PRESERVATION I

Bioabsorbable Cardiac Matrix for the prevention of remodeling of the left ventricle after large ST-elevation myocardial infarction

ClinicalTrials.gov Identifier: NCT01226563

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on behalf of the PRESERVATION I Investigators

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and Duke Clinical Research Institute, Durham, NC, USA
Disclosure

- U.Z. has received honoraria
- S.V.K and M.W.K. have received compensation for their participation as members of the Executive Committee of the PRESERVATION I trial
Background

Pathologic ventricular remodeling after large MI impairs left ventricular (LV) function and is associated with heart failure and mortality.

Device: Bioabsorbable Cardiac Matrix (IK-5001)

- Large infarcts are associated with the degradation of extracellular matrix (ECM) and calcium overload
- BCM is a combination of alginate with calcium gluconate in water, it is biologically and immunologically inert, and does not undergo metabolism
- In the presence of high concentration ionized calcium, BCM turns to flexible hydrogel
- The gel replaces the degraded ECM, which results in reducing wall stress, and a thicker scar formation in the infarct zone
- Upon normalization of extracellular calcium levels, BCM becomes fluid again and is excreted via the kidney
- BCM provides mechanical support and prevents consistently remodeling in several animal models and a human pilot study
Trial hypothesis

- Can the intracoronary deployment of an inert bioabsorbable cardiac matrix replace the damaged extracellular matrix and provide a temporary physical support during infarct healing and repair and prevent remodeling?
Trial Organization

• Steering committee
  – Mitchell Krucoff (study chair), Sunil Rao (co-PI), Uwe Zeymer (co-PI)
  – Pamela Douglas, Norbert Frey, Jaroslav Kasprzak, Paul Vermeersch, Jerome Roncalli, José López-Sendón, Victor Guetta, Henry Krum, Derek Chew, Jean-François Tanguay, Tim Henry, Hussein Al-Khalidi, Howard Levy, Reinilde Heyrman

• Coordinating Center: DCRI
• Data safety monitoring board: Chaired by Magnus Ohman (DCRI)
• Event Adjudication Committee (DCRI)
• Core laboratories for
  – Echocardiography (DCRI, Pamela Douglas)
  – 24-hour Holter & ECG (DCRI, Mitchell Krucoff)
  – Deployment angiogram (PERFUSE, Michael C. Gibson)

• Sponsor: Bellerophon Therapeutics
Trial design
Prospective, randomized, double blind trial

Successful index PCI for STEMI Day 0

Deployment procedure (index visit) Day 2–5

Post-Deployment

6 months

Randomization

Inclusion criteria:
- Large STEMI defined by
  - Peak cardiac markers
  - Clinical presentation (delayed PCI, ECG, shock)
  - Imaging (EF ≤ 35% or MI size > 20%)

Exclusion criteria: cardiogenic shock during planned deployment, ventricular arrhythmias, renal insufficiency, inadequate echo images

Primary endpoint

Δ LVEDVI
Echo (2 & 3D)
Δ KCCQ / SF-12
Δ 6MWT
Δ NYHA class
Δ NT-Pro-BNP
ECG
Clinical outcomes
AEs/SAEs

AEs/SAEs

Primary endpoint
Endpoints

**Primary endpoint:**
- Change in LV end diastolic volume index (LVEDVI) from baseline to 6 months
  - 80% power with 276 pairs to detect a difference of 5 mL/m² based on a standard deviation of 13.89 mL/m², \( \alpha = 0.05 \)
- 3D echocardiographic assessment of LV dilation
  - Accuracy and reproducibility equivalent to cardiac magnetic resonance imaging
  - Readily available in most centers and easily accepted by patients

**Secondary endpoints:**
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Six-minute walk test (6MWT)
- New York Heart Association (NYHA) functional classification
- Time to death or non-fatal heart failure events or cardiovascular hospitalizations adjudicated by a clinical events committee
- Time to first rehospitalization due to any cardiovascular event
Deployment procedure

• An intracoronary injection of 4 mL BCM or saline control (sham procedure) in a second procedure 2–5 days after primary PCI was performed.
• Patients had to have TIMI 3 flow before injection.
• The deployment was performed via a dedicated catheter proximal to the stent of the infarct-related artery.
**CONSORT diagram**

Enrolment in 64 centers in 9 countries between 04/2012-12/2014

<table>
<thead>
<tr>
<th>Screen failure reasons</th>
<th>Count</th>
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<tr>
<td>Did not meet inclusion criteria</td>
<td>27</td>
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<tr>
<td>Met exclusion criteria</td>
<td>6</td>
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<tr>
<td>No TIMI 3 flow at protocol-specified catheterization</td>
<td>5</td>
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<tr>
<td>Death</td>
<td>3</td>
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<tr>
<td>Other</td>
<td>28</td>
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</table>

