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Allogeneic Cardiosphere-derived Cells for the Treatment of Heart Failure with Reduced Ejection Fraction: Results of the Dilated cardiomYopathy iNtervention with Allogeneic Myocardially-regeneratIve Cells (DYNAMIC) trial

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EM owns founder's equity in Capricor and serves as unpaid scientific advisor to Capricor. JR, RRS, LM and DA are employees of Capricor. KM and JMP are paid consultants to Capricor. The remaining authors report no conflicts.

Abstract

Aims

The DYNAMIC trial assessed the safety and explored the efficacy of multivessel intracoronary infusion of allogeneic cardiosphere-derived cells (CDCs) in patients with heart failure and reduced ejection fraction (HFrEF).

Methods and results

We enrolled 14 patients with EF≤35% and NYHA III-IV despite maximal medical- and device-based therapy in this single-center, open-label trial. Intracoronary catheterization delivered four escalating doses (totaling 37.5-75 million cells) by sequential non-occlusive technique to all three major coronary arteries. The primary safety endpoint was a composite of post-infusion TIMI flow, ventricular tachycardia/fibrillation, sudden death, major adverse cardiac events or acute myocarditis within 72 hours. Twelve patients were male and EF averaged 23.0% (±4.5%). No primary safety endpoints were observed. Two patients died of HFrEF progression 9- and 12-months following infusion. Compared to baseline, there was an improvement in EF (26.8% vs. 22.9%, p=0.023) and left ventricular end-systolic volume (139.5 vs. 177.8, p=0.03) at 6 months. Quality of life (QoL) scores and NYHA class (p=0.006) improved at 6 months. At 12 months, the improvement in EF and QoL remained significant.

Conclusions

Global intracoronary infusion of allogeneic CDCs is safe and feasible. The efficacy of allogeneic CDCs in HFrEF needs to be tested in larger randomized trials.

Classifications

Depressed left ventricular function

Dilated non ischemic cardiomyopathy

Ischemic cardiomyopathy

Cell-based regenerative therapy

Abbreviations

CDC	Cardiosphere-derived cell
MI	Myocardial infarction
DYNAMIC	Dilated cardiomYopathy iNtervention With Allogeneic MyocardIally-regenerative Cells
ALLSTAR	ALLogeneic heart STem Cells to Achieve myocardial Regeneration
HOPE	Halt cardiOmyopathy ProgrEssion
HFrEF	Heart failure with reduced ejection fraction
EF	Ejection fraction
TTE	Transthoracic echocardiogram
CT	Computed tomogram
NYHA	New York Heart Association
TnI	Troponin I
CK-MB	Creatine kinase-MB
ICD	Implantable cardioverted defibrillator
6MWT	Six-minute walk test
QoL	Quality of life
LV	Left ventricle
LVESV	Left ventricular end-systolic volume
LVEDV	Left ventricular end-diastolic volume
MLFHQ	Minnesota Living with Heart Failure Questionnaire

Condensed abstract

The DYNAMIC trial assessed the safety and explored the efficacy of multivessel intracoronary infusion of allogeneic cardiosphere-derived cells (CDCs) in 14 patients with NYHA III-IV heart failure and reduced ejection fraction (HFrEF). The principal finding from DYNAMIC is that nonocclusive multivessel intracoronary infusion of allogeneic CDCs is feasible and safe. Despite the small sample size and lack of a control group, the trial also demonstrated concordant efficacy signals, especially evident at 6 months. The favorable safety profile, in conjunction with the hints of efficacy, support proceeding to a randomized, placebo-controlled trial of allogeneic CDCs for patients with HFrEF.

Introduction

Intracoronary administration of autologous cardiosphere-derived cells (CDCs) post-myocardial infarction (MI) is safe and results in decreased scar size, increased viable myocardium and improved regional function of infarcted myocardium 1-year post-treatment[1, 2]. While the initial clinical studies with CDCs were focused on autologous therapy, preclinical studies revealed that allogeneic CDC administration without immunosuppression was safe, promoted cardiac regeneration, and improved heart function, with efficacy comparable to autologous CDCs[3-5]. Experiments in small and large animal models of ischemic and non-ischemic cardiomyopathy have demonstrated that exogenously-administered CDCs act by transiently stimulating endogenous reparative and regenerative pathways (rather than through direct differentiation into newly-formed myocardium)[6-10]. This indirect mechanism of action rationalizes the efficacy of allogeneic cells, which have been shown to persist in the host myocardium of experimental animals long enough to initiate the same cascade of indirect effects as autologous CDCs, thereby conferring indistinguishable benefits[3, 5]. The comparable effects of allogeneic versus autologous CDC therapy led to 3 clinical trials evaluating the safety and efficacy of allogeneic CDC therapy: the Dilated cardiomYopathy iNtervention With Allogeneic MyocardIally-regenerative Cells (DYNAMIC) trial (NCT02293603, reported here); the ALLogeneic heart STem Cells to Achieve myocardial Regeneration (ALLSTAR) trial (NCT01458405) in patients post-MI[11]; and the Halt cardiOmyopathy ProgrEssion (HOPE)-Duchenne trial (NCT02485938) in patients with Duchenne muscular dystrophy. Here we report the results of the DYNAMIC trial, a single-center, prospective, dose-escalation study of non-occlusive sequential triple-vessel intracoronary infusion of allogeneic CDCs in patients with heart failure with reduced ejection fraction (HFrEF).

Methods

Trial Design

The study protocol (**Figure 1**; complete protocol in the *Supplementary Appendix*) was approved by the institutional review board of Cedars-Sinai Medical Center. All participants provided written informed consent. DYNAMIC enrolled 14 subjects with HFrEF (EF ≤ 35% as determined by a transthoracic echocardiogram (TTE) within the preceding 6 months and EF ≤ 40% on screening cardiac computed tomogram (CT) and New York Heart Association (NYHA) class III or ambulatory Class IV heart failure, despite guideline-directed medical and device therapy for at least 3 months. Subjects meeting all inclusion and no exclusion criteria were enrolled. Although it was not mandated by the study protocol, all patients underwent coronary angiogram prior to enrollment to confirm that there was no need for revascularization prior to enrollment in the study.

Within 28 days of the initial baseline assessment, all subjects underwent intracoronary infusion of allogeneic CDCs in an open-label fashion into 3 coronary territories: left anterior descending, left circumflex and right coronary artery; or the bypass grafts to the corresponding coronary territories. The technical suitability of coronary anatomy for intracoronary infusion was determined by the eligibility committee comprising a team of interventional cardiologists. The enrolled subjects were assigned to 4 dosing groups in a sequential manner (**Figure 2**): Group 1 (n=3) allogeneic CDC infusion dose of 12.5 million cells in each cardiac territory; Group 2 (n=3) allogeneic CDC infusion dose of 25 million cells in one cardiac territory and 12.5 million cells in the remaining cardiac territories; Group 3 (n=3) allogeneic CDCs infusion dose of 25 million cells in two cardiac territories and 12.5 million cells in the other cardiac territory, and Group 4 (n=5) allogeneic CDCs infusion dose of 25 million cells in each cardiac territory. The

initial study design included enrollment of additional 28 patients in a randomized, placebo-controlled manner following the enrollment of the first 14 subjects for the dose-finding study. However, the study sponsor decided not to proceed with the randomized placebo-controlled study following review of the dose-finding study results.

Infusion protocol

Allogeneic CDCs were manufactured as previously described[11]. Briefly, the tissue derived from donor hearts was cultured as explants. Cardiospheres were generated from the explant-derived cells, and CDCs were expanded from cardiospheres. Detailed infusion protocol is described in the *Supplementary Appendix*. Intracoronary infusion of allogeneic CDCs was performed (**Figure 2)** using Finecross MG coronary micro-guide catheters **(**Terumo Medical Corporation, Somerset, NJ**)**, advanced into the proximal segment of each coronary artery or corresponding bypass graft. After infusion of 2 ml of wash solution over 30 seconds, allogeneic CDCs were infused over 5 minutes (for 12.5 million cells) or 10 minutes (for 25 million cells), followed by another 2 mL of wash solution over 30 seconds. Once TIMI 3 flow was confirmed post-infusion and following a 5-minute interval between infusions in individual coronary territories, the infusion sequence was repeated 2 more times to treat the remaining coronary territories. Assessment of infusion-induced myocardial injury was performed by serial measurement of ischemic biomarkers (troponin I (TnI) and creatine kinase-MB (CK-MB)) every 8 hours for 16-24 hours post-infusion.

