Dilated CardiomYopathy INtervention with Allogeneic MyocardIally-regenerative Cells (DYNAMIC): 12 Month Safety & Exploratory Efficacy Results

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Introduction

- Intracoronary administration of autologous cardiosphere-derived cells (CDCs) post-MI is safe and results in decreased scar size, increased viable myocardium and improved regional function of infarcted myocardium 1 year post-treatment (CADUCEUS trial).
- Phase 1 results of the ALLSTAR Trial confirmed the safety of intracoronary administration of allogeneic CDCs (CAP-1002) by stop-flow technique post-MI and demonstrated a decrease in scar size and an increase in viable myocardium.
- Here we report the results of the DYNAMIC trial, a single-center, prospective, dose-escalation study of non-occlusive sequential triple-vessel intracoronary (IC) infusion of CAP-1002 in patients with dilated cardiomyopathy (DCM) (EF ≤ 35%) and NYHA III-ambulatory IV heart failure (HF).

Methods

DYNAMIC trial enrolled 14 adult subjects with dilated cardiomyopathy, EF ≤ 35% and NYHA III heart failure despite maximal medical- and device-based therapy. Four escalating CAP-1002 doses (37.5M to 75M cells) were infused via sequential non-occlusive IC catheter technique, divided among the LAD, RCA and LCx territories.

Primary objective: To determine the safety of CAP-1002 administered by multi-vessel, non-occlusive IC infusion in subjects with HF with reduced ejection fraction (HFrEF).

Secondary objective: To further assess the safety and explore the efficacy of CAP-1002 administration by multi-vessel, non-occlusive intracoronary infusion in subjects with HFrEF.

Primary safety end-point: Composite of post infusion reduction of TIMI flow for > 3 min, VT/VF, sudden death, or major adverse cardiac (MACE) events w/in 72 hours post infusion, or acute myocarditis w/in 1 month.

Statistical analysis: The null hypothesis for the primary safety endpoint was that the proportion of subjects experiencing the primary safety endpoint (p_s) = 0.20, tested against the one-sided alternative $p_s < 0.20$ using an exact binomial test. Null hypotheses of change from baseline in efficacy parameters = 0 were tested against two-sided alternatives using signed rank or binomial tests. Due to small sample sizes, dose groups were pooled for statistical analyses. All tests were done using a 0.05 significance level.

Results

Table 1: Demographics and Baseline Characteristics by Dose Group and Combined

Demographic or Baseline Variable	37.5M (n=3)	50M (n=3)	62.5M (n=3)	75M (n=5)	Total (n=14)
Age					
Mean (SD)	71 (3.46)	63 (14.84)	55 (19.63)	56 (8.35)	61 (12.57)
Median [Min, Max]	73 [67, 73]	67 [47, 76]	66 [32, 66]	57 [47, 66]	66 [32, 76]
Gender [n (%)]					
Male	3 (100%)	3 (100%)	2 (66.7%)	4 (80.0%)	12 (85.7%)
Female	0 (0%)	0 (0%)	1 (33.3%)	1 (20.0%)	2 (14.3%)
Ethnicity [n (%)]					
Not Hispanic or Latino	3 (100%)	3 (100%)	3 (100%)	5 (100%)	14 (100%)
TTE LVEF (%)					
Mean (SD)	23.3 (4.73)	21.7 (2.89)	24.3 (6.03)	22.6 (5.32)	22.9 (4.46)
Median [Min, Max]	25.0 [18, 27]	20.0 [20, 25]	25.0 [18, 30]	23.0 [17, 30]	24.0 [17, 30]
NYHA Class [n (%)]					
Class III	3 (100%)	3 (100%)	3 (100%)	5 (100%)	14 (100%)
Etiology [n (%)]					
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%)

