mesoblast

the regenerative medicine company

Clinically Meaningful Outcome in Phase 2b Trial of MPC-150-IM in LVAD Recipients Provides Pathway for Regulatory Approval

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Nasdaq: MESO ASX: MSB

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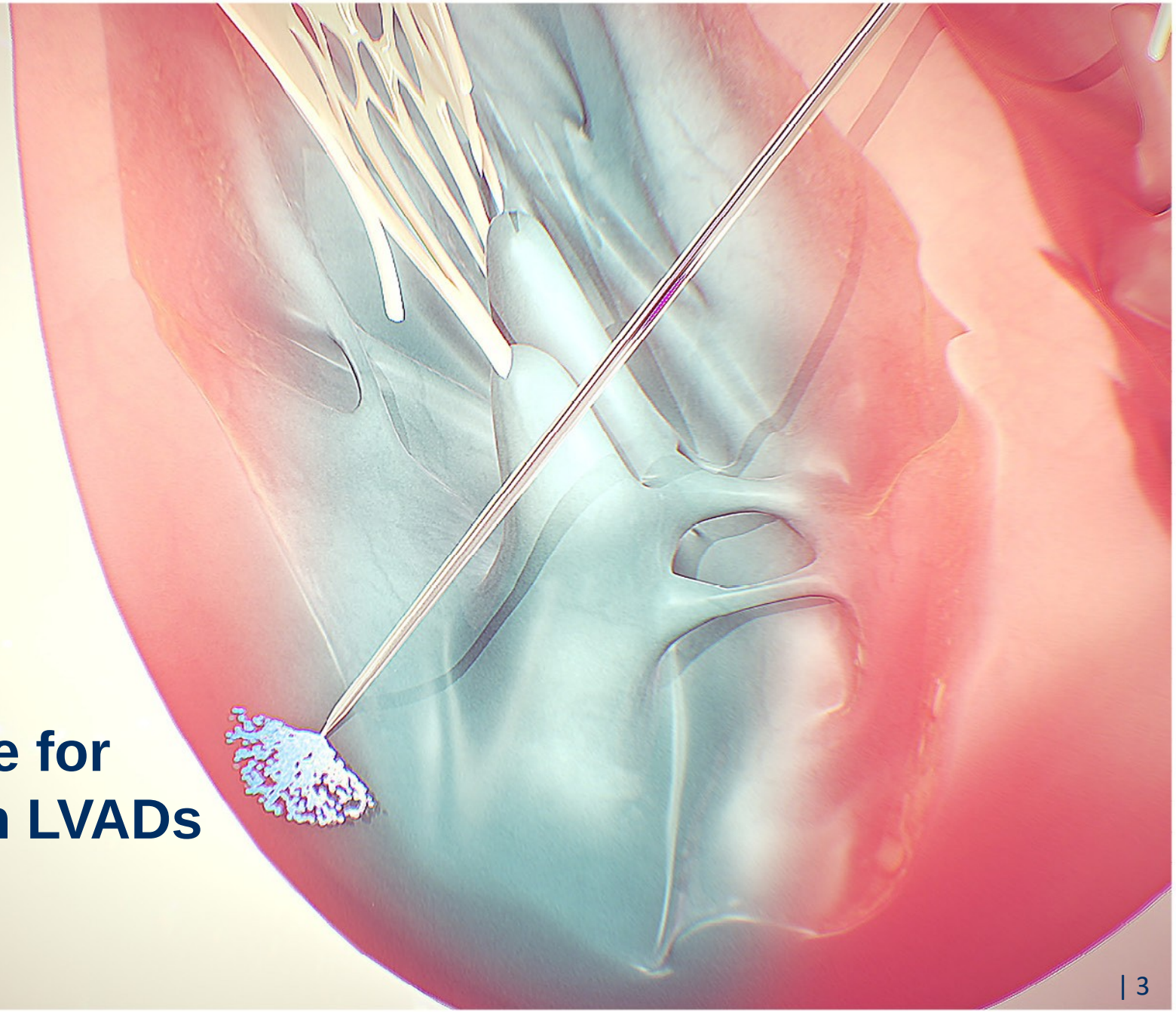
MPC-150-IM for End-Stage Heart Failure for Patients Implanted with LVADs



