Intracoronary ALLogeneic Heart STem Cells to Achieve Myocardial Regeneration (ALLSTAR): A Randomized, placebo-controlled, double-blind trial

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For the ALLSTAR Investigators
Disclosures

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Funded in part by California Institute for Regenerative Medicine (CIRM; Phase 2)

**Co-PIs**  Timothy D. Henry & Raj Makkar

**Steering Committee**
- Anthony DeMaria, MD – Chair
- Gary S. Francis, MD
- Frank Aguirre, MD
- Thomas Povsic, MD, PhD
- Richard Schatz, MD
- Eduardo Marbán, MD, PhD – Advisor
Introduction

- Previous trials have demonstrated potential benefit of stem cell therapy in patients with recent MI
- Phase 1 data with autologous cardiosphere-derived cells (CDCs) demonstrated scar size reduction and evidence for myocardial regeneration
- Allogenic CDCs (CAP-1002) are equivalent to autologous CDCs in preclinical studies
- Over 100 peer reviewed papers regarding CAP-1002 since 2007
Rationale for Using CDCs to Treat Post MI Cardiomyopathy

- Diverse effects of CDCs support their potential to retard or reverse the multiple pathological processes that contribute to post-MI cardiomyopathy.
CADUCEUS: Phase I Autologous CDCs

- Cedars-Sinai & Johns Hopkins
- Recent MI
- LVEF 25-45% following successful PCI
- 2:1 allocation to autologous CDCs or routine care
- Dose escalation 12.5-25M
- cMRI at baseline, 6, 12 months

Malliaras K, et al., J Am Coll Cardiol. 2014
### ALLSTAR Trial Design

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>DSMB Review</th>
<th>Phase 2</th>
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</thead>
<tbody>
<tr>
<td>Recent MI</td>
<td>-</td>
<td>CAP-1002</td>
</tr>
<tr>
<td>Chronic MI</td>
<td>-</td>
<td>Placebo</td>
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<tr>
<td>(N=14)</td>
<td></td>
<td>Up to 260</td>
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</table>

**Open Label Safety Cohort**

- Donor-specific antibodies (DSA)
- Exploratory Cohort
- Primary Cohort

**DSMA Match**

- Yes
- No

**(2:1)**

- Up to 260
- Up to 40

* Funded by NIH ARRA RC3
* Funded by CIRM
Key ALLSTAR Eligibility Criteria

Inclusion Criteria

• History of STEMI or NSTEMI w/in 12 mo
• Successful PCI (TIMI flow = 3) in infarct related artery
• LVEF \(< 45\%$
• LV infarct size \(\geq 15\%\) of LV mass in qualifying infarct-related region (by MRI core lab)
• No further revascularization needed
• Age \(\geq 18\) years

Exclusion Criteria

• Prior CABG
• Hx ACS within 4 wks prior to infusion
• Hx previous stem cell therapy
• Prior ICD or pacemaker at site not certified to conduct cMRI with device
• Estimated GFR < 30 mL/min
• Participation in another clinical trial w/in the last 30 days
• Current alcohol or drug abuse
ALLSTAR Open Label Phase I Efficacy

15% reduction in scar size at one year

4% improvement in EF at one year
ALLSTAR Phase II Efficacy Endpoints

- **Primary efficacy endpoint**: % change from baseline in infarct size (cMRI as a % of LV mass) at 12 months

- **Secondary efficacy endpoint**: absolute and % change from baseline in LV structure and function, clinical function, and cardiac biomarkers at 6 and 12 months post-infusion
ALLSTAR Phase II Enrollment & Baseline Characteristics

245 pts screened

202 pts randomized to CDCs

103 pts randomized to PBO

5 pts not infused

90 pts infused

97 pts followed matched (n=77); unmatched (n=13)

46 pts followed matched (n=45); unmatched (n=0)