Follow-up

Patients were followed up at 2 weeks and at 1, 2, 3, 6, and 12 months after allogeneic CDC infusion (**Figure 1**). Adverse events were monitored by the National Heart, Lung, and Blood Institute Gene and Cell Therapy Data and Safety Monitoring Board. Host immunologic response to donor cells was assessed in two ways: 1) for monitoring humoral immunity, single antigen

bead testing to detect donor specific antibodies (Texas Medical Specialty, Inc., Dallas, TX); 2) for monitoring cellular immunity, ELISpot assay (Cellular Technology Ltd., Shaker Heights, OH).

Study end-points

The primary objective was to determine the safety of allogeneic CDCs administered by multi-vessel, non-occlusive intracoronary infusion in subjects with HFrEF. The primary safety endpoint was defined as the occurrence of any of the following events during or after intracoronary delivery: (1) New TIMI flow 0-2 or TIMI myocardial perfusion grade 0-2, noted immediately following infusion of allogeneic CDCs and persisting >3 min after cell infusion, despite intracoronary vasodilator administration; (2) Acute myocarditis within 1 month of infusion, possibly attributable to allogeneic CDCs; (3) Ventricular tachycardia or fibrillation resulting in death, appropriate discharge of an implantable cardioverter-defibrillator (ICD), or requiring medical intervention, within 72 hours of infusion; (4) Sudden unexpected death within 72 hours of infusion; and (5) Major adverse cardiac events (death, non-fatal MI and re-hospitalization for cardiovascular events, including heart failure hospitalizations) within 72 hours of infusion. The diagnosis of acute myocarditis was made based on clinical presentation, with or without a clinically indicated endomyocardial biopsy.

The secondary objective of the study was to further explore the efficacy of allogeneic CDC administration by multi-vessel, non-occlusive intracoronary infusion in subjects with HFrEF. Several exploratory efficacy endpoints were assessed, including absolute and relative changes in cardiac functional and structural parameters, 6-minute walk test (6MWT), maximum oxygen consumption ($V_{O2\ max}$), NYHA class and quality of life (QoL) questionnaires. TTEs were

analyzed at the Cedars-Sinai Heart Institute by 2 readers blinded to study visit as well as the cell dosing administered to each subject. The EF was calculated using the biplane Simpson's method.

Statistical analysis

The null hypothesis for the primary safety endpoint was that the proportion of subjects experiencing the primary safety endpoint (p_s) was ≥ 0.20. The null hypothesis was tested against the one-sided alternative $p_s < 0.20$ using a 0.05 significance level. Null hypotheses of change from baseline in efficacy parameters = 0 were tested against two-sided alternatives using signed rank tests i.e., only subjects with both "pre" (baseline) and "post" (6- or 12-month) data were included. There were no imputations for missing data. The analyses only included subjects who had data at both baseline and the time point being analyzed. A two-sided exact binomial test was used to test the null hypothesis that the probability of improvement in NYHA class was = 0.5. All efficacy analyses were done using 0.05 significance levels. No adjustments for multiple efficacy endpoints were applied since the efficacy analysis was exploratory and hypothesis-generating. Continuous measures are presented as mean ± standard deviation (SD) in the text and tables and as mean ± standard error (SEM) in the figures. Due to small sample sizes within dose groups, efficacy results are presented as pooled across dose groups.

Results

Patients

Of 24 patients screened for enrollment, 14 were enrolled in the study (**Figure 3**). Baseline characteristics of enrolled patients are summarized in **Table 1**. The mean EF was 22.9% ± 4.5% and left ventricular (LV) end-diastolic diameter was 69.3 ± 8.9 mm. The etiology of cardiomyopathy was evenly divided between ischemic (n=7) and non-ischemic (n=7). One patient was diagnosed with dilated cardiomyopathy 9 months prior to enrollment; the remaining

13 patients had a diagnosis of dilated cardiomyopathy for at least 1 year prior to enrollment. Six patients underwent invasive coronary angiogram and 4 patients underwent non-invasive CT coronary angiogram within 30 days of the procedure and 4 patients underwent invasive coronary angiogram between 1 – 3 months prior to the procedure.

Product

Donor CDCs were tested against release specifications for allogeneic CDCs and found to meet identity and purity criteria by flow cytometry (>90% $CD105^+$, <10% $CD45^+$), potency criteria by TTE (≥4% EF improvement when administered in immunosuppressed mice), and safety criteria (e.g. viral, sterility, mycoplasma, endotoxin)[11].

Safety

Multivessel intracoronary infusion of allogeneic CDCs was successfully completed in all 14 subjects. No primary safety events were observed. TnI elevations within 24 hours post-infusion were observed in 8 subjects (Group 1, n=2; Group 2, n=1; Group 3, n=2 and Group 4, n=2), accompanied by normal CK-MB; these elevations were transient, without other associated clinical signs or symptoms of ischemia. On average, TnI increased from 0.03 ± 0.03 ng/ml before cell infusion to a peak of 0.12 ± 0.18 ng/ml at 16 hours post-infusion, with full resolution by 14 days (0.03 ± 0.02 ng/ml). Six subjects experienced a total of 9 secondary safety events within 12 months of follow-up (**Supplemental Table 1**). Two subjects died of cardiac failure due to progression of disease 9- and 12-months following infusion. No significant tachy- or brady-arrhythmias were noted on 24-hour ambulatory ECG monitoring during follow-up.

Immunogenicity

No development of cellular immunity to infused cells was observed; alloreactive responses to infused cell lines were all negative at 1-month post-infusion by ELISpot testing for the 13 of 14

subjects with available blood samples. Two patients (14%) developed *de novo* donor specific antibodies to donor-specific HLA (defined by mean fluorescence intensity > 5000 in the single antigen bead assay[12]) at 2 and 3 months-post infusion. In both cases the humoral immune response was transient and had resolved by 6 months post-infusion.

Efficacy

The impact of allogeneic CDC infusion on cardiac function was assessed by TTE at 6 and 12 months (**Table 2 and Figure 4)**. Compared to baseline, there was an improvement at 6 months in LVEF (26.8% ± 7.2% vs. 22.9% ± 4.5%, mean change 3.8 ± 4.9%, p=0.023) and a trend towards improvement in fractional shortening (13.8% ± 6.2% vs. 10.3% ± 5.0%, mean change 3.0 ± 4.6%, p=0.061). There was a reversal of LV remodeling at 6 months, manifested as a decrease in end-systolic volume (LVESV) (177.8 ± 64.2 vs. 139.5 ± 46.2 cm^3, mean change -38.8 ± 55.7 cm^3, p=0.034) and a non-statistically significant decrease in end-diastolic volume (LVEDV) (231.8 ± 103.6 vs. 191.5 ± 59.3 cm^3, mean change -40.7 ± 72.0 cm^3, p=0.077). At 12 months, the improvement in LVEF, compared to baseline, continued to be significant (28.3% ± 8.8% vs. 22.9% ± 4.5%, mean change 4.7 ± 6.9, p=0.029); however, the changes in the other parameters of LV function and remodeling were not significant at 12 months (fractional shortening (p=0.11), LVESV (p=0.26) or LVEDV (p=0.21)) (**Figure 4**). No patient underwent coronary revascularization or biventricular ICD placement during the duration of the study. There were no changes in cardioprotective medications made during the study.

Supplemental Table 2 summarizes the secondary efficacy endpoints. Compared to baseline, there was an improvement in NYHA functional class at 6 months (p=0.006, compared to baseline, **Figure 5A**). By 12 months the changes in NYHA remained significant in the high-dose group (**Figure 5B**), but not when patients from all dosage groups were pooled (**Figure 5A**).

While we did not observe a relationship between the CDC dose and LVEF at 12 months, there was a trend towards improvement in 6MWT and NYHA class with increasing CDC doses (**Supplemental figure 1A-C**). Measures of health-related QoL scores improved at 6 months: Minnesota Living with Heart Failure Questionnaire (MLFHQ) scores decreased (25.1 ± 23.3 vs. 50.9 ± 29.9, mean change -21.3 ± 23.6, p=0.012) and SF-36 physical functioning score increased (59.6 ± 21.4 vs. 44.6 ± 26.3, mean change 13.3 ± 19.6, p=0.038) over the 6 months of follow-up. At 12 months, the change in the QoL scores was not significant.

