Dilated CardiomYopathy INtervention with Allogeneic MyocardIally-regenerative Cells (DYNAMIC): 6 Month Safety & Exploratory Efficacy Results

Author(s): Tarun Chakravarty, MD[1]; Raj Makkar, MD[1]; Timothy D. Henry, MD[1]; Michelle Kittleson, MD, PhD[1]; John Freidman, MD[1]; Dan Berman, MD[1]; Joao Lima, MD[2]; Richard George, MD[2]; Robert Siegel, MD[1]; Leandro Slipczuk, MD, PhD[1]; Eduardo Marban, MD, PhD[1]; Janice M. Pogoda, PhD[3]; Linda Marban, PhD[3]; Deborah D. Ascheim, MD[3]

Institution(s) : [1]Cedars Sinai Heart Institute; [2]Johns Hopkins University, Dept of Medicine, Division of Cardiology; [3]Capricor, Inc.

Introduction

Intracoronary administration of autologous cardiosphere-derived cells (CDCs) In the CADUCEUS study and allogeneic CDCs (CAP-1002) in the ALLSTAR phase 1 study decreased infarct size and increased viable tissue in post-MI subjects. The DYNAMIC Phase I study was designed to evaluate the safety and feasibility of multi-vessel intracoronary infusion of allogeneic CDCs (CAP-1002) and to explore the efficacy of CAP-1002 in subjects with dilated cardiomyopathy. We report the 6 month results of the open-label dose-escalating Phase 1a safety arm of the DYNAMIC study. The results of this trial will inform the design of the follow-up double blind, randomized, placebo controlled trial.

Methods

DYNAMIC Phase Ia 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. The 1° safety endpoint is a composite of post infusion reduction of TIMI flow for > 3 min, VT/VF, sudden death, major adverse cardiac (MACE) events w/in 72 hours post infusion, or acute myocarditis w/in 1 month. The null hypothesis is that the proportion (p) of subjects who experienced the 1° safety endpoint = 0.20 vs. the one-sided alternative that p < 0.20. Safety and exploratory efficacy endpoints are also assessed at 6 and 12 months. Null hypotheses of change from baseline in efficacy parameters = 0 were tested using t-tests or signed rank tests. An exact binomial test was used to test the null hypothesis of probability of improvement in NYHA class = 0.5. All efficacy analyses were 2-sided and were post hoc.

Results

Table 1: Demographics and Baseline Characteristics by Dose Group and Combined
Due to small sample sizes within dose groups, efficacy results are presented as pooled across dose groups.

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%)
Race [n (%)]					
White	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%)

Primary Endpoint: No primary safety events[1]

Event	Total (n=14)
Primary Safety Endpoint [n (%)]	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.