103 pts excluded

5 pts not infused

90 pts infused

45 pts followed

**CAP-1002 (N = 90)**

**Placebo (N = 44)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAP-1002</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>84.4%</td>
<td>86.4%</td>
</tr>
<tr>
<td>Age [mean (SD)]</td>
<td>54.8 (11.25)</td>
<td>53.8 (10.23)</td>
</tr>
<tr>
<td>LVEF [mean (SD)]</td>
<td>39.9% (6.62)</td>
<td>38.7% (8.12)</td>
</tr>
<tr>
<td>LV Scar [mean (SD)]</td>
<td>21.9% (5.15)</td>
<td>23.0% (5.19)</td>
</tr>
<tr>
<td>LVESV [mL (SD)]</td>
<td>129.6 (39.4)</td>
<td>140.2 (46.2)</td>
</tr>
<tr>
<td>LVEDV [mL (SD)]</td>
<td>213.1 (47.4)</td>
<td>225.5 (52.4)</td>
</tr>
<tr>
<td>NTproBNP [pg/mL (SD)]</td>
<td>883.8 (1122.8)</td>
<td>736.2 (700.9)</td>
</tr>
<tr>
<td>MI other than index</td>
<td>15.6%</td>
<td>15.9%</td>
</tr>
</tbody>
</table>

12 mos of on-study observation followed by 4 years of LT F/U
Interim Analysis

• Pre-specified interim analysis – after all subjects observed ≥ 6 months
  – All data for 134 treated subjects (Primary Cohort, n=121; Exploratory Cohort, n=13)

• Given low probability that treatment effect would be observed in primary 12 month efficacy analysis, all subjects were transitioned to annual follow-up
Change in Scar Size by MRI

Matched
Primary mITT Population

Unmatched
Exploratory CAP-1002 & Placebo mITTs

*Placebo (N = 42) | CAP-1002 (N = 74)*

Month 6: $p = 0.63$
Month 12: $p = 0.39$

*Placebo (N = 42) | CAP-1002 (N = 12)*

Month 6: $p = 0.22$
Month 12: $p = 0.01$
LV Volumes

"Matched"

LVEDV

- Month 6
  - Placebo (N = 43)
  - CAP-1002 (N = 74)
  - % Change from Baseline

  p = 0.11

- Month 12
  - Placebo (N = 43)
  - CAP-1002 (N = 74)
  - % Change from Baseline

  p = 0.52

LVESV

- Month 6
  - Placebo (N = 43)
  - CAP-1002 (N = 74)
  - % Change from Baseline

  p = 0.30

- Month 12
  - Placebo (N = 43)
  - CAP-1002 (N = 74)
  - % Change from Baseline

  p = 0.86

"Unmatched"

- Month 6
  - Placebo (N = 43)
  - CAP-1002 (N = 12)
  - % Change from Baseline

  p = 0.004

- Month 12
  - Placebo (N = 43)
  - CAP-1002 (N = 12)
  - % Change from Baseline

  p = 0.10

- Month 6
  - Placebo (N = 43)
  - CAP-1002 (N = 12)
  - % Change from Baseline

  p = 0.0005

- Month 12
  - Placebo (N = 43)
  - CAP-1002 (N = 12)
  - % Change from Baseline

  p = 0.009
NT-proBNP

"Matched"

- Month 6: $p = 0.053$
- Month 12: $p = 0.16$

"Unmatched"

- Month 6: $p = 0.47$
- Month 12: $p = 0.06$
Overall Outcomes
(all CAP-1002 vs placebo, 6 months)

\[ \Delta \text{LVEDV} \quad p = 0.0206 \]

\[ \Delta \text{LVESV} \quad p = 0.0259 \]

\[ \Delta \text{NT-proBNP} \quad p = 0.0115 \]

Deltas from Baseline to 6 months. Post hoc analysis, Mann-Whitney tests, 2-tailed
Safety and Clinical Events

Safety

- No primary safety endpoint events were observed during the study
- No significant treatment group difference in SAE rates

Clinical Events (adjudicated)

<table>
<thead>
<tr>
<th>Clinical Events</th>
<th>CAP-1002 (N = 90)</th>
<th>Placebo (N = 44)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>--</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>3 (3.3)</td>
<td>4 (9.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>HF Hosp</td>
<td>4 (4.4)</td>
<td>3 (6.8)</td>
<td>0.68</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0.0)</td>
<td>1 (2.3)</td>
<td>0.33</td>
</tr>
<tr>
<td>MACE</td>
<td>7 (7.8)</td>
<td>5 (11.4)</td>
<td>0.49</td>
</tr>
</tbody>
</table>
Conclusions

