BioCardia®

Science of CardiAMP Heart Failure Cell Therapy
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Science of CardiAMP Cell Therapy - Overview

- **Background**
  - What is bone marrow cell therapy?
  - Cardiac cell therapy mechanisms of action
  - Cardiac cell therapy – paracrine effects

- **Bone marrow cell therapy – Preclinical Experience**
  - Rats: Paracrine stimulus study - reduces scar and leads to micro vessel formation
  - Pigs: Dose dependent study - shows higher dose reduces scar and leads to increased microvessel formation

- **Effective Dosage:**
  - Helix increases efficiency of delivery
  - Cell Potency Assay should enhance patient responsiveness to therapy

- **CardiAMP Heart Failure Trial**
  - Clinical background
  - Phase 1 design & results
  - Phase 2 design & results
  - Phase 3 design & results
What is Bone Marrow Cell Therapy?

• Stem cell therapies may offer the potential to treat diseases or conditions for which few treatments exist.

• Sometimes called the body’s “master cells,” stem cells are the cells that develop into blood, brain, bones, and all of the body’s organs.

• They have the potential to repair, restore, replace, and regenerate tissues, and could possibly be used to treat many medical conditions and diseases.

• The hip bone or iliac crest contains a large volume of bone marrow cells that have historically been harvested for bone marrow transplantation and as a source of stem cell therapies.

Bone marrow cells include a number of important cell populations that have each been studied for therapeutic benefit for treating the heart and have shown benefit in animal and clinical studies

• Hematopoietic stem and progenitor cells
• Mesenchymal stem cells

https://www.fda.gov/forconsumers/consumerupdates/ucm286155.htm
Cardiac Cell Therapy: Mechanistic Basis for Regeneration

- Transplanted bone marrow cells have been hypothesized to benefit the heart through direct and indirect pathways.

- **Direct Regeneration:** Transplanted cells actively home to injury sites and differentiate into new functional tissue to augment organ function. No cell therapy for cardiovascular regeneration in clinical trials is yet believed to integrate into heart tissue permanently. Of note, studies that showed cells did not turn into heart cells also showed some improvements in treated animal hearts.

- **Indirect Regeneration:** Transplanted cells secrete stimulatory cytokines to instigate an innate regenerative response from resident stem cells.

Cardiac Cell Therapy: Paracrine Stimulus

- Cell therapies have been shown to provide paracrine mediators that promote a number of valuable mechanisms of action.
- Significant compelling preclinical data sets using bone marrow derived cells

Dzau, VI et al. (2011); J Mol Cell Cardiol. 50(2): 280-289.
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Bone marrow Cells – Preclinical Experience

- Small (rats, mice) and large animal (swine, canine) studies support safety and efficacy of bone marrow cells. A few of these are provided.
  - **Takahashi et al.** (2006):
    - Explored paracrine mechanism in rats
    - BMC media injected after overnight incubation under normoxia and hypoxia
  - **Sun J et al** (2009):
    - Cardiac function enhanced after BMC or BMC medium transplantation in rats
  - **Silva et al.** (2011):
    - Explored dose effect of bone marrow mononuclear cells, delivered via transendocardial injection in post infarct pig model
    - 50, 100, 200 Million BMC injected in infarcted heart
Paracrine Stimulus: BMC Media (Normoxia and Hypoxia) led to reduced fibrotic scar and enhanced microvessel density in the infarcted rat myocardium 28 Days after treatment.
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Silva et al. Tex Heart Inst J (2011);38(3):219-24
Cardiac Function Enhanced After BMC or BMC Medium Transplantation in Rats

Results of echocardiography showing more rapid loss of function and ventricular dilation in the control group

[sham group, n = 6; medium group, n = 9; and bone marrow cell-transplanted (BMC) group, n = 9]
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Silva et al. Tex Heart Inst J (2011);38(3):219-24
**Bone Marrow Cells – Preclinical Experience (Pig)**

**Dose Dependence:** Higher dose of MNC led to less fibrosis and increased microvessel formation in infarcted pig myocardium 60 days after treatment.