Discussion

The DYNAMIC study design has several unique features. We administered cells derived from unrelated donor (i.e., allogeneic) hearts, building upon our previous work demonstrating safety and efficacy of allogeneic CDCs in animal models of ischemic cardiomyopathy[3-5] and in human subjects with MI[13]. Potential clinical validation of allogeneic cells would obviate the major technical, timing, logistic and economic constraints associated with autologous therapy and facilitate broad clinical adoption of cell therapy. We used a sequential three-vessel non-occlusive intracoronary delivery strategy which has been previously validated in a clinically-relevant large animal model[14-16]. This delivery method is technically straightforward (without the need for specialized injection catheters), enables administration of higher cell dosages (compared to single-artery infusion), and achieves broad coverage of the myocardium. We used "non-occlusive" technique for cell administration in this study, instead of the "stop-flow" technique. A randomized trial of 34 patients receiving intracoronary stem cell infusion by "stop-flow" or "non-occlusive" technique demonstrated that there was no difference in cell retention with either technique; but the risk of ventricular arrhythmias or intolerance was significantly decreased with the "non-occlusive" technique[17].

The principal finding from DYNAMIC is that non-occlusive multi-vessel intracoronary infusion of allogeneic CDCs in an advanced HFrEF population is feasible and safe. No pre-specified primary safety endpoint events were observed and no serious adverse events were classified as at least possibly related to allogeneic CDCs or the infusion procedure. While we observed modest, transient increases of TnI (but not CK-MB) in 8/14 infused patients, the incidence of such low-level "leaks" falls well within the range associated with percutaneous coronary interventions[18]. The troponin leak was noted in all dosing groups undergoing CDC administration; thus, there did not seem to be a correlation between the CDC dose and troponin leak. Regarding host allosensitization to donor cells, we observed a limited (in 2/14 patients) transient humoral immune response, and a complete absence of cellular immune response. The lack of host memory response to donor cells is particularly relevant in patients with advanced HF, as potential allosensitization of these patients could complicate future cardiac transplantation (if the CDC donor and organ donor share similar HLA haplotypes)[19].

Despite the small sample size and lack of a control group, the trial also demonstrated concordant efficacy signals, especially evident at 6 months. Treated patients exhibited improvements in global systolic function (LVEF) and reverse remodeling (LVESV). All patients enrolled in the study had been on maximum tolerated medical- and device-based therapy for at least 3 months prior to enrollment. Thus, it is unlikely that the improvement in EF was influenced by the cardioprotective medications or biventricular pacemaker/ICD implantation. There appears to be an improvement in functional status (NYHA class) and quality of life (MLFHQ and SF-36) at 6-months post-infusion; however, the open label-design of the study and lack of a control group could have influenced the improvement in the functional class and quality of life parameters. Except for persistent improvement in LVEF, the other efficacy parameters

were no longer significant at 12 months. This is likely related to continued progression of advanced cardiomyopathy. The death of the two subjects (14%) during the study period is consistent with advanced HFrEF, with an expected 1-year mortality rate up to 30-35%[20]. Since the benefits of allogeneic CDC therapy were arguably greater at 6 months than at 12 months (unlike our previous experience with autologous CDCs in asymptomatic post-MI patients)[1, 2], repeat dosing of allogeneic CDCs may be an alternative to produce durable sustained, and perhaps even cumulative, benefits of cell therapy[521].

Limitations

While we did not observe any safety concerns with triple vessel infusion of allogeneic CDCs in patients with advanced cardiomyopathy, the study is limited by small sample size, an open-label design and lack of a control group. Thus, the safety results are preliminary and need to be verified in larger patient populations. In the randomized, placebo-controlled trial of allogeneic CDCs versus placebo for post-MI left ventricular dysfunction (ALLSTAR trial)[13], administration of CDCs was not associated with decrease in scar size or improvement in ejection fraction. Thus, the efficacy signals reported in the open-label DYNAMIC study will need to be reproduced in larger, placebo-controlled studies.

Conclusion

In summary, global intracoronary infusion of up to 75 million allogeneic CDCs in patients with HFrEF was feasible, safe and possibly efficacious. Whether allogeneic CDCs offer patients with advanced HF a regenerative and reparative option in addition to the currently available approaches remains to be determined. The favorable safety profile observed in this trial, in conjunction with the hints of efficacy, support proceeding to a randomized, double-blind, placebo-controlled trial of allogeneic CDCs for patients with advanced heart failure.

Impact on daily practice

In patients with advanced HFrEF, nonocclusive multivessel intracoronary infusion of allogeneic CDCs is feasible and safe. Despite the small sample size and lack of a control group, the trial also demonstrated concordant efficacy signals, especially evident at 6 months. The favorable safety profile, in conjunction with the hints of efficacy, support proceeding to a randomized, placebo-controlled trial of allogeneic CDCs for patients with advanced HFrEF.

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Figure legends:

Figure 1: Schedule of assessments

Figure 2: Intracoronary infusion protocol of allogeneic cardiosphere-derived cells

Figure 3: Patient consort

Figure 4: Echocardiographic end-points at 6 month and 12 months following intracoronary cell infusion

Figure 5: New York Heart Association class at baseline, 6 months and 12 months in the overall cohort (Panel A) and high-dose (75 million cells) group (Panel B)

Table legends:

Table 1: Baseline demographics in CDC-treated patients

Table 2: Echocardiographic end-points in CDC-treated patients

Table 1: Baseline demographics

Variable, Mean (SD) or N (%)	37.5 M Cells (n=3)	50.0 M Cells (n=3)	62.5 M Cells (n=3)	75.0 M Cells (n=5)	All Patients (n=14)
Male	3 (100.0%)	3 (100.0%)	2 (66.7%)	4 (80.0%)	12 (85.7%)
Age	71.0 (3.5)	71.0 (3.5)	52.7 (18.0)	56.2 (8.6)	60.1 (12.5)
Dilated cardiomyopathy etiology					
Ischemic	1 (33.3%)	2 (66.7%)	1 (33.3%)	3 (60.0%)	7 (50.0%)
Non-ischemic	2 (66.7%)	1 (33.3%)	2 (66.7%)	2 (40.0%)	7 (50.0%)
Prior heart failure hospitalization					
None	2 (66.7%)	2 (66.7%)	2 (66.7%)	4 (80.0%)	10 (71.4%)
Within 6 months of infusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
> 6 months but < 12 months before infusion	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (7.1%)
≥ 12 months before infusion	1 (33.3%)	1 (33.3%)	0 (0.0%)	1 (20.0%)	3 (21.4%)
ICD	3 (100.0%)	3 (100.0%)	3 (100.0%)	5 (100.0%)	14 (100.0%)
Biventricular pacemaker	3 (100.0%)	3 (100.0%)	3 (100.0%)	3 (60.0%)	12 (85.7%)

LVEF (%)	23.3 (4.7)	21.7 (2.9)	24.3 (6.0)	22.6 (5.3)	22.9 (4.5)
BNP (pg/mL)	329.7 (311.3)	342.7 (286.0)	243.3 (193.2)	192.0 (196.3)	264.8 (222.7)
Current heart failure medications					
ACE or ARB	2 (66.7%)	3 (100.0%)	2 (66.7%)	4 (80.0%)	11 (78.6%)
Beta blocking agent	2 (66.7%)	2 (66.7%)	3 (100.0%)	5 (100.0%)	12 (85.7%)
Diuretic	2 (66.7%)	3 (100.0%)	3 (100.0%)	4 (80.0%)	12 (85.7%)
Aldosterone antagonist	0 (0.0%)	2 (66.7%)	1 (33.3%)	2 (40.0%)	5 (35.7%)

ACE indicates angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BNP, brain natriuretic peptide; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection faction; NYHA, New York Heart Association

Table 2: Echocardiographic end-points

Parameter, Median (min, max)	Baseline (n=14)	Absolute difference at 6 months (n=12)	p-value*	Absolute difference at 12 months (n=12)	p-value*
LVEF (%)	24.0 (17.0, 30.0)	3.0 (-5.0, 13.0)	0.02	3.5 (-8.0, 20.0)	0.03
LV fractional shortening (%)	8.5 (5.5, 22.1)	1.85 (-2.6, 11.8)	0.06	2.25 (-11.1, 18.3)	0.27
LV stroke volume (mL)	53.0 (24.0, 114.0)	-2.0 (-73.0, 38.0)	0.69	-6.0 (-58.0, 8.0)	0.09
LV end diastolic volume (mL)	208.0 (128.0, 509.0)	-29.8 (-225.0, 47.0)	0.08	-12.8 (-262.0, 85.0)	0.21
LV end systolic volume (mL)	169.0 (92.0, 384.0)	-33.0 (-180.0, 33.0)	0.03	-32.5 (-207.0, 93.0)	0.26
LV end diastolic diameter (cm)	6.6 (5.9, 9.0)	-0.150 (-0.90, 1.36)	0.28	-0.035 (-1.3, 0.48)	0.33
LV end systolic diameter (cm)	6.0 (5.3, 8.3)	-0.090 (-0.90, 0.50)	0.39	0.075 (-1.30, 0.65)	0.91