MPC-150-IM: Adjunctive Therapy to Improve Clinical Outcomes in LVAD Patients

Burden of Illness

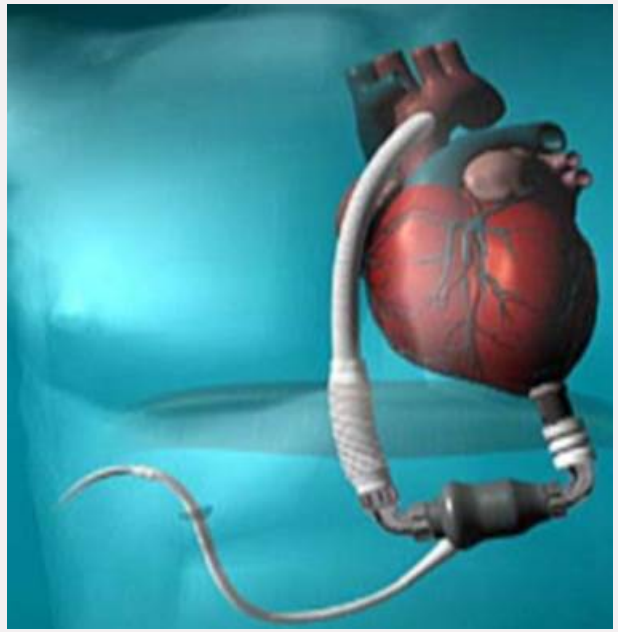
- In the USA, there are approximately 250,000–300,000 patients annually who suffer from advanced systolic heart failure (NYHA Class IIIb–IV). [1]
- Despite optimal medical therapy (excluding mechanical assist devices) Class IIIb have a one-year mortality >25% and exceeding 50% in class IV patients.[1]

Ongoing Unmet Need

- LVADs have improved survival, but high morbidity remains high with patients on average experiencing greater than two hospitalization annually.[2]
- Gastrointestinal (GI) bleeding is a leading cause of device attributable hospitalizations[2]
- **Device attributable major adverse events (DAEs) can cost on average from up to $46.5k per hospitalization[2]**

Market Opportunity

- ~4,500 – 5,500 assist devices are implanted annually in the Untied States.[3, 4]
- **US LVAD market is growing double-digit CAGR and represents > $500m market opportunity[3,4]**
- Orphan indication with US targeted commercial footprint provides low cost market entry



[1]Gustafsson G, Rogers J. (2017) Left ventricular assist device therapy in advanced heart failure: patient selection and outcomes, [2] Mehra, MR Salerno C, Cleveland JC (2018) Health care resources use and cost implications in the MOMENTUM 3 long-term outcome study: a randomized controlled trial of a magnetically levitated cardiac pump in advanced heart failure, [3]Agency for Healthcare Research and Quality – Healthcare Cost and Utilization Project – claims analysis using ICD-9 37.6 implantation of heart and circulatory assist systems, [4] Data on File