### Reduced Fibrosis
>100 Million BMC resulted in less fibrosis.

### Increased Capillary Density
200 Million BMC (>20 Million BMC/segment) resulted in highest capillary density and least fibrosis.

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Silva et al. Tex Heart Inst J (2011);38(3):219-24

05141-A (MKT) Science of CardiAMP Cell Therapy
Content Overview – CardiAMP Cell Therapy Science

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  - Helix increases efficiency of delivery
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Effective Dosage A Pharmacokinetic Approach to Better Understand Pharmacodynamic Responses in Cardiac Cell Therapy Trials

Dose response relationships have been described in some phase I-II clinical trials.

Cross correlation between studies should take into account the myocardial retention (efficiency of the delivery method and absolute dose).

Cross correlations should take into account the release criteria of the cell graft (which requires consensus regarding what qualifies a relevant cell: requirements for identity-purity, functionality, viability of cell graft as verified by flow and/or functional assays).

Perin et al, FOCUS-CCTRN Trial, JAMA. 2012; 307(16)
Lipinsky et al, JACC 2007, 50(18)
Perin et al Circ Res 2015
Effective Dosage: Absolute Dose Delivered & Retained in Myocardium

Effective dosage is the actual cell dose for delivery, corrected by the efficiency of the delivery route (actual dose retained locally in the myocardium).

Response to therapy (pharmacodynamics) may be better understood by tracking the effective dosage (myocardial retention) at a specified time post delivery (pharmacokinetics) by a standardized test.

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Cell Dose</th>
<th>% CD34 Reported/Estimated</th>
<th>CD34 Counts</th>
<th>Estimated Retention (%)</th>
<th>Calculated Effective CD34+ Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>REPAIR AMI 2006¹</td>
<td>236,000,000</td>
<td>1.5%*</td>
<td>3,540,000</td>
<td>1%</td>
<td>35,400</td>
</tr>
<tr>
<td>BM CMI 2009²</td>
<td>98,000,000</td>
<td>2.4%</td>
<td>2,352,000</td>
<td>6%</td>
<td>141,120</td>
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<tr>
<td>ACT34-CMI 2011³</td>
<td>7,000,000</td>
<td>100%</td>
<td>7,000,000</td>
<td>6%</td>
<td>420,000</td>
</tr>
<tr>
<td>TABMMI 2011⁴</td>
<td>100,000,000</td>
<td>1.9%</td>
<td>1,900,000</td>
<td>18%</td>
<td>342,000</td>
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<tr>
<td>FOCUS 2011⁵</td>
<td>30,000,000</td>
<td>1.5%</td>
<td>450,000</td>
<td>6%</td>
<td>27,000</td>
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<tr>
<td>FOCUS 2012⁶</td>
<td>100,000,000</td>
<td>2.6%</td>
<td>2,600,000</td>
<td>6%</td>
<td>156,000</td>
</tr>
<tr>
<td>TACHFT 2013⁷</td>
<td>200,000,000</td>
<td>1.9%</td>
<td>3,800,000</td>
<td>18%</td>
<td>684,000</td>
</tr>
</tbody>
</table>

*CD34+/CD45+ population reported

Modified from Altman et al International Conference on Cell Therapy for Cardiovascular Disease 2014.

Intramyocardial Cell Delivery with Helix/Morph Delivery System

- The CardiAMP cells are intramyocardially injected using the Helix percutaneous delivery system (10 injections of 0.5 cc)

Clip courtesy of Dr. Todd Brinton, Stanford University
CardiAMP Cell Therapy Delivery Approach

Morph Guide
Enhanced Navigation

Contrast Confidence in Engagement

Helical Needle Stability in the heart

5/1/2019
Qualitative Assessment of CardiAMP Cell Delivery Approaches: Transendocardial (Helix), Transepicardial, and Coronary Artery Delivery

PET imaging of cells in swine model with external calibration (1) shows superior myocardial retention with Helix delivery.