LV indicates left ventricular; LVEF, left ventricular ejection fraction; max, maximum; min, minimum; SD, standard deviation

* Signed rank test of the null hypothesis that change from baseline = 0

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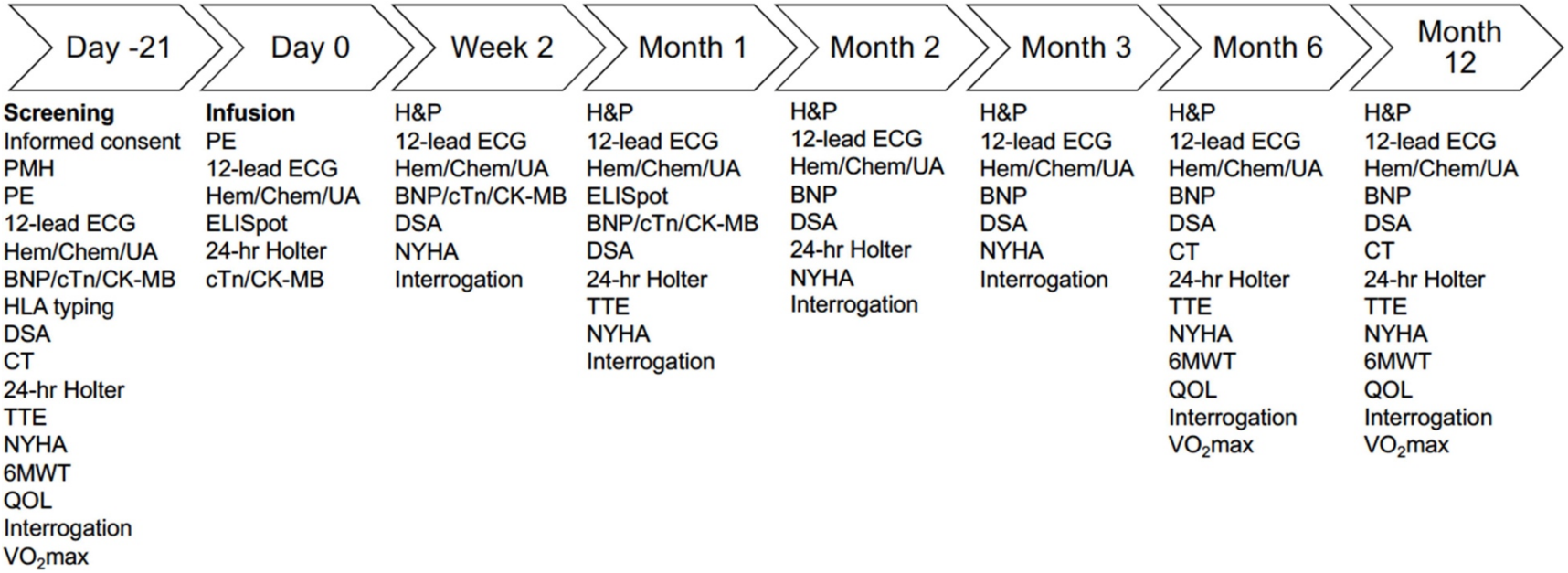