**Enrolled:** 372

**Randomized:** 303

- **BCM:** 201
  - Data at 6 months: LVEDVI: 191 (95%) Safety: 201 (100%)
- **Saline control:** 102
  - Data at 6 months: LVEDVI: 93 (91%) Safety: 102 (100%)
## Baseline characteristics

|                                | BCM  
|                                | N=201 | Saline control  
|                                |       | N=102 |
| Age                            | 58.4 ± 10.84 | 57.6 ± 10.75 |
| Male                           | 82.1% | 80.4% |
| Diabetes                       | 18.9% | 15.7% |
| Anterior MI                    | 93.0% | 92.2% |
| LVEF (%)                       | 33.9 ± 6.40 | 35.4 ± 7.13 |
| Infarct size (%) (CMR or SPECT) | (n=40) | (n=25) |
|                               | 36.0 ±14.14 | 29.4 ±9.73 |
| NT-pro-BNP                    | 499.9 ± 562.94 | 376.1 ± 399.82 |
| End-diastolic volume index     | 84.8 ± 16.21 | 82.1 ± 14.74 |
Medical treatment at discharge

<table>
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<tr>
<th>Medical Treatment</th>
<th>BCM</th>
<th>Saline control</th>
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<tbody>
<tr>
<td>Statin</td>
<td>79.1%</td>
<td>86.3%</td>
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<tr>
<td>Beta-blocker</td>
<td>86.6%</td>
<td>86.3%</td>
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<tr>
<td>ACE-I</td>
<td>79.6%</td>
<td>81.4%</td>
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<tr>
<td>ARB</td>
<td>12.9%</td>
<td>7.8%</td>
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<tr>
<td>Mineralocorticoid antagonist</td>
<td>30.8%</td>
<td>32.4%</td>
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</table>
Primary endpoint: LVEDVI

6-mo point estimate 3.8
(95% CI -0.5–8.0)
Change from baseline at 6 months for secondary endpoints

<table>
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<tr>
<th>Parameter</th>
<th>BCM Mean ± SD</th>
<th>Saline control Mean ± SD</th>
<th>Point estimate (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔKCCQ</td>
<td>0.5 ± 22.65</td>
<td>0.8 ± 26.80</td>
<td>0.3 (-5.9–6.4)</td>
<td>0.931</td>
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<tr>
<td>Δ6MWT, min</td>
<td>135.6 ± 146.13</td>
<td>101.4 ± 139.22</td>
<td>34.3 (-0.2–68.7)</td>
<td>0.051</td>
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<td>NYHA improvement</td>
<td>25.1%</td>
<td>22.8%</td>
<td></td>
<td>0.623</td>
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<tr>
<td>NYHA worsening</td>
<td>20.1%</td>
<td>21.8%</td>
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<tr>
<td>CV hospitalization</td>
<td>14.7%</td>
<td>10.2%</td>
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<td>0.143</td>
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<tr>
<td>Death</td>
<td>2.0%</td>
<td>2.9%</td>
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<td>n.s.</td>
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<td>Number of deaths, non-fatal CHF, CV hospitalization</td>
<td>15.6%</td>
<td>11.2%</td>
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<td>0.153</td>
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Safety parameters

*Kaplan-Meier of composite of CV death, acute MI, revascularization, stent thrombosis, arrhythmia, or myocardial rupture*

- **BCM**
- **Saline Control**

$p$-value: 0.5

Number at Risk
- **BCM** (N): 201
- **Saline Control** (N): 102

Time from Randomization (days):
- 0
- 60
- 120
- 180
- 240
- 300
- 360

% Composite Event:
- 0
- 5
- 10
- 15
- 20
- 25
- 30
- 35
- 40
Procedural safety

• Repeat catheterization
  – 22% had staged PCI scheduled

• No difference between BCM and saline on 24-hour Holter
  - arrhythmias
  - ischemia: BCM 9.0% - Saline 7.8%,

• Angiographic assessment coronary artery flow
  – 5 occlusions in BCM (but only 3 also ischemia on Holter)
  – 1 occlusion in saline control
Conclusions

• Able to identify and enroll large STEMI patients
  – BCM deployed 2–5 days after primary PCI was well tolerated compared to saline control
  – The additional invasive procedure carries risks, albeit minimal

• In patients with large STEMI, intracoronary BCM does not prevent LV remodeling compared to saline control nor the occurrence of heart failure
  – Secondary endpoints (NYHA class, functional capacity) did not show clinical difference between BCM and saline control
Discussion

• Reasons for discrepant findings compared to animal data?
• Did microvascular obstruction and edema prevent BCM to get into the infarcted myocardium?
• Future direction:
  – Different patient population?
  – Earlier timing of deployment?
  – Device deployment technology?
  – Combination with stem cells?
## Investigator enrollment

*With our sincere thanks to all participating patients*

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Statistical analysis by DCRI: Hussein Al-Khalidi & Jennifer White

With thanks to CROs:
- DCRI in NA (Diane Joseph)
- WCT in ROW (Helen Treece)