Table 2: Exploratory efficacy parameters

Efficacy Measure	Baseline (BL)	Month 6	Change from BL[1]
Functional Assessments			
NYHA Class	n=14	n=12	--
Class I	0 (0%)	2 (16.7%)	--
Class II	0 (0%)	9 (75.0%)	--
Class III	14 (100%)	1 (8.3%)	--
6MWT (m)	n=13	n=11	n=11
Mean (SD)	346 (10.5)	394 (73.3)	17.4 (44.47)
Median [Min, Max]	375 [180, 525]	400 [225, 525]	0.0 [-13.3, 112.5]
VO_2 Max (m/kg/min)	n=14	n=11	n=11
Mean (SD)	14.0 (4.51)	15.2 (5.06)	14.6 (44.71)
Median [Min, Max]	13.9 [4.4, 22.4]	13.7 [10.6, 28.5]	3.0 [-24.5, 140.9]
Quality of Life	n=14	n=12	n=12
MLHFQ (↓=improved)			
Mean (SD)	50.9 (29.90)	25.8 (24.03)	-20.7 (23.31)
Median [Min, Max]	48.0 [7, 105]	18.0 [1, 69]	-16.0 [-71, 19]
SF-36 Physical (↑=improved)			
Mean (SD)	44.6 (26.35)	59.6 (21.37)	13.3 (19.58)
Median [Min. Max]	47.5 [5, 85]	67.5 [30, 85]	10.0 [-20, 45]
SF-36 Gen'l Health (↑=improved)			
Mean (SD)	46.1 (23.71)	58.3 (13.03)	10.0 (23.06)
Median [Min, Max]	52.5 [10, 90]	55.0 [40, 80]	12.5 [-50, 45]
BNP (pg/L)	n=14	n=12	n=12
Mean (SD)	285 (247)	290 (228)	44.8 (86.31)
Median [Min, Max]	206 [43, 914]	254 [13, 775]	26.0 [-85.1, 205.7]
TTE: Ventricular Function & Size	n=14	n=12	n=12
LV Ejection Fraction (%)			
Mean (SD)	22.9 (4.41)	26.8 (7.2)	16.8 (21.02)
Median [Min, Max]	24.0 [17, 30]	27.5 [18, 41]	14.3 [-20.0, 65.0]
LV End Systolic Volume (mL)			
Mean (SD)	178 (84)	140 (46)	-14.8 (22.58)
Median [Min, Max]	169 [92, 384]	131 [79, 218]	-20.4 [-46.9, 35.5]
LV End Diastolic Volume (mL)			
Mean (SD)	232 (104)	192 (59)	-11.1 (22.84)
Median [Min, Max]	208 [128, 509]	175 [109, 293]	-15.2 [-44.2, 36.7]
LV End Systolic Diameter (cm)			
Mean (SD)	6.2 (0.87)	6.0 (0.93)	-2.0 (7.63)
Median [Min, Max]	6.0 [5.3, 8.3]	6.0 [4.9, 8.0]	-1.0 [-14.0, 7.5]
LV End Diastolic Diameter (cm)			
Mean (SD)	6.9 (0.89)	6.8 (0.99)	-1.9 (8.91)
Median [Min, Max]	6.6 [5.9, 9.0]	6.6 [5.7, 8.4]	-2.4 [-13.6, 20.8]
LV Fractional Shortening (%)			
Mean (SD)	10.2 (4.98)	13.8 (6.2)	40.6 (69.82)
Median [Min, Max]	8.4 [5.4, 22.1]	13.6 [6.7, 27.2]	14.4 [-25.2, 214.5]

[1]MLHFQ, SF-36, and NYHA are absolute change, all other parameters are percent change. Change from baseline data were not available for 2 subjects in time for the data cutoff.

Improvement in functional assessment

Figure 1A: Mean (SE) % change from baseline in 6MWT and VO2 Max

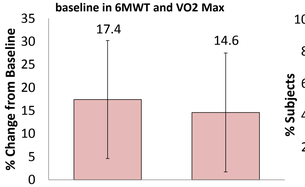
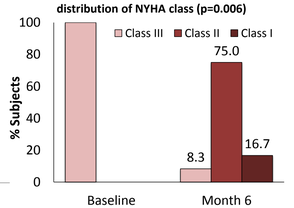
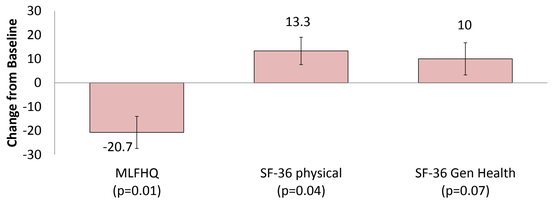


Figure 1B: Change from baseline in distribution of NYHA class (p=0.006)



Improvement in quality of life (QoL)

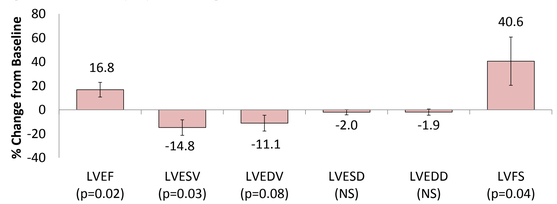
Figure 2: Mean (SE) change from baseline in QoL parameters*



** MLFHQ: Decrease = improved; SF-36 physical and SF-36 Gen' Health: Increase=improved*

Improvement in LV function and dimensions

Figure 3: Mean (SE) % change from baseline in LV function



Abbreviation NS: p > 0.10.

Conclusions

- Multi-vessel intracoronary infusion of allogeneic cardiosphere-derived cells (CAP-1002) up to 75M cells, appears to be **safe and feasible**.
- Despite the small sample size, the trial also demonstrated an **efficacy signal with concordant improvements from baseline to 6 months in functional status, QoL, and ventricular function and size**.
- 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 heart failure to confirm these promising, preliminary, results.