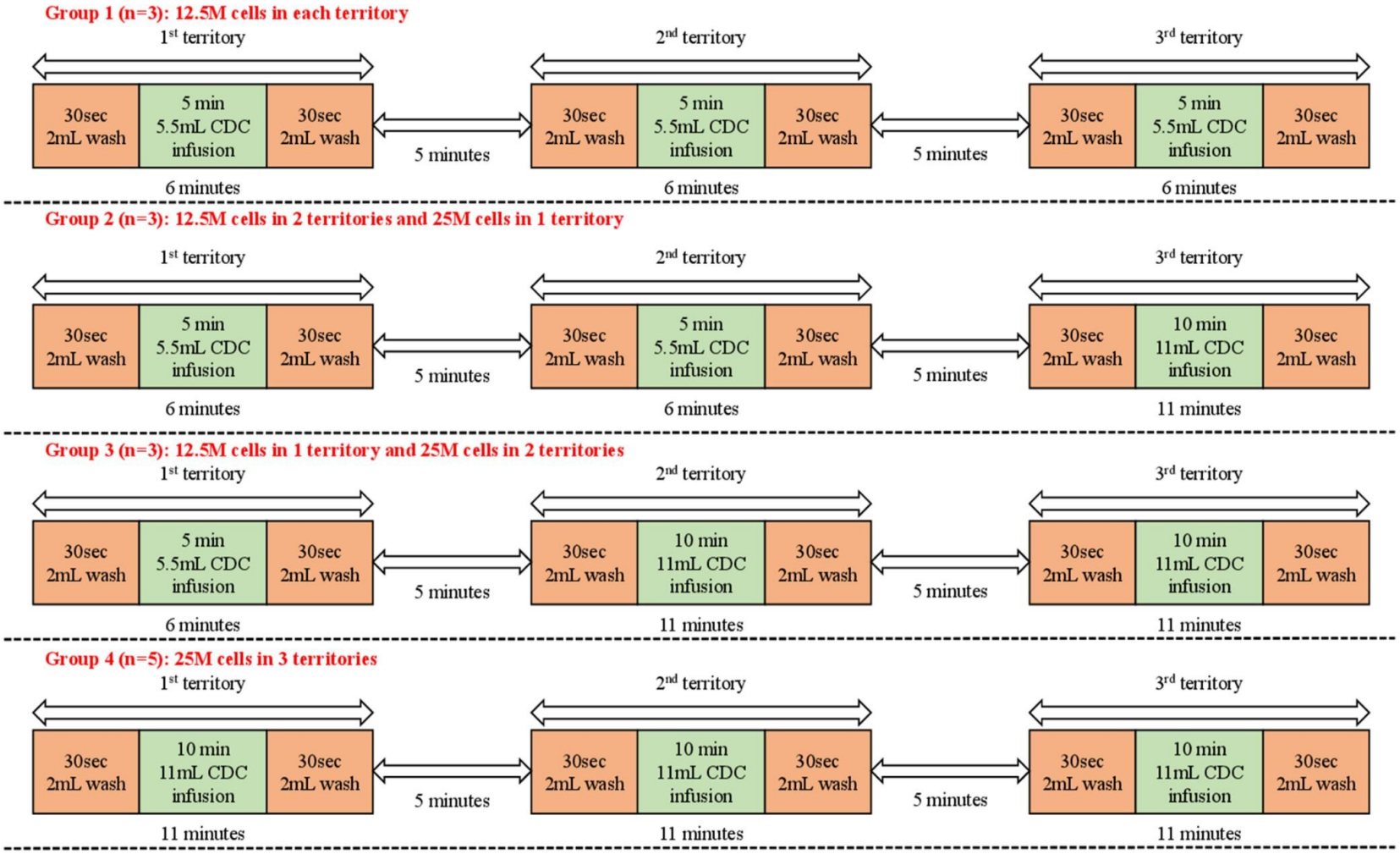

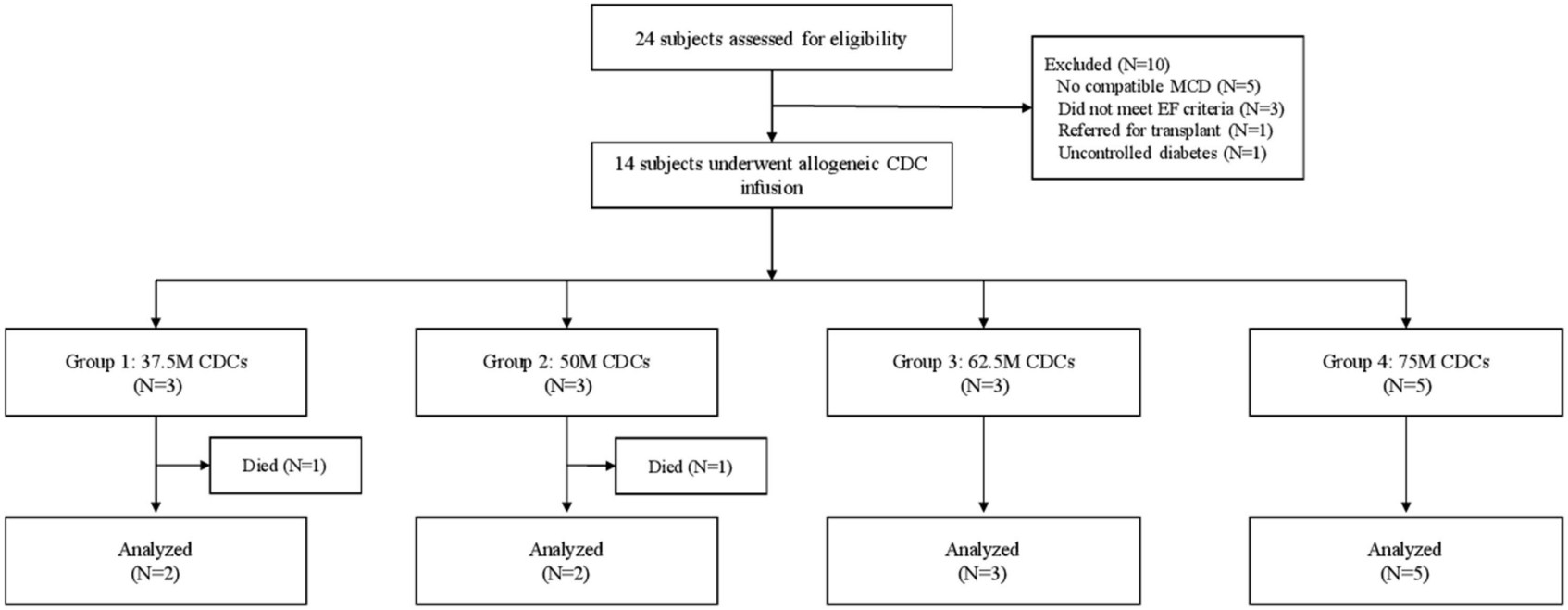

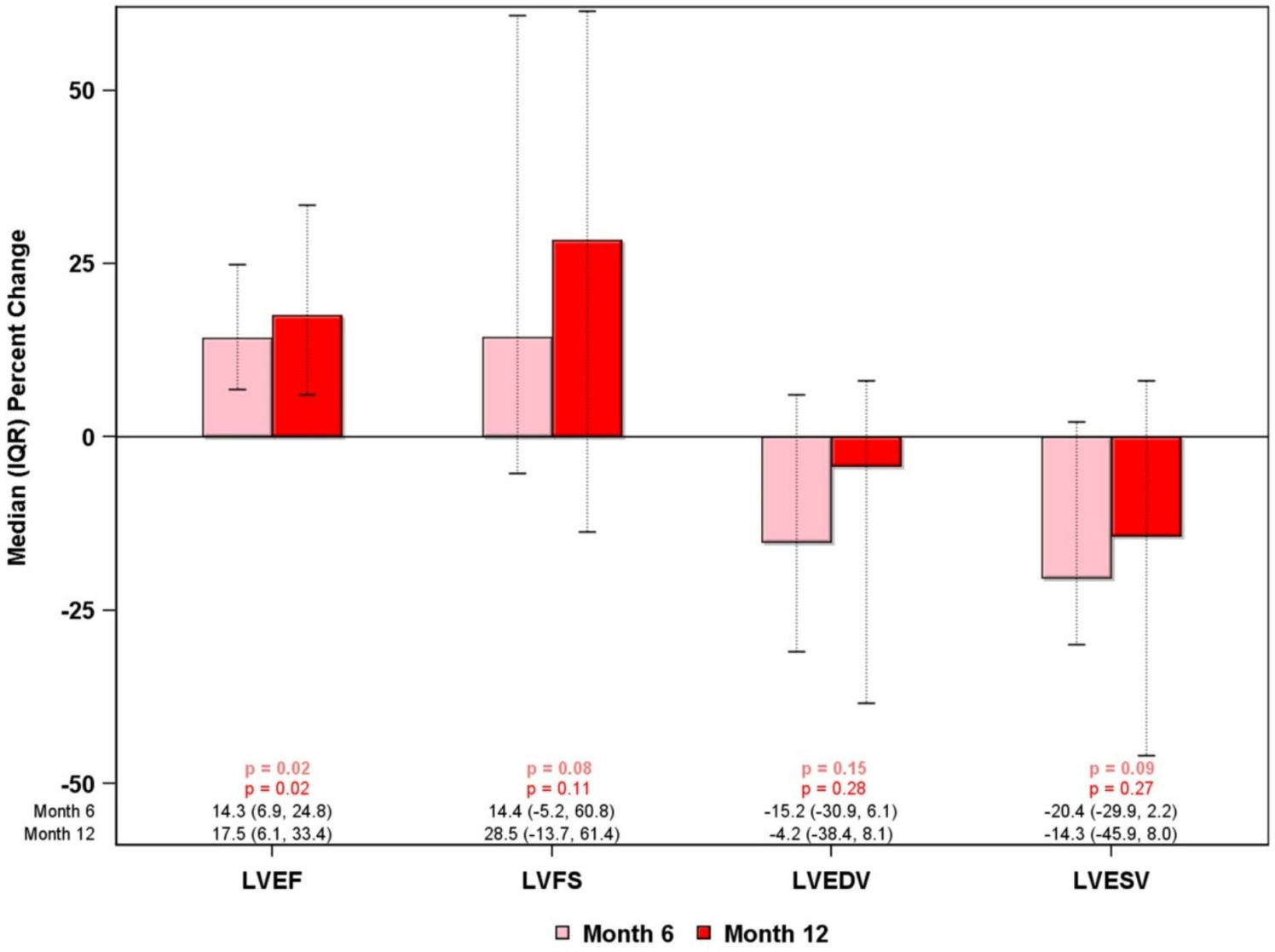

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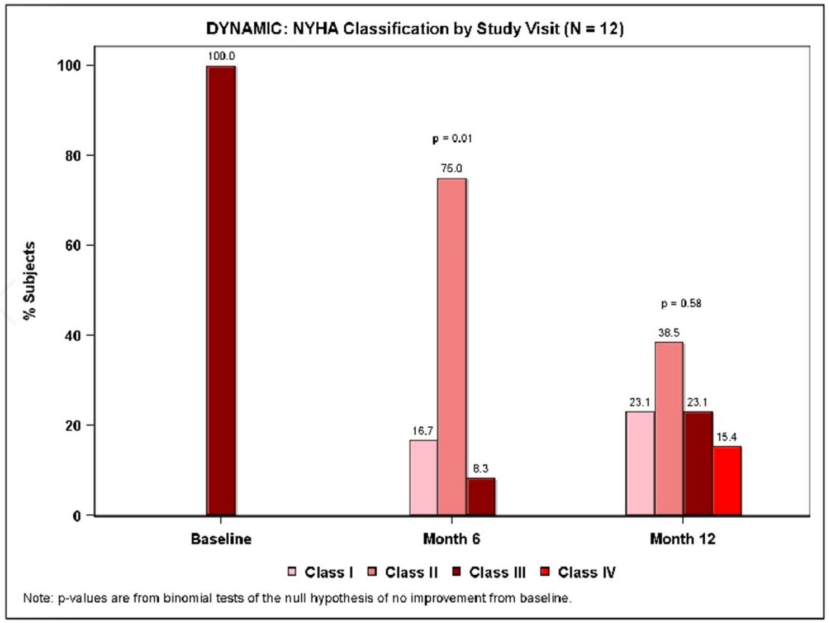

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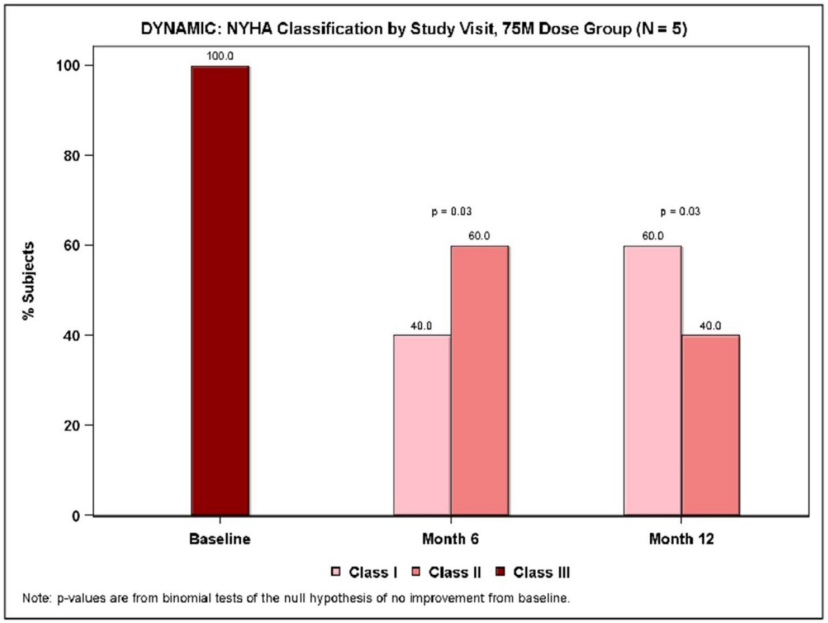