Quantitative Assessment of CardiAMP Cell Delivery Approaches: Transendocardial (Helix), Transepicardial, and Coronary Artery Delivery

Helical shaped needle in Helix/Morph delivery device results in superior myocardial retention and higher effective dose of delivered BM MNC.

In CardiAMP HF trial, patients receive a target dose of 200 Mill MNC with expected CD34+ effective dose approximately that of ACT34-CMI 2011, due to efficiency of delivery and patient selection.

Additional Screening with CardiAMP Cell Potency Assay

- **CardiAMP Potency Assay** bone marrow biomarker panel analysis at core lab:

  Anticipated to select 70% most likely to respond based on therapeutic potential of their bone marrow

- **Personalized approach to autologous cell therapy:**
  - Reduces problematic patient-to-patient variation in bone marrow cells
  - Significantly lowers cost of therapy by enabling point of care treatment and excluding patients from therapy not likely to respond
  - Attractive to patients, physicians and payors
Biomarkers identified in previous BioCardia trials and scientific literature have shown to correlate independently to the efficacy of CV cell therapy.

Proprietary biomarker analysis at central core lab to assess the presence of minimal bone marrow requirements to promote myocardial repair in the bone marrow sample taken days before the treatment procedure.

Central core flow cytometry and cell biology labs at Baylor University, Houston.

Biobanking of blood and bone marrow samples for in depth analysis.

One of the markers is the CD34+ cell titer in the bone marrow.

Estimated effective CD34+ cell dosage from leading trials

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Modified from Wong et al.: International Conference on Cell Therapy for Cardiovascular Disease 2014.
Additional Screening with CardiAMP Cell Potency Assay

Some centers are believed to do large volume aspirations which result in poor cellularity of the BM aspirate. Potential value of CPA is exclusion of such (large volume) sampling.

Dresch, et. al: Increasing the draw volume leads to peripheral blood contamination.

Fennema, et. al: Multiple aspirations from the same site results in lower cellular concentrations.

This data is part of a campaign intended to impact cellularity focus of BMA draws.
CardiAMP Procedure: Cell Processing

- Isolation and approx. 7-10x concentration of nucleated BM fraction at point-of-care
- Isolation of 60 cc of BM aspirate able to create target dose of 200 Mill BM MNC
- Minimal processing believed to preserve cell viability

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Clinical Background
2012 Closest Work to CardiAMP

Relevant Conclusions:
• Every 3% higher level of CD34 cells was associated with on average a 3.0% greater absolute unit increase in LVEF in multiple variable model that included age and treatment as predictor variables [95% CI, 0.14-5.98]; (P = 0.04)

• An analogous computation for CD133 cells (range, 0.1% - 3.6%; SD =0.62) revealed that every 3% higher level of CD133 cells was associated with on average a 5.9% greater absolute unit increase in LVEF [95% CI, 0.36% = 7.77%]; P = 0.04.)

Perin, EC et al. JAMA 2012, 307(16), pg. 418
Clinical Background
2018 Meta Analysis Update - Highlights

• **Mortality rate in patients** - with BM MNC therapy was significantly lower (15.4%; RR 0.38) on meta analysis of 21 randomized trials in 1010 pts

• Cell therapy was associated with a **reduction** in non-fatal MI (RR 0.40) and arrhythmias (RR 0.46) over long term follow-up.

• **Periprocedural adverse events** associated with cell/placebo injection procedure were **infrequent**.

CardiAMP HF Phase I Trial Design and Results

Transendocardial Autologous Bone Marrow in Myocardial Infarction (TABMMI) NCT00507468
Safety: No Treatment Emergent-MACE

20 Ischemic Heart Failure Patients
LVEF<40%
NYHA Class I, II, and III

Open Label Safety Study
100 Million BMC
10 peri-infarct injection sites - Helix System

Left ventricular EF measurements - 2D echocardiography
24-hour Holter Monitor
Exercise Tolerance Testing (ETT)


Exercise Tolerance Time
Improvement at 12 & 24M:
~ +125 sec, p=0.006

Improved LV Ejection Fraction
Improvement at 12 & 24M:
~ +7 %, p<0.001

Improved survival at 3 and 5 year follow-up
1st 10 patients – No death
All 20 patients – 2 deaths:
D177 Elective heart transplant
D695 Unknown causes
CardiAMP HF: Phase 2 Trial Design

