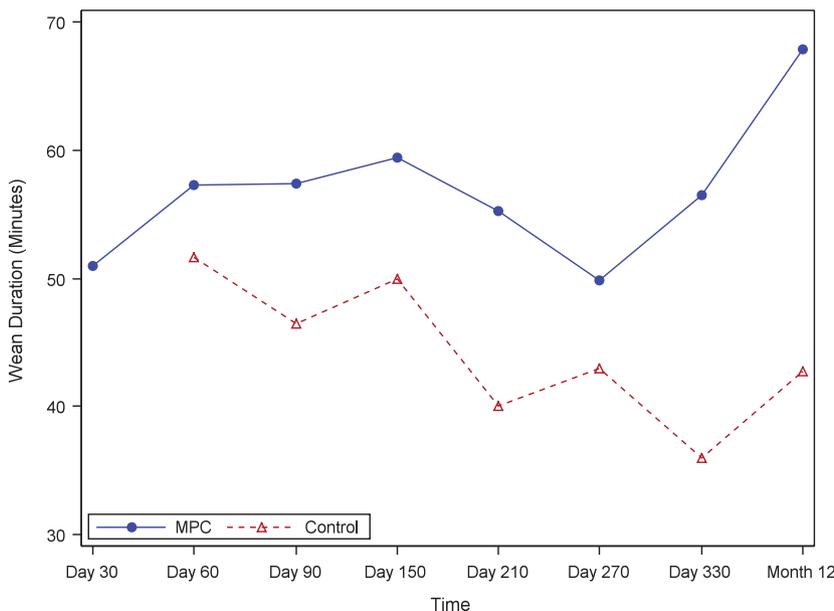
reported<sup>32</sup> and are the same between treatment groups. (See Table I in the online-only Data Supplement for 30 day adverse event rates.)

The median length of stay for the index hospitalization was similar between the 2 groups and, although somewhat prolonged, was not dissimilar to length of stay data reported previously in the LVAD population.<sup>33</sup> The frequency of readmissions by both 90 days and 1 year after randomization for patients discharged after their index hospitalization was also similar between the treatment groups and consistent with the expected range for the LVAD population.<sup>34</sup> Interestingly, although the rate of readmissions was similar between the treatment groups, the median time to first readmission was earlier in the control group (51 days [first and third quartiles, 10 and 150]) than in the treatment group (91 days [first and third quartiles, 44 and 263]). The most common cause of

readmission, similar to previous results in continuous-flow device trials, was gastrointestinal bleeding.<sup>35-41</sup>

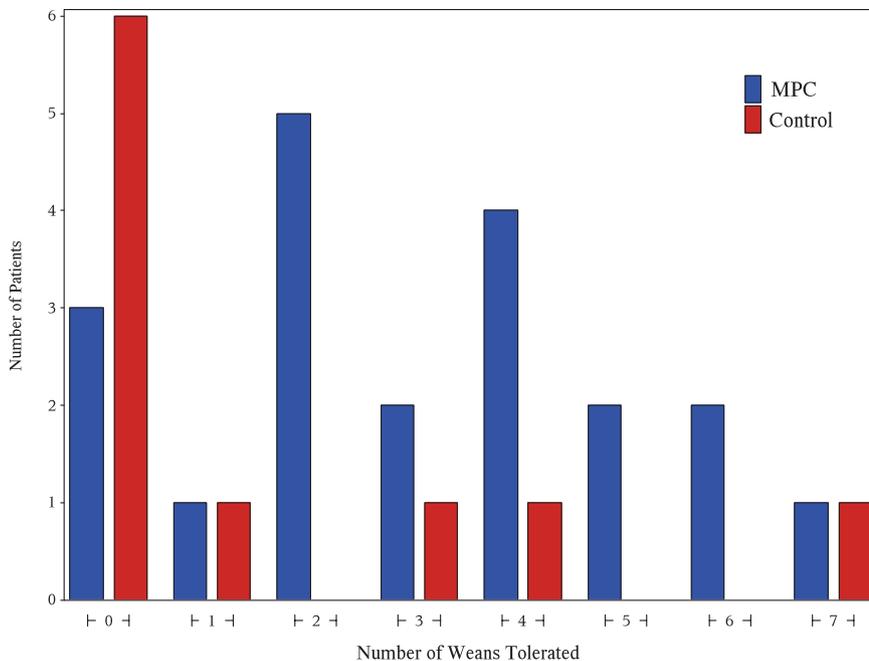
The 90-day mortality rate was 30% in the control group and 0% in the MPC group. In a post hoc analysis, the posterior probability that mortality at 90 days is reduced in the MPC group exceeded 80%. At 1 year, the mortality rates were the same for both groups (30%). Factors known to increase mortality in LVAD recipients, such as prior cardiac surgery, history of stroke, diabetes mellitus, and dialysis, were balanced across the treatment groups and within the expected range for the advanced heart failure population, and no patient received a right ventricular assist device implantation at the time of surgery.<sup>30,38-41</sup>

Despite the low dose of cells deployed in this trial, a likely efficacy signal was observed; a greater proportion of MPC patients experienced successful temporary weans at 90 days.