Infusion protocol

Allogeneic CDCs were manufactured as previously described11. Briefly, the tissue derived from donor hearts was cultured as explants. Cardiospheres were generated from the explant-derived cells, and CDCs were expanded from cardiospheres. The identity and purity of the CDCs was tested by flow cytometry to confirm the presence of CD105 as a surface marker and the absence of CD45 that would identify contaminating hematopoietic cells. Intracoronary infusion of allogeneic CDCs was performed (Figure 2) using Finecross MG coronary micro-guide catheters (Terumo Medical Corporation, Somerset, NJ), advanced into the proximal segment of each coronary artery. In case of infusion through a bypass graft, the Finecross catheter was positioned in the bypass graft close to the anastomosis with the native coronary artery. After infusion of 2 ml of wash solution over 30 seconds, allogeneic CDCs were infused over 5 minutes (for 12.5 million cells) or 10 minutes (for 25 million cells), followed by another 2 mL of wash solution over 30 seconds. The 12.5 million cell dose was suspended in a 5.5 ml solution containing 10% DMSO, 900 units of heparin and 225 μg nitroglycerin; the 25 million cell dose was suspended in an 11 ml solution containing 10% DMSO, 1800 units of heparin and 450 μg nitroglycerin. Normal saline containing heparin (1200 units per 10 mL) with or without nitroglycerin (600 mcg per 10 mL) was used as the wash solution between boluses of allogeneic CDCs. Once TIMI 3 flow was confirmed post-infusion and following a 5-minute interval between infusions in individual coronary territories, the infusion sequence was repeated 2 more times to treat the remaining coronary territories. Assessment of infusion-induced myocardial injury was performed by serial measurement of ischemic biomarkers (troponin I (TnI) and creatine kinase-MB (CK-MB)) every 8 hours for 16-24 hours post-infusion.

Supplementary Table 1: Secondary safety end-points

Event	Number of events	Number of subjects	Study day*
Appropriate ICD firing	2	1	Day 54 and Day 101 post-infusion
Acute on chronic cardiac failure	3	2	Subject # 1 (Day 335 post-infusion); Subject # 2 (Day 258 and Day 279 post-infusion)
Worsening dyspnea	1	1	Day 63 post-infusion
Sensitization to donor-specific HLA$	2	2	Subject # 1 (Day 57 post-infusion); Subject # 2 (Day 91 post-infusion)
Hospitalization for stroke	1	1	Day 228 post-infusion

ICD indicates implantable cardioverter defibrillator; HLA, human leukocyte antigen

* Collection date - infusion date.

$ Defined as mean fluorescence intensity (MFI) ≥ 5000.

Supplementary Table 2: Secondary efficacy end-points

Parameter, Median (min, max)	Baseline	Absolute difference at 6 months	p-value*	Absolute difference at 12 months	p-value*
BNP (pg/mL)	n=14	n=12		n=12	
	151.5 (32.0, 689.0)	29.5 (-128.0, 364.0)	0.33	19.5 (-81.0, 2906.0)	0.30
Cardiopulmonary exercise testing	n=14	n=11		n=11	
VO2 max (mL/kg/min)	13.9 (4.4, 22.4)	0.40 (-5.4, 6.2)	0.43	-0.30 (-6.5, 7.0)	0.85
Percent of Predicted Max VO2 /kg (%)	53.0 (19.0, 74.0)	7.0 (-16.0, 26.0)	0.15	2.0 (-19.0, 38.0)	0.39
VE/VCO_2 Slope	30.6 (0.50, 41.0)	4.1 (-9.3, 23.7)	0.21	-2.3 (-9.0, 24.0)	1.00
Respiratory quotient	1.1 (0.9, 1.2)	0.03 (-0.11, 0.22)	0.23	0.00 (-0.22, 0.13)	0.30
Six-minute walk test (m)	n=13	n=11		n=10	
	363.0 (180.0, 525.0)	0.0 (-50.0, 240.0)	0.38	-6.5 (-72.0, 215.0)	0.68
MLFHQ	n=14	n=12		n=13	
	48.0 (7.0, 105.0)	-16.0 (-71.0, 19.0)	0.01	-19.0 (-76.0, 33.0)	0.11
SF-36	n=14	n=12		n=13	

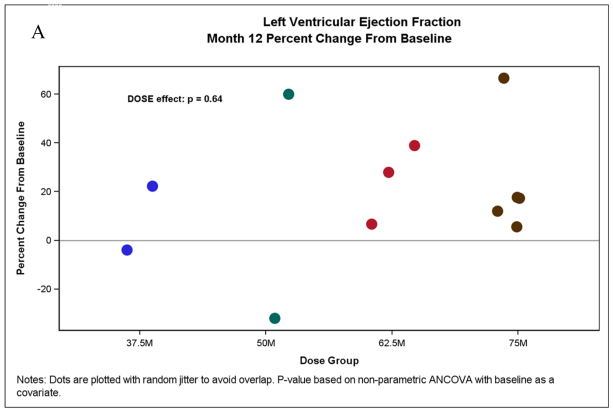
	Physical functioning	48.0 (7.0, 105.0)	-16.0 (-71.0, 19.0)	0.01	-19.0 (-76.0, 33.0)	0.11
	Physical health	25.0 (0.0, 100.0)	12.5 (-100.0, 100.0)	0.26	0.0 (-100.0, 100.0)	0.69
	Emotional problems	83.3 (0.0, 100.0)	0.0 (-66.7, 66.7)	0.81	0.0 (-100.0, 66.7)	0.85
	Energy/Fatigue	47.5 (0.0, 85.0)	2.5 (-25.0, 45.0)	0.47	5.0 (-30.0, 50.0)	0.28
	Emotional well being	74.0 (32.0, 92.0)	4.0 (-24.0, 20.0)	0.84	0.0 (-32.0, 24.0)	0.90
	Pain	77.5 (10.0, 100.0)	11.3 (-10.0, 45.0)	0.03	12.5 (-12.5, 45.0)	0.04
	General Health	52.5 (10.0, 90.0)	12.5 (-50.0, 45.0)	0.07	10.0 (-30.0, 30.0)	0.30
WPAI		n=9	n=6		n=7	
	Work Absenteeism	0.0 (0.0, 20.0)	-4.4 (-20.0, 0.0)	0.25	0.0 (-20.0, 71.4)	0.88
	Work Presentism	20.0 (0.0, 80.0)	-5.0 (-70.0, 50.0)	0.63	-15.0 (-60.0, 60.0)	0.59
	Work productivity loss	27.1 (0.0, 82.1)	-12.0 (-72.1, 50.0)	0.63	-23.6 (-62.1, 74.3)	1.00
	Activity impairment	55.0 (0.0, 80.0)	-5.0 (-60.0, 70.0)	0.59	-10.0 (-80.0, 90.0)	0.66

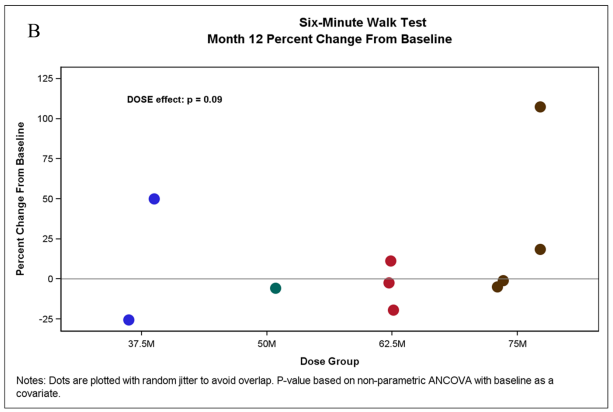
BNP indicates brain natriuretic peptide; MLFHQ, Minnesota Living With Heart Failure Questionnaire; SF-36, San Francisco 36; WPAI, Work productivity and activity impairment

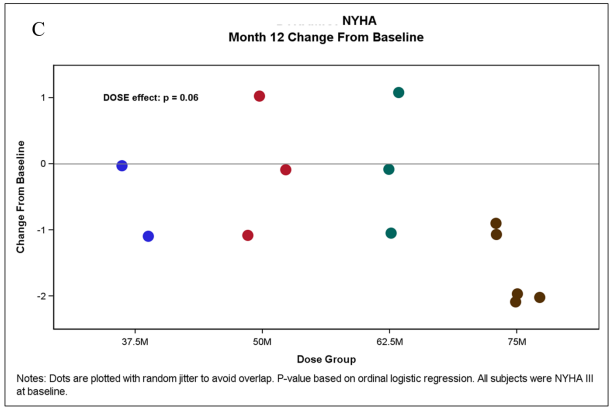
* Signed rank test of the null hypothesis that change from baseline = 0

Supplementary Figure 1: Impact of cardiosphere-derived cell dosage on end-points

(A) Percent change in left ventricular ejection fraction at 12 months, compared to baseline; (B) Percent change in 6-minute walk test at 12 months, compared to baseline; and (C) Percent change in New York Heart Association class at 12 months, compared to baseline.