Transendocardial Autologous Cells in Heart Failure Trial (TAC-HFT), NCT00768066

34 Ischemic Heart Failure Patients
- LVEF<50%
- NYHA Class I, II, and III

Open Label Dose Escalation
- 100 M to 200M Cells (N=4)
- 2:1 Randomized, Placebo-Controlled Therapy of 200M cells (N=30),
  10 peri-infarct injection sites
  Helix System

Primary endpoint was safety based on TE MACE.
Secondary efficacy endpoints: six minute walk distance, quality of life, NYHA Class, echocardiography

Wong Po Foo et al, World Congress of Regenerative Medicine, 2015.
CardiAMP HF Phase 2 Placebo Controlled Randomized Trial Results

- TAC-HFT BMC were results superior to TAC-HFT MSC
- Primary safety endpoint was met: no treatment-emergent MACE at 30 days pp
- No death or MACE in BMC treatment group at one year follow-up
- All secondary efficacy endpoints **at one year follow-up favor cell therapy** (below)
- Multiple endpoints that are statistically significant and clinically meaningful

<table>
<thead>
<tr>
<th>Secondary Efficacy Endpoints</th>
<th>Active (Mean)</th>
<th>Placebo (Mean)</th>
<th>Treat. Difference</th>
<th>favors CardiAMP Therapy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 minute walk (meters) N=28, Mean ± St Dev</td>
<td>+14.3 ± 59.6</td>
<td>-42.0 ± 18.1</td>
<td>+56.3</td>
<td>✓</td>
<td>0.049</td>
</tr>
<tr>
<td>MLHF quality of life (pts) N= 29, Mean ± St Dev</td>
<td>-7.7 ± 17.8</td>
<td>+9.7 ± 24.8</td>
<td>-17.4</td>
<td>✓</td>
<td>0.038</td>
</tr>
<tr>
<td>Maximum Oxygen Use (mL/kg·min)</td>
<td>+0.16</td>
<td>-0.870</td>
<td>+1.03</td>
<td>✓</td>
<td>0.321 NS*</td>
</tr>
<tr>
<td>NYHA HF Class</td>
<td>-0.42</td>
<td>-0.25</td>
<td>-0.17</td>
<td>✓</td>
<td>0.638 NS</td>
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<tr>
<td>LV End Systolic Volume (ml)</td>
<td>+3.2</td>
<td>+47.2</td>
<td>-44</td>
<td>✓</td>
<td>0.129 NS</td>
</tr>
<tr>
<td>LV End Diastolic Volume (ml)</td>
<td>+4.5</td>
<td>+51.2</td>
<td>-46.7</td>
<td>✓</td>
<td>0.149 NS</td>
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<tr>
<td>LV Ejection Fraction (%)</td>
<td>+0.97</td>
<td>-2.38</td>
<td>+3.35</td>
<td>✓</td>
<td>0.252 NS</td>
</tr>
</tbody>
</table>

*NS: not significant

Wong Po Foo et al, World Congress of Regenerative Medicine, 2015.
CardiAMP Phase 2 Placebo Controlled Randomized Trial Results

- Primary safety endpoint: No treatment emergent SAE at 30 days follow up
- Secondary efficacy endpoints show that placebo patients deteriorate while treated patients improve.