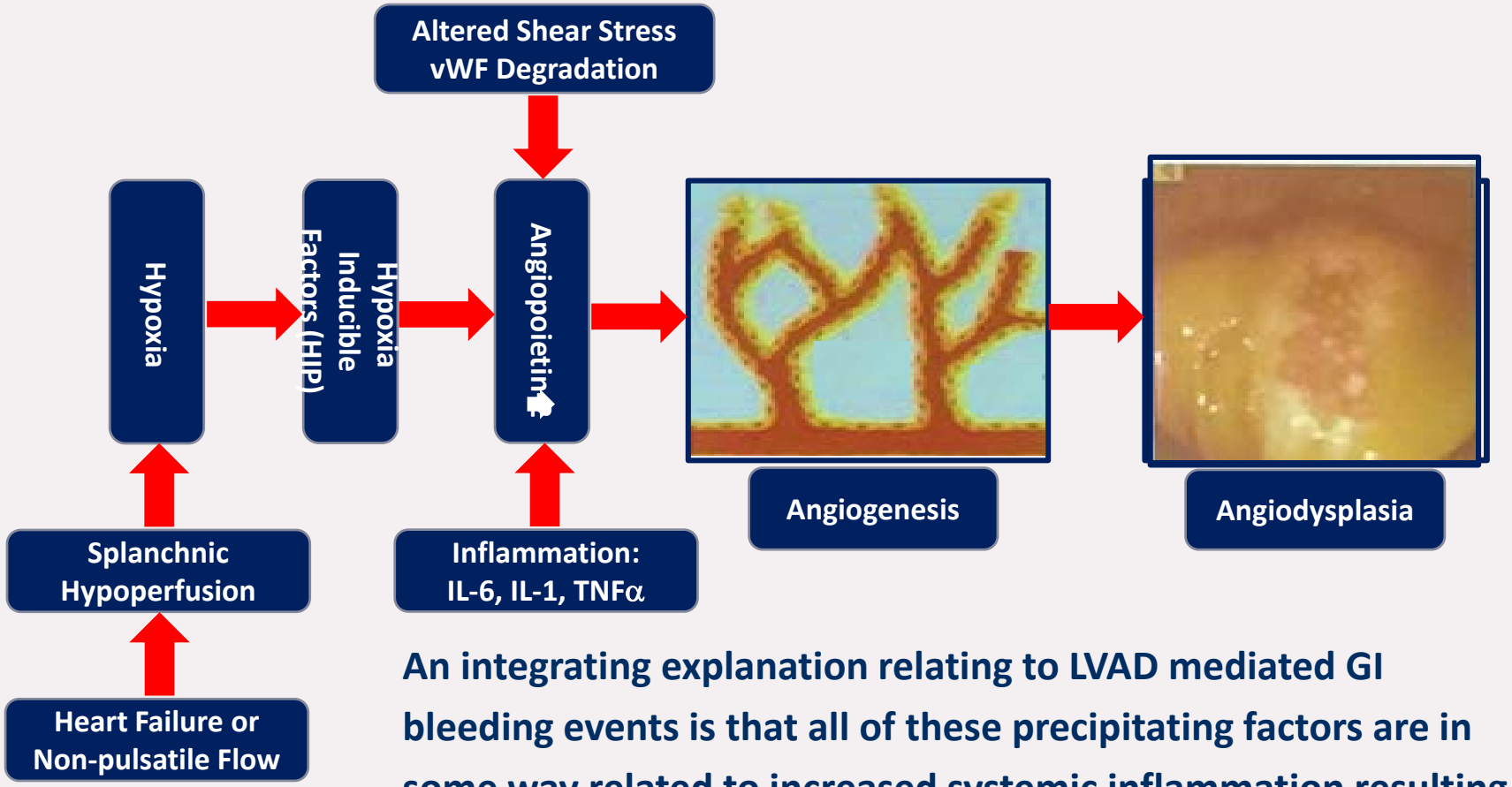
INTERMACS* Adverse Event Rates in LVAD Patients: Most Common Cause of Non-surgical Hospitalization is Major GI Bleeding[1]

Adverse Event	Events	Rate
Bleeding	4,420	7.79
Cardiac/vascular		
Right-sided heart failure	276	0.49
Myocardial infarction	34	0.06
Cardiac arrhythmia	2,303	4.06
Pericardial drainage	305	0.54
Hypertension	115	0.20
Arterial non-CNS thrombosis	94	0.17
Venous thrombotic event	286	0.50
Hemolysis	314	0.55
Infection	4,132	7.28
Stroke	916	1.61
Renal dysfunction	876	1.54
Hepatic dysfunction	326	0.57
Respiratory failure	1,551	2.73
Wound dehiscence	96	0.17
Psychiatric episode	525	0.93
Total burden	16,569	29.20

*Interagency Registry for Mechanically Assisted Circulation (INTERMACS): Events per 100 Patient-Months in the First 12 Months Post-Implant, based on 7,286 patients with CF-LVADs between 2012-2014.