Table 2: Secondary Safety Endpoints

Event	Number of events	Number of subjects	Study Day Post-infusion
Appropriate ICD firing	2	1	Day 54 and Day 101
Major adverse cardiac event: cardiac failure	3	2	Day 335 (Subject # 1); Day 258 and Day 279 (Subject # 2)
Major adverse cardiac event: dyspnea	1	1	Day 63
Sensitization to donor-specific HLA[$]	2	2	Day 57 (Subject # 1); Day 91 (Subject # 2)
Hospitalization for stroke	1	1	Day 228

[$] Defined as mean fluorescence intensity (MFI) ≥ 5000

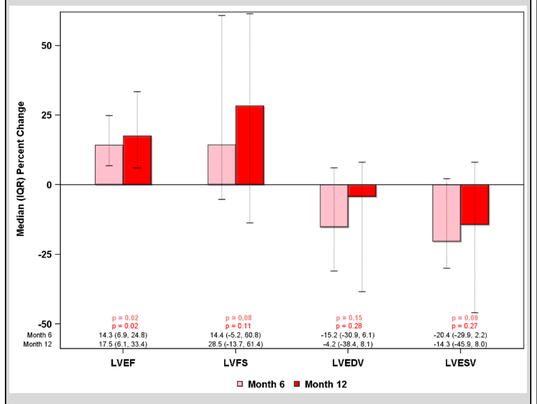
Table 3: Primary Safety Endpoint: No Events[1]

Event	Total (n=14) n (%)
Primary Safety Endpoint	0 (0%)
TIMI Flow Score 0-2	0 (0%)
Acute Myocarditis Within One Month of Infusion	0 (0%)
Ventricular Tachycardia or Ventricular Fibrillation Within 72 Hours of Infusion	0 (0%)
Sudden Unexpected Death Within 72 Hours of Infusion	0 (0%)
MACE Within 72 Hours of Infusion	0 (0%)

[1] p=0.04 for the test of the primary safety endpoint hypothesis.
Note: Troponin elevations were observed in 4 subjects within 24 hours post infusion, accompanied by normal CK-MB; they were transient, without other associated clinical signs or symptoms of ischemia.

Improvement in LVEF

Figure 1: Mean (SE) % change from baseline in LV structure and function by TTE



Significant Improvement in NYHA Class

Figure 2: Distribution of NYHA Class

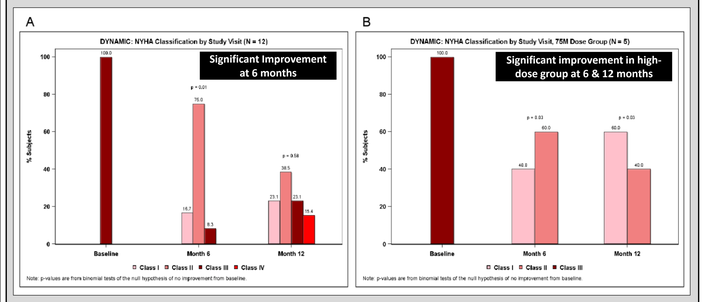


Table 4: Impact on Functional Capacity [Median (range)]

Parameter	Baseline	Change at 6 months	p-value	Change 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
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

Table 5: Impact on Quality of Life [Median (range)]

Parameter	Baseline	Change at 6 months	p-value	Change At 12 months	p-value
MLHFQ	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
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

MLFHQ, Minnesota Living With Heart Failure Questionnaire
Note: Better quality of life is indicated by lower scores for MLHFQ and higher scores for SF-36.

Conclusions

- Multi-vessel intracoronary infusion of allogeneic cardiosphere-derived cells (CAP-1002) up to 75M cells is **safe and feasible**.
- Despite the small sample size, the trial also demonstrated an **efficacy signal with concordant improvements from baseline, especially evident at 6 months, in functional status and ventricular function**.
- The impact of CDCs on clinical outcomes observed complements prior CDC trials that demonstrated improvement in myocardial scar burden & supports proceeding to a randomized, double blind, placebo controlled trial of CDCs in patients with HFrEF to confirm these promising, preliminary, results.