**Improved functional capacity**

Treatment vs. placebo: **+56.3 m,**
(p=0.049, at 12 mo FU)

**Improved Quality of Life**

Treatment vs. placebo: **-17.4 pts,**
(p=0.038, at 12 mo FU)

Johnston P, AHJ, 2018
Wong Po Foo et al, World Congress of Regenerative Medicine, 2015.
CardiAMP HF Phase 2 Efficacy Results in Six Minute Walk Relative to CRT and Entresto heart failure therapies

- CRT = Cardiac Resynchronization Therapy or Biventricular Pacing, a $3Bn US Market
- 50% of patients in CardiAMP placebo controlled Phase II already had AICD or CRT devices
- 6MWD has been used for approval in PAH, and CRT
- This data is from trials used for CRT product registration

1. CRT, Miracle-ICD, JAMA, 2003
2. Cells, REVASCOR, Circ Res 2005
3. CRT, Contak CD, JACC, 2003
4. CRT, PAVE, ICE 2005
5. CRT, Miracle, Circ, 2003
6. CRT, Path CHF, JACC, 2002
7. Cells, CardiAMP, JAMA 2013, WCRM 2015
8. CRT, Mustic, JACC, 2002

5/1/2019
Novel aspects of CardiAMP program

- High effective dose of stem cells due to delivery efficiency
- Cell Potency Assay
- Point of Care Device
- Efficient procedure of 60-90 min
CardiAMP Heart Failure Trial is an Investigational Device Trial

Intended to provide the primary data to support safety and efficacy to support a marketing application of the CardiAMP Cell Therapy System.
CardiAMP Heart Failure Update and Data

Design of Phase III Pivotal Trial

CardiAMP Heart Failure Trial, NCT02438306, IDE Trial for Premarket Approval

Study Design: Prospective, multi-centered, 3:2 randomized, controlled, double-blinded phase III clinical trial to assess CardiAMP cell therapy in 260 patients with post-infarction heart failure.

Treatment Group: 160 Subjects treated with autologous BM MNC using the CardiAMP cell therapy and optimal medical therapy

Sham Control Group: 100 Subjects treated with optimal medical therapy

Roll-in Phase: Maximum of 10 subjects

Total Number of Patients: 260 subjects

Changes from Phase II:
- NYHA Class I patients are not included
- Inclusion of Cell Potency Assay

Raval A et al. The CardiAMP Heart Failure trial:, AM Heart Journal, April 2018.
CardiAMP Heart Failure Trial: Screening

Key Inclusion Criteria

• New York Heart Association (NYHA) Class II or III
• Diagnosis of chronic left ventricular dysfunction, due to previous myocardial infarction (TTE)
• Left ventricular ejection fraction of 20 - 40% as determined by 2D/3D echocardiogram, and not in the setting of a recent ischemic event
• No recent MI within last 6 months
• Previous treatment with thrombolytic therapy, coronary artery bypass surgery, or percutaneous coronary revascularization
• On stable evidence-based medical and device therapy for heart failure, per the 2013 ACC/AHA Heart Failure guidelines, for at least 3M prior to randomization
  – Optimal pharmacotherapy (BB, ARB/ACE-I, diuretics, aldosteron.inh.)
  – Cardiac resynchronization therapy (CRT/ CRT-D) if appropriate
    • CRT or CRT-D implanted at least 3M prior to randomization
    • Eligible or anticipated to be eligible for CRT or CRT-D > 6M
• Cell Potency Assay Score of 3, as determined by the Cell Analysis Core Lab
Key Exclusion Criteria

- Bronchospastic lung disease, orthopedic, muscular, or neurologic conditions that could limit the ability to perform the 6MWD Test
- Performance in 6 MWD test at baseline is <100, or > 450 m
- Need for coronary artery revascularization. (PCI/CABG should occur at least 3 months prior to randomization)
- Severe mitral, tricuspid or aortic regurgitation (≥3+)
- Presence of aortic stenosis (≥3+, AVA < 1.5 cm²)
- Mechanical aortic valve or heart constrictive device
- A life-threatening arrhythmia
- Complete heart block or QTc interval >550 ms
- AICD firing in the past 60 days prior to the procedure
- Peripheral artery disease involving the aorta or iliofemoral system that impacts the feasibility or safety of the study intervention.
Baseline Screening