Study protocol

Sponsor: Capricor, Inc.

Name of Study Therapy: Allogeneic Cardiosphere-Derived Cells - CAP-1002

Study Title: A Phase I Study of the Safety of Multi-Vessel Intra-Coronary Delivery of Allogeneic Cardiosphere-Derived Stem Cells in Patients with Dilated Cardiomyopathy (DCM)

Study Name: DYNAMIC: **D**ilated cardiom**Y**opathy i**N**tervention with **A**llogeneic **M**yocard**I**ally-regenerative **C**ells

Study Phase: Single-center Phase Ia study, followed by a Phase Ib study after DSMB review of one-month Phase Ia safety data

Objectives:

Primary: To determine the safety profile of CAP-1002 administered by multi-vessel intracoronary infusion in subjects with DCM.

Secondary: To further assess safety and exploratory efficacy endpoints of CAP-1002 administered by multi-vessel intracoronary infusion in subjects with DCM to guide future trials with CAP-1002.

Study Design:

Subjects with DCM meeting all inclusion and no exclusion criteria will be enrolled. These subjects will undergo sequential intracoronary infusion of CAP-1002 or placebo in up to three coronary arteries supplying three major cardiac territories to the heart (anterior, lateral, inferior/posterior). Subjects with prior history of coronary artery bypass grafting (CABG) will undergo CAP-1002 or placebo (Phase Ib only) [investigational product (IP)] infusion in the native coronary arteries distal to the bypass graft-coronary artery anastomosis (with the exception of not reaching the anastomosis from a left internal mammary artery (LIMA) and/or right internal mammary artery (RIMA) graft. In such cases, the infusion

catheter will be placed in the vessel as distally as possible). All three major cardiac territories will be treated (via patent native and bypass vessels). Patency of these vessels is required as an inclusion criterion in Phase Ia. In Phase Ib, where a known chronically-occluded coronary artery/bypass graft or a small non-dominant coronary artery is present, the IP will be infused into at least two coronary territories, as long as there is consensus that the two coronary territories undergoing IP infusion together supply at least two-thirds of the blood supply to the left ventricle. All subjects considered for the clinical trial will be presented to an Eligibility Committee to assess the coronary/bypass anatomy to determine the feasibility of the cell infusions.

Phase Ia: The first fourteen (14) subjects will receive intracoronary infusion of CAP-1002 in an open-label fashion. Phase Ia will consist of four dosing groups enrolled in a sequential manner: Group 1 (n=3) CAP-1002 infusion dose of 12.5 million cells to each cardiac territory; Group 2 (n=3) CAP-1002 infusion dose of 25 million cells in one cardiac territory and 12.5 million cells in the remaining cardiac territories (2); Group 3 (n=3) CAP-1002 infusion dose of 25 million cells in two cardiac territories and 12.5 million cells in the other cardiac territory, and Group 4 (n=5) CAP-1002 infusion dose of 25 million cells in each cardiac territory. To minimize the likelihood of rapid clearance of infused cells in immunosensitized subjects, study participants will be matched with allogeneic CDC cell lines to which they have no pre-existing donor-specific antibodies by single antigen bead testing. Subject infusions will be staggered by at least three days to allow for detection of acute procedure-related complications should they occur. Dose escalation will occur:

- ≥ 14 days post first infusion date at the previous dosage level;
- ≥ 3 days post final infusion date at the previous dosage level.

The subject's infusion will take place within 28 days of the first screening procedure. After completion of the screening procedures, Phase Ia subjects will receive CAP-1002 administered via intracoronary infusion. Phase Ia subjects will be followed at Week 2 and at Months 1, 2, 3, 6 and 12 after CAP-1002 infusion. Key safety assessments will include new TIMI flow 0-2 or TIMI myocardial perfusion grade (TMPG) 0-2 (persisting > 3 minutes after termination of cell infusion), presence of myocarditis, documented ventricular tachycardia or ventricular fibrillation resulting in death or requiring medical intervention, sudden unexpected death and other major adverse cardiac events (MACE). Since CAP-1002 is grown from donors unrelated to recipients, humoral and cellular immune responses will also be evaluated. Phase Ia

subjects will be evaluated overall, once all 14 subjects in the cohort have reached the primary safety endpoint assessed at the 1 month visit. The DSMB will conduct a review of the Phase Ia data and recommend whether to proceed with enrollment of the next 28 subjects in Phase Ib. Regardless of recommendation, the subjects in Phase Ia will continue to undergo protocol assessments through the Month 12 follow-up, including DSMB reviews after all 14 subjects have completed their Month 2 and 6 visits.

Phase Ib: The Phase Ib cohort will include 28 subjects randomized in a double-blind fashion to receive either CAP-1002 or placebo in a 1:1 ratio. After completion of the screening procedures, subjects will receive either CAP-1002 or placebo [investigational product (IP)] administered via intracoronary infusion. The infusion will take place within 28 days of the first screening procedure. All treated subjects (those who have undergone IP infusion) will be followed until the last enrolled subject has reached Month 12 follow-up. Subjects will be followed at Week 2 and at Months 1, 2, 3, 6 and 12 after IP infusion.

Telephone follow-up calls will be performed on an annual basis for up to five years, if the subject provides consent. Primary and secondary safety as well as exploratory efficacy will be assessed at all post-screening visits. An analysis of the final Month 6 data will be performed when all randomized subjects have completed the Month 6 visit. The ischemic DCM and non-ischemic DCM strata will be analyzed together as well as separately for both safety and efficacy.

Patient Population: Forty-two (42) subjects with DCM (Phase Ia, n=14 and Phase Ib, n=28) with left ventricular ejection fraction (LVEF) ≤35% by transthoracic echocardiography (TTE) and a LVEF <40% by cardiac CT will be considered for enrollment in the study.

Diagnosis and Main Criteria for Inclusion/Enrollment:

Major Inclusion Criteria

1. DCM with LVEF ≤35% as determined by a historical TTE within the previous 6 months;
2. New York Heart Association (NYHA) Class III or ambulatory Class IV heart failure;

3. Use of evidence based medical-therapy (beta-blockers, ACE-inhibitors/angiotensin receptor blockers, aldosterone antagonist) and with or without device-therapy (Implantable cardioverter-defibrillator or cardiac resynchronizing therapy), in accordance with the ACC/AHA guidelines for the management of heart failure, for at least three months prior to enrollment or documented contraindication or intolerance or patient preference (Hunt et al., 2009);
4. Coronary anatomy suitable* for IP infusion, as determined by the Eligibility Committee (a team of cardiology experts);
5. Ability to provide informed consent and follow-up with protocol procedures;
6. Screening cardiac CT left ventriculogram ejection fraction <40% with left ventricular dilatation;
7. Age ≥ 18 years.

*The vessel (native coronary artery or bypass graft) should be free of a 70% or greater stenosis. If the infusion is through the left main artery, the vessel should be free of a 50% or greater stenosis. The Eligibility Committee will assess and determine if the subject's anatomy is suitable for the infusion procedure.