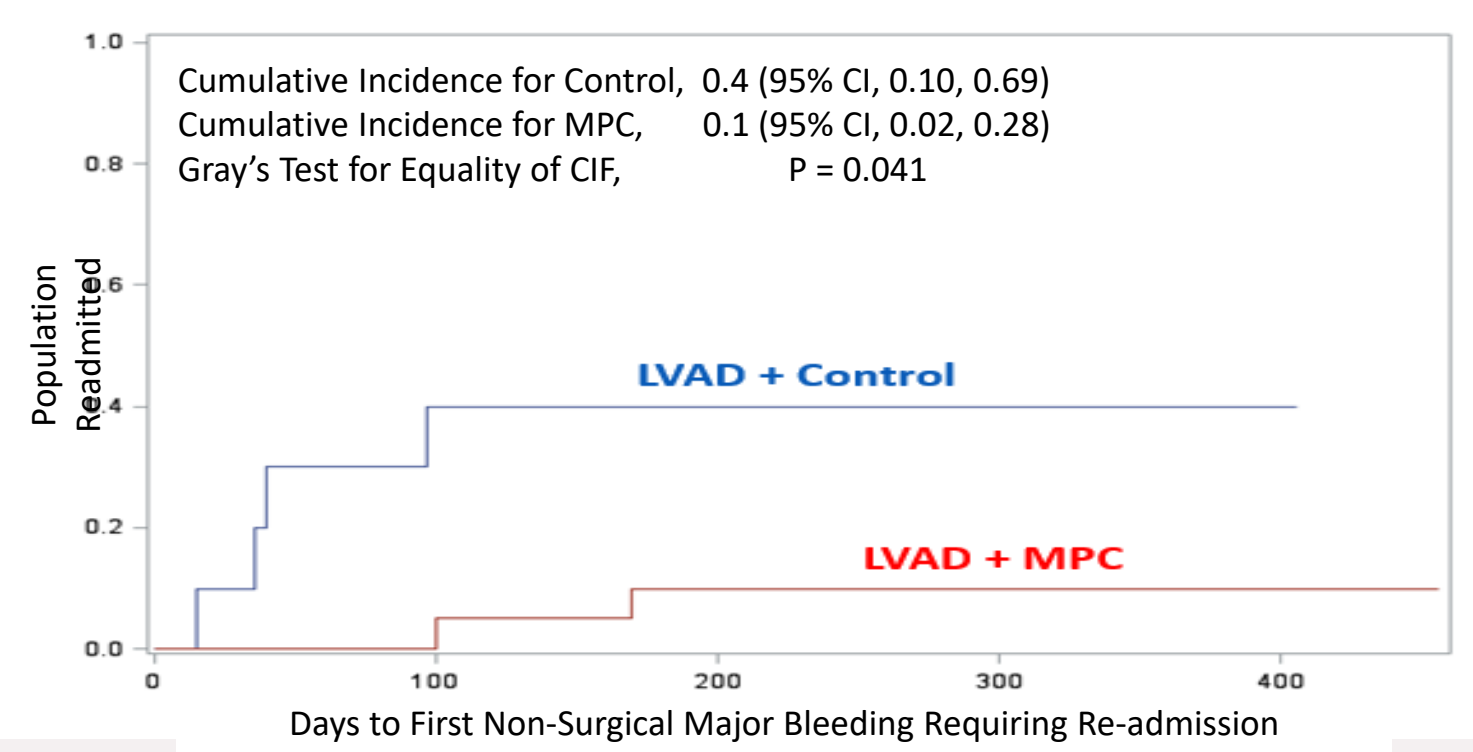
1.Left Ventricular Assist Devices for Lifelong Support Pinney SP, et al. JACC 2017;69:2845-61.

Proposed Pathway of Angiogenesis and Non-surgical GI Bleeding During CF-LVAD



An integrating explanation relating to LVAD mediated GI bleeding events is that all of these precipitating factors are in some way related to increased systemic inflammation resulting in increased serum levels of angiopoietin-2, a well-documented agent that causes vascular disruption and destabilization.