- Informed consent
- Medical history (including current medication and recent adverse events)
- Physical examination
- NYHA HF functional class
- Minnesota Living with Heart Failure Questionnaire
- 6 minute walking test
- 12-Lead ECG
- 24 hour holter monitor or ICD interrogation
- Blood and urine analysis
  - Clinical chemistry
  - Hematology (w differential)
  - Pregnancy test
  - Urinalysis
  - NT-proBNP
  - Troponin, CKMB
  - Serology for HBV, HCV, HTLV
- Echocardiogram (contrast enhanced)
- Cell Potency Assay of Bone Marrow (5ml)
The CardiAMP Heart Failure Trial: Efficacy Outcomes from Roll-In Phase

Peter V. Johnston¹, Henricus J. Duckers², Amish N. Raval³, Thomas D. Cook³, Jay H. Traverse⁴, William T. Abraham⁵, Peter A. Altman², Carl J. Pepine⁶

Clinical Results: Roll-in Phase (primary endpoint)

Change in 6MWD Relative to Baseline

Mean +/-SEM; n=10 at all time points

In 8 out of 10 patients, the 6 minute walking performance improved at 12 months

#Wong Po Foo et al, World Congress of Regenerative Medicine 2015.
## Slide modified from Johnston et al, rapid communications, AHA meeting 2018
**Clinical Results: Roll-in Phase – NYHA HF Class and Quality of Life**

Distribution of NYHA HF class (left), n=10 for NYHA HF Class at 3 & 6 mos, n=9 at 9 & 12 mos

Quality of Life (right; MLHFQ), Mean +/-SEM; n=10 for all time points.

7 out of 10 patients **improved at 12 month follow-up (QoL)**

#Wong Po Foo et al, World Congress of Regenerative Medicine 2015.
## Slide modified from Johnston et al, rapid communications, AHA meeting 2018
Clinical Results: Roll-in Phase – LV Function at 12 months

Global LV Function

Change in LV Function

Mean +/-SEM; n=10 vs. 9 vs. 9; Transthoracic echocardiograms assessed by blinded readers in Echo Core Lab (Yale School of Medicine)

In 7 out of 10 patients, the global LV ejection fraction improved at 12 month follow-up

# Slide modified from Johnston et al, rapid communications, AHA meeting 2018

5/1/2019

05141-A (MKT) Science of CardiAMP Cell Therapy
Clinical Results: Roll-in Phase – LV Function at 12 months

Decrease in Akinetic Wall Segments (myocardial recruitment)

Akinetic Wall Segments

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akinetic Segments</td>
<td>6.1</td>
<td>5.0</td>
<td>4.2</td>
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</tbody>
</table>

Δ Akinetic Segments

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Akinetic Segments</td>
<td>-1.1</td>
<td>-1.9</td>
<td></td>
</tr>
</tbody>
</table>

p=0.08

*p=0.04

- Mean +/-SEM; n=10; Transthoracic Echocardiograms assessed by blinded readers in Echo Core Lab (Yale School of Medicine)
- Pre-specified 2º Endpoint: Recruitment of myocardial segments

- In 8 out of 10 patients treated with CardiAMP Cell Therapy, the total number of akinetic myocardial segments were significantly decreased at 12 month follow-up

# Slide modified from Johnston et al, rapid communications, AHA meeting 2018
Clinical Results: Roll-in Phase – LV Function at 12 months

**Improvement in Wall Motion Score**

- **Mean +/-SEM; n=10; Transthoracic Echocardiograms assessed by blinded readers in Echo Core Lab (Yale School of Medicine)**
- Pre-specified 2º Endpoint: Recruitment of myocardial segments

**In all 10 out of 10 patients treated with CardiAMP Cell Therapy, the (Total) Wall Motion Score was significantly improved at 12 month follow-up**

# Slide modified from Johnston et al, rapid communications, AHA meeting 2018

5/1/2019
CardiAMP Heart Failure Trial – (S)AEs in first 10 patients
(roll-in phase)

- Safety
  - No SAEs or unanticipated events at first 30 days after therapeutic procedure
  - Minor AEs managed and resolved within 30 days

The (blinded) DSMB convened at Sept 20th 2017 to review the interim DSMB report.

There were NO safety concerns:

“The committee found the data to be reassuring, also relating to the low biomarker elevation findings. The committee recommends enrollment to continue into the Pivotal Phase.”
Thank you