Major Exclusion Criteria

1. Diagnosis of active myocarditis;
2. Immunologic incompatibility with all available Master Cell Banks (MCBs) by single-antigen bead (SAB) serum antibody profiling;
3. Left Ventricular Assist Devices (LVAD) or those actively in the process of acquiring one;
4. Recent placement of a cardiac pacemaker and/or resynchronization pacing therapy within the past three months or those actively in the process of acquiring one;

5. History of sustained ventricular tachycardia (VT) requiring cardiopulmonary resuscitation [with the exception of subjects who subsequently received an implantable cardioverter defibrillator (ICD)];
6. Non-cardiovascular disease with life expectancy of <3 years;
7. Known hypersensitivity to contrast agents;
8. Estimated glomerular filtration rate (GFR) <50 mL/min;
9. Active infection not responsive to treatment;
10. Active allergic reactions, connective tissue disease or autoimmune disorders;
11. History of cardiac tumor or cardiac tumor demonstrated on screening;
12. History of previous stem cell therapy;
13. History of treatment with immunosuppressive agents, including chronic systemic corticosteroids, biologic agents targeting the immune system, anti-tumor and anti-neoplastic drugs or anti-VEGF within 6 months prior to enrollment (not including drug eluting coronary stents);
14. History of receipt of chemotherapeutic agents known to be implicated in cardiac dysfunction [Adriamycin, trastuzumab (Herceptin)];
15. Known moderate-severe aortic stenosis/insufficiency or severe mitral stenosis/regurgitation;
16. Participation in an on-going protocol studying an experimental drug or device;
17. Current active alcohol or drug abuse or inability to comply with protocol-related procedures;
18. Pregnant/nursing women and women of child-bearing potential without use of active and highly reliable contraception;
19. Known history of Human Immunodeficiency Virus (HIV) infection;
20. Known history of chronic viral hepatitis;

21. Abnormal liver function (SGPT >10 times the upper reference range) and/or abnormal hematology (hematocrit <25%, WBC <3000 µl, platelets <100,000 µl) studies without a reversible, identifiable cause;
22. Evidence of tumor on screening of chest/abdominal/pelvic (body) CT scan;
23. Any prior organ transplant;
24. Being actively listed for, or under active consideration (i.e., work-up) for, a solid organ transplant of any kind;
25. Known hypersensitivity to bovine products;
26. Known hypersensitivity to dimethyl sulfoxide (DMSO);
27. Any malignancy within past 2 years (except for in-situ non-melanoma skin cancer and in-situ cervical cancer);
28. Any prior radiation therapy/treatment to the chest;
29. Uncontrolled diabetes (HbA1 >9.0);
30. Any condition or other reason that, in the opinion of the Investigator or Medical Monitor, would render the subject unsuitable for the study.

Phase Ia/Ib Endpoints:

Primary Safety Endpoints:

The primary endpoint is the proportion of subjects experiencing any of the following events during or post intracoronary infusion delivery:

1. New TIMI flow 0-2 or TIMI myocardial perfusion grade (TMPG) 0-2, noted immediately following intracoronary infusion of CAP-1002 and persisting >3 min after cell infusion, despite intracoronary vasodilator administration;
2. Acute myocarditis within one month of intracoronary infusion, possibly attributable to CAP-1002, diagnosed with consideration of clinical context, with or without a clinically indicated endomyocardial biopsy. In order to be

considered related to CAP-1002, humoral or cellular immune reaction specific to CAP-1002 must also be documented;

3. Ventricular tachycardia or ventricular fibrillation (defined as occurring with ECG documentation of these arrhythmias during ambulatory ECG monitoring in an outpatient setting, or during routine ECG monitoring while hospitalized) resulting in death, appropriate discharge of an ICD or requiring medical intervention, within 72 hours of intracoronary infusion;
4. Sudden unexpected death within 72 hours of intracoronary infusion defined as occurring within one hour of symptom onset, or un-witnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause;
5. Major adverse cardiac events (MACE) within 72 hours of intracoronary infusion, including death, non-fatal myocardial infarction and re-hospitalization for cardiovascular event (including heart failure hospitalizations). Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol performed following administration of CAP-1002 or placebo. Troponin and CK-MB will be obtained every 8 hours at minimum for 20-24 hours after CAP-1002 infusion.

Secondary Safety Endpoints:

The following will be evaluated as secondary safety endpoints during the six and twelve month follow-up period:

1. Acute myocarditis possibly attributable to CAP-1002, diagnosed with consideration of clinical context, with or without a clinically indicated endomyocardial biopsy. In order to be considered related to CAP-1002, humoral or cellular immune reaction specific to CAP-1002 must also be documented;
2. Ventricular tachycardia or ventricular fibrillation (defined as occurring with ECG documentation of these arrhythmias during ambulatory ECG monitoring in an outpatient setting, or during routine ECG monitoring while hospitalized) resulting in death or requiring medical intervention or appropriate discharge of an ICD;
3. Sudden unexpected death defined as occurring within one hour of symptom onset, or unwitnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause;

4. Major adverse cardiac events (MACE), including death, non-fatal myocardial infarction, hospitalization for cardiovascular event (including heart failure hospitalizations), emergency room treatment for heart failure (including outpatient infusion), left ventricular assist device or heart transplant;
5. Any hospitalization due to a cardiovascular cause or related to CAP-1002 (or placebo in Phase Ib);
6. Any inter-current cardiovascular illness or one related to CAP-1002 (or placebo in Phase Ib) which prolongs hospitalization. Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol. Troponin and CK-MB will be obtained per institution's protocol;
7. Development of, or an increase in the frequency of VT with a duration of 30 seconds or longer ascertained by protocol-mandated ECG ambulatory monitoring;
8. Development of increased anti-Human Leukocyte Antigen (HLA) antibody levels with development of sensitization to HLA antigens specific to the CAP-1002 CDC donor at immunologically significant titers;
9. Total number of appropriate ICD firings;
10. Peak elevation in troponin and CKMB levels following CAP-1002 or placebo infusion.

Secondary Efficacy (Exploratory) Endpoints:

The following will be evaluated as secondary efficacy endpoints during the six and twelve month follow-up periods:

1. Absolute and relative change in functional and structural parameters measured by TTE, including:
   A) LVEF (%);
   B) Left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD);
   C) Left ventricular end-diastolic volume and end-systolic volumes;
   D) Left ventricular stroke volume;
   E) Left ventricular fractional shortening [(LVEDD – LVESD)/LVEDD x 100];
   F) Regional left ventricular function assessment;
2. Absolute and relative change in functional and structural parameters measured by cardiac CT, including:
   A) LVEF (%);
   B) Left ventricular end-diastolic volume and end-systolic volumes;
   C) Left ventricular stroke volume;
   D) Regional left ventricular function assessment;
3. Incidence of appropriate firings of implantable cardioverter-defibrillators (ICDs) to terminate tachyarrhythmias in subjects with such devices;
4. Absolute and relative change in BNP;
5. Absolute and relative change of six minute walk test (6MWT);
6. Absolute and relative change of VO_2 max;
7. Absolute and relative change in Quality of Life (QOL) questionnaires.

Test Product, Dose, and Mode of Administration:

All Phase Ia subjects will receive a dose of 12.5 million cells or 25 million cells (CAP-1002), depending on the treatment group, delivered to three separate major cardiac territories (i.e. anterior, lateral, inferior/posterior). All Phase Ib subjects randomized to receive CAP-1002 will receive a dose of 25 million cells (or 12.5 million cells if a lower dose is determined to be the maximum safe dose, based on Phase Ia study) delivered via the coronary arteries (or grafts) to two or three separate cardiac territories – for a possible maximum total of 50-75 million cells (or 25-37.5 million cells, if 12.5 million

cell infusions are performed). Depending on the dose of the cell infusion, a single maximum dose administration of 25 million cells or 12.5 million cells (CAP-1002) will be delivered with a TERUMO Finecross^{TM} MG guiding catheter to each cardiac territory. Additionally, an intermediate wash solution is also administered to each subject between boluses of CAP-1002 (or placebo in Phase Ib) (see Figure 1). The 12.5 million cell dose was suspended in a 5.5 ml solution containing 10% DMSO, 900 units of heparin and 225 µg nitroglycerin; the 25 million cell dose was suspended in an 11 ml solution containing 10% DMSO, 1800 units of heparin and 450 µg nitroglycerin. Normal saline containing heparin (1200 units per 10 mL) with or without nitroglycerin (600 mcg per 10 mL) was used as the wash solution between boluses of allogeneic CDCs. Subjects randomized to the placebo group will receive intracoronary placebo infusions consisting of CAP-1002 minus the active Cardiosphere Derived Cell (CDC) constituent.

Duration of Treatment:

Treated subjects (those who have received intracoronary infusion of IP) will be followed, until all subjects have completed the Month 12 follow-up visit.