MPCs Reduced Major GI Bleeding in 30 Patient Pilot Trial[1]



- MPC group had significantly longer time to first hospitalization due to major GI bleeding ($p<0.05$, Kaplan-Meier statistics)
- 71% reduction in number of patients with at least one hospitalization from GI bleeding through 6 months (16% in LVAD group vs 55% in controls, $p=0.03$ by chi-square test)
- 70% reduction in rate of hospitalizations due to GI bleeding per 100 patient-months of follow-up (4.2 in LVAD group vs 14.2 in controls, $p=0.06$ by binomial test)

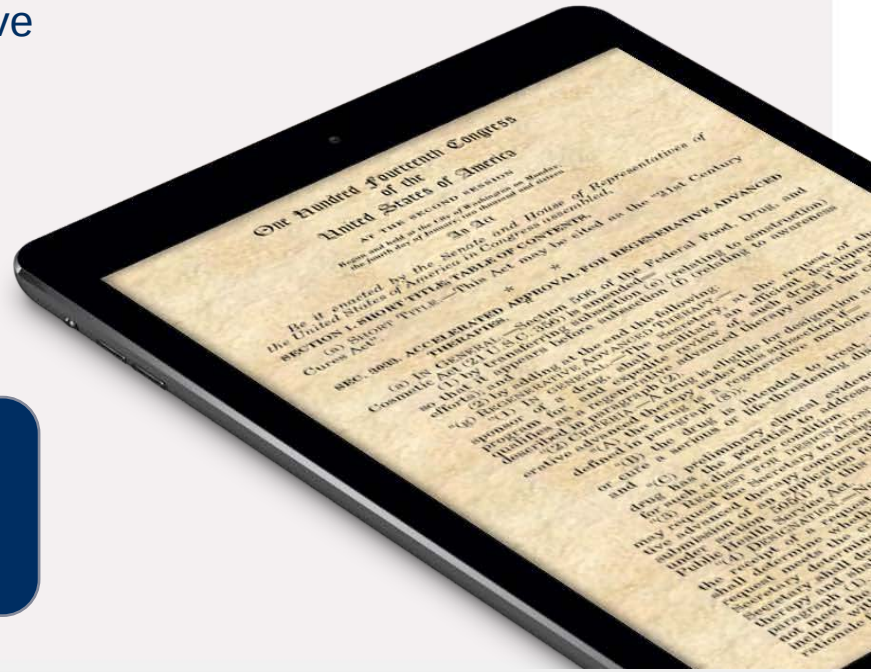
1. Source: Data on file.

The 21st Century Cures Act (Cures Act)

Legislation for An Expedited Approval Path for Cellular Medicines Designated as Regenerative Medicine Advanced Therapies (RMAT)

- Cellular medicines may be designated as regenerative advanced therapies, if they are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition, and there is preliminary clinical evidence indicating the potential to address the unmet medical need

- Key benefits of the legislation for cell-based medicines, designated as regenerative advanced therapies, include:
  - Potential eligibility for priority review and accelerated approval
  - Potential to utilize surrogate endpoints for accelerated approval
  - Potential to utilize patient registry data and other sources of "real world evidence" for post approval studies, subject to approval by the FDA



MPC-150-IM for End-Stage Heart Failure Patients with LVADs Received RMAT Designation

FDA Regulatory Interaction for MPC-150-IM using LVADs

December 2017	FDA grants RMAT designation for Mesoblast's novel MPC therapy for the treatment of heart failure due left ventricular systolic dysfunction of either ischemic or non-ischemic etiology in patients with LVADs. Based on pilot trial data that demonstrated: • Successful weans in MPCs compared to control • Reduction in hospitalization due to GI bleeding
June 2018	FDA meeting (Type B meeting) to discuss regulatory pathway for MPC-150-IM in an LVAD population. Feedback: 1. Non-surgical GI bleeding and/or epistaxis are clinically meaningful issues for patients with LVADs and represents an unmet clinical need 2. Temporary wean considered a biomarker and not a clinically meaningful outcome in and of itself – Weaning to explantation is a clinically meaningful outcome but it is a rare event and is limited to select center o Not clear that successful weans would reasonably predict explantation outcome o Concerns about interpretability of binary wean data 3. Need to show the adverse event, including allosensitization, and survival are not unfavorably affected by the MPC product 4. Need sufficient safety database for adverse event analysis of meaningful subgroups

Can MPCs Reduce GI Bleeding Complications in End-Stage Heart Failure Patients with LVADs?

Rationale

- Intra-myocardial injections of allogeneic MPCs may reduce myocardial and systemic inflammation
- MPCs improve coronary and systemic artery endothelial dysfunction in ovine systemic inflammation
- MPCs may reverse endothelial dysfunction in the heart and GI vascular beds in LVAD-related inflammation

2018 American Heart Association Scientific Sessions - *Late Breaking*

Objective and Target Population

Objective : To assess whether one-time injections of high dose MPCs into the native myocardium of LVAD recipients is safe and improves cardiac recovery

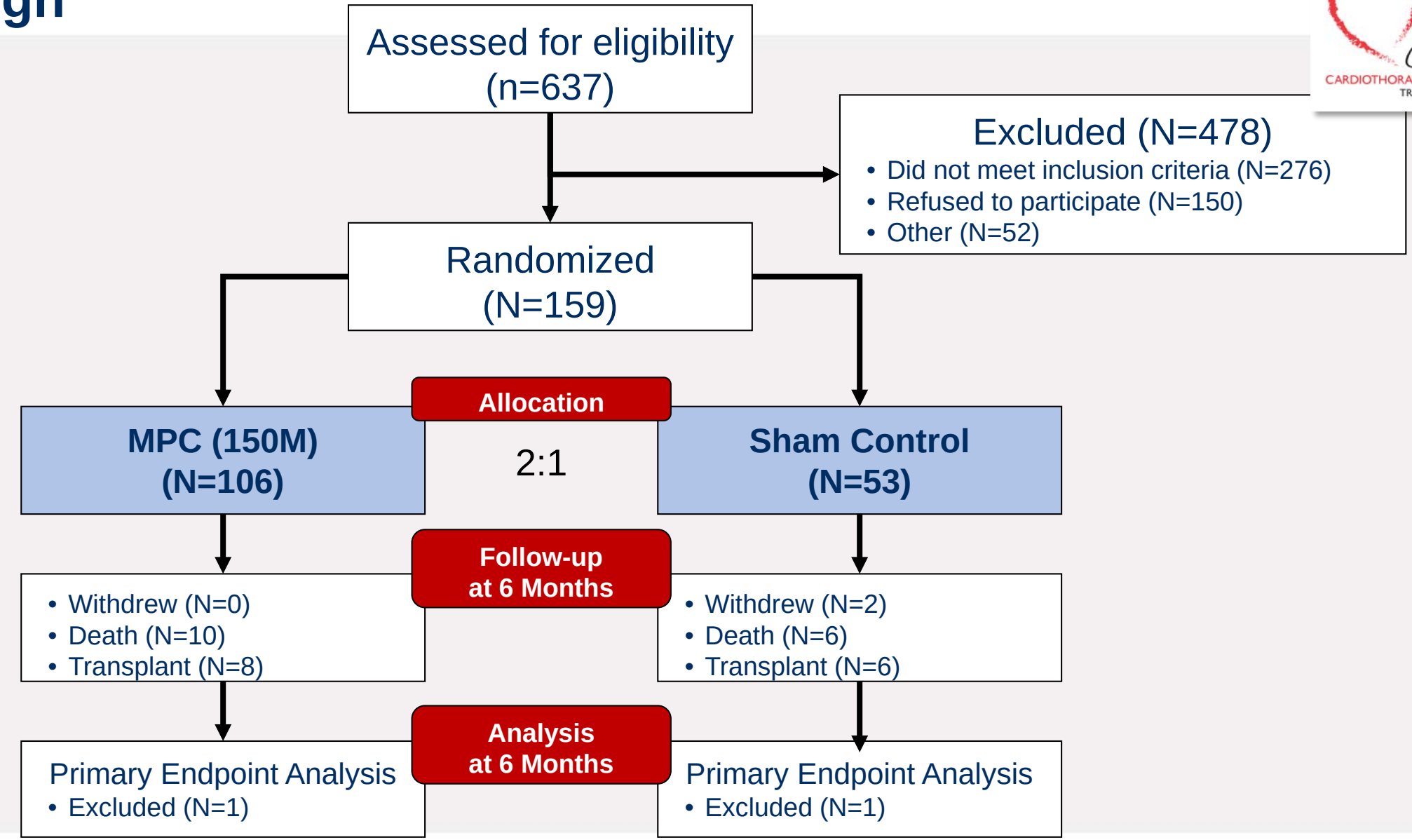
Inclusion Criteria

- Adults with advanced HF
  - Ischemic
  - Non-ischemic
- Scheduled for implantation of an FDA- or HC-approved LVAD for
  - BTT
  - DT

Exclusion Criteria

- Percutaneous LVAD or BV support
- Planned ablation or aortic valve intervention
- Recent CT surgery or prior cardiac Tx
- LV reduction surgery or cardiomyoplasty
- >10% anti-HLA antibody titers with known specificity to MPC-donor HLA antigens
- Prior cell therapy for cardiac repair

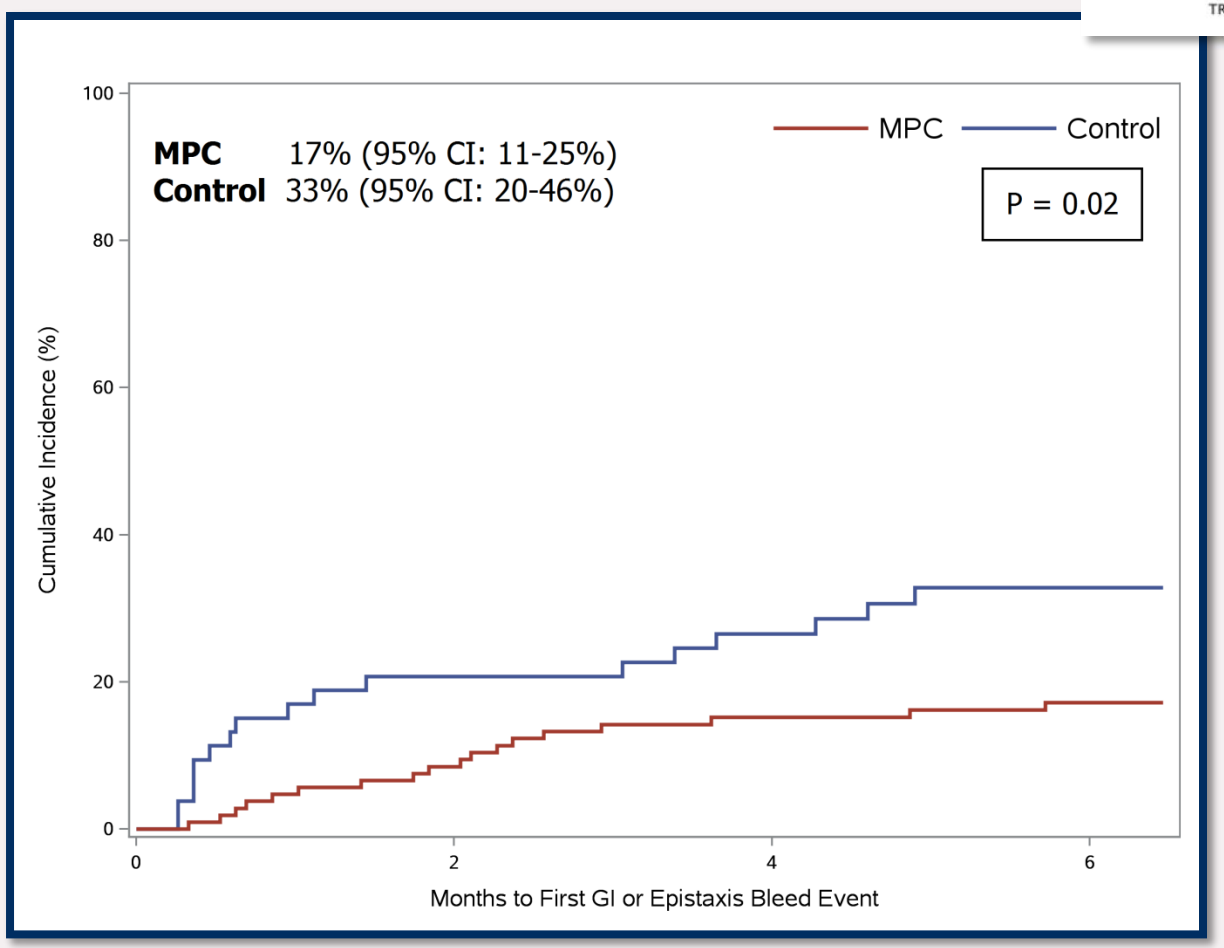
Trial Design