• No significant difference in scar size based on 6 or 12 month MRI
• Signs of improvement in LV volumes and BNP
• Very low clinical events \(\Rightarrow\) favoring the treatment group
• Challenges
  – Recruitment of patients with large anterior MI
  – MRI endpoint dropout and variability
• To be investigated: Influence of matched vs unmatched cells
Acknowledgments

- Cedars-Sinai Medical Center – R. Makkar & T. Henry (17)*
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- Prairie Education and Research – F. Aguirre (11)
- Sanger Heart & Vascular Institute – G. Kowalchuk (10)
- Scripps Green Hospital – R. Schatz (9)*
- Minneapolis Heart Institute – J. Traverse (6)*
- Unv. Massachusetts Memorial – J. Rade (6)
- Unv. Pittsburgh Medical Center – C. Toma (6)
- Unv. Utah – C. Selzman (6)
- Unv. Kentucky – A. Abdel-Latif (5)
- Austin Heart – R. Gammon (4)
- Ohio Health Research Institute – C. Sanchez (4)
- SUNY Buffalo – V. Iyer (4)
- Rush University Medical Center – G. Schaer (3)
- Duke University Hospital – T. Povsic (3)
- MHVI - J. Chambers (3)

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- The Ohio State University – K. Boudoulas (3)
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- Michigan CV Institute – S. Kassas (2)
- Ottawa Heart Institute – M. Le May (2)
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- NC Heart – J. Zidar (1)
- Unv. Pennsylvania – S. Khandhar (1)
- Unv. Texas/Mem Hermann – H.V. Anderson (1)
- Unv. Washington – C. Don (1)

*Participated in Phase I
BACKGROUND SLIDES
## ALLSTAR Phase II Demographic & Baseline Characteristics

<table>
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<tr>
<th>Characteristic</th>
<th>CAP-1002 (N = 90)</th>
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<tr>
<td>Sex, male</td>
<td>84.4%</td>
<td>86.4%</td>
</tr>
<tr>
<td>Age (years) [mean (SD)]</td>
<td>54.8 (11.25)</td>
<td>53.8 (10.23)</td>
</tr>
<tr>
<td>Race, white</td>
<td>87.8%</td>
<td>81.8%</td>
</tr>
<tr>
<td>LVEF [mean (SD)]</td>
<td>39.9% (6.62)</td>
<td>38.7% (8.12)</td>
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<td>MI other than index event</td>
<td>15.6%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Angioplasty other than index event</td>
<td>23.3%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58.9%</td>
<td>63.6%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21.1%</td>
<td>31.8%</td>
</tr>
<tr>
<td>ACE or ARB</td>
<td>87.8%</td>
<td>86.4%</td>
</tr>
<tr>
<td>ACE/neprilisyn inhibitors</td>
<td>1.1%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>97.8%</td>
<td>100%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>14.4%</td>
<td>29.5%</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>31.1%</td>
<td>22.7%</td>
</tr>
<tr>
<td>Antithrombotic agents</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Lipid lowering agents</td>
<td>96.7%</td>
<td>95.5%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>96.7%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Overall Outcomes (All CAP-1002)

**LVEDV**

- **Month 6**
  - Placebo: 4.2
  - CAP-1002: 2.9
  - p = 0.04

- **Month 12**
  - Placebo: 3.6
  - CAP-1002: 2.2
  - p = 0.36

**LVESV**

- **Month 6**
  - Placebo: 4.3
  - CAP-1002: 4.0
  - p = 0.096

- **Month 12**
  - Placebo: 3.6
  - CAP-1002: 2.2
  - p = 0.58

**NT-proBNP**

- **Month 6**
  - Placebo: 0.0
  - CAP-1002: 0.3
  - p = 0.07

- **Month 12**
  - Placebo: 0.2
  - CAP-1002: 0.5
  - p = 0.08
Interim Analysis

• Pre-specified interim analysis – after all subjects observed ≥ 6 months
  – All data for 134 treated subjects (Primary Cohort, n=121; Exploratory Cohort, n=13)

• Results of the analysis demonstrated:
  – No difference in primary endpoint (% change from baseline in scar as % LV mass)
  – Reduction \( p = 0.054 \) in LVEDV, trend in reduction of LVESV \( p = 0.09 \) and NT-proBNP \( p = 0.11 \)
  – No Safety signals in CAP-1002 cohort

• Given low probability that treatment effect would be observed in primary 12 month efficacy analysis, all subjects were transitioned to annual follow-up