**Figure 4.** Duration of left ventricular assist device wean. MPC indicates mesenchymal precursor cell.

# of Patients	Day 30	Day 60	Day 90	Day 150	Day 210	Day 270	Day 330	Month 12
MPC	4	7	10	10	9	9	7	6
Control	0	3	2	2	2	1	1	4



**Figure 5.** Number of successful weans. MPC indicates mesenchymal precursor cell.

Moreover, the total number of temporary weans tolerated by MPC patients was double that of the control group. Similarly, the significantly lower early mortality rate and fewer hospitalizations in MPC patients compared with control are promising. However, the treatment effect was not seen at 1 year. This argues for evaluating higher doses in this population, especially because sensitization concerns were addressed at the lower dose. Consideration also should be given to redosing after 90 days to determine whether this might improve the durability of a treatment effect. Redosing by systemic intravenous infusion is being used in another trial of the same MPCs in a noncardiovascular application.

This trial has several limitations. It is a small, exploratory trial; the efficacy end points such as weaning, LVEF, and 6MW at 90 days are based on a comparison of 10 patients

in the MPC group and 2 patients in the control group, limiting the insight that can be drawn. A larger follow-up trial is being planned. In addition, efficacy end points such as functional status and rehospitalizations, which are often used in other heart failure trials, are not straightforward within the context of LVAD support.<sup>42,43</sup> We selected an efficacy end point that combines tolerance of LVAD weaning (without symptoms of cardiovascular compromise) with additional assessment of functional status. However, the ability to wean is also affected by noncardiovascular factors, such as debilitation secondary to comorbidities or inability to optimize anticoagulation, which, in turn, is critical to safely turning down the pump speed. These factors are unrelated to the intervention and in a small trial may affect a potential efficacy signal.

LVADs offer a unique “clinical laboratory” for evaluation of adjunctive cardiac regenerative therapies. The cells used in this trial have many potential advantages, including “off-the-shelf” availability and the potential for immunologic privilege. This exploratory trial confirms feasibility and safety and suggests early efficacy of MPCs, opening up the field for further clinical investigation.

**Table 3. Hospitalization Experience**

	MPC (n=20)	Control (n=10)	P Value
<b>Index hospitalization</b>			
Length of stay, median (quartiles 1 and 3), d	29.5 (20.5, 43)	35 (17, 45)	0.91
<b>Readmissions at 1 y</b>			
Patients with ≥1 readmissions, No. (%)	12 (67)	6 (75)	
Time to first readmission, median (quartiles 1 and 3), d	91 (44, 263)	51 (10, 150)	
Readmissions, total No. (rate per patient-year)	34 (2.1)	14 (2.1)	
<b>Reasons for readmission, No. (%)</b>			
LVAD related	8 (24)	1 (7)	
Cardiovascular non-LVAD related	3 (9)	2 (14)	
Noncardiovascular	23 (68)	11 (79)	

LVAD indicates left ventricular assist device; and MPC, mesenchymal precursor cell.

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## Disclosures

Dr Feldman has served as a consultant for Thoratec Inc and HeartWare Inc. Dr Goldstein has served on the medical advisory board for Thoratec Inc and as a consultant for HeartWare Inc. Dr Milano has served as a consultant for Thoratec Inc and HeartWare Inc. Dr Naka has served as a consultant for Thoratec Inc. Dr Rame has received research funding from Thoratec Inc and HeartWare Inc. Dr Rogers has served as a consultant for Thoratec. Dr Rose has served on the Board of Directors for Mesoblast Inc. Dr Skerrett has served as the Chief Medical Officer for Mesoblast Inc. Dr Sun has served as a consultant for Thoratec Inc and Sunshine Heart. Dr Taylor is a founder of Miromatrix Medical Inc. The other authors report no conflicts.

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### CLINICAL PERSPECTIVE

Allogeneic mesenchymal precursor cells (MPCs) injected during left ventricular assist device (LVAD) implantation may contribute to myocardial recovery. This trial explores the safety and efficacy of this strategy. In this multicenter, double-blind, sham-procedure controlled trial, 30 patients were randomized (2:1) to intramyocardial injection of 25 million MPCs or medium during LVAD implantation. The primary safety end point was incidence of infectious myocarditis, myocardial rupture, neoplasm, hypersensitivity reaction, and immune sensitization (90 days after randomization). Key efficacy end points were functional status and ventricular function while subjects were temporarily weaned from LVAD support (90 days after randomization). Patients were followed up until transplantation or 12 months after randomization, whichever came first. Mean age was 57.4 ( $\pm$ 13.6) years, mean LVEF was 18.1%, and 66.7% were destination therapy LVADs. No safety events were observed. Successful temporary LVAD weaning was achieved in 50% of MPC and 20% of control patients at 90 days ( $P=0.24$ ); the posterior probability that MPCs increased the likelihood of successful weaning was 93%. At 90 days, 3 deaths occurred in control patients, and none occurred in MPC patients. Mean left ventricular ejection fractions after successful wean were 24.0% (MPC=10) and 22.5% (control=2;  $P=0.56$ ). At 12 months, 30% of MPC and 40% of control patients were successfully temporarily weaned from LVAD support ( $P=0.69$ ), and 6 deaths occurred in MPC patients. Donor-specific HLA sensitization developed in 2 MPC and 3 control patients and resolved by 12 months. MPCs in LVAD patients are safe, and a potential efficacy signal was observed. Higher or additional doses may enhance the ability to wean LVAD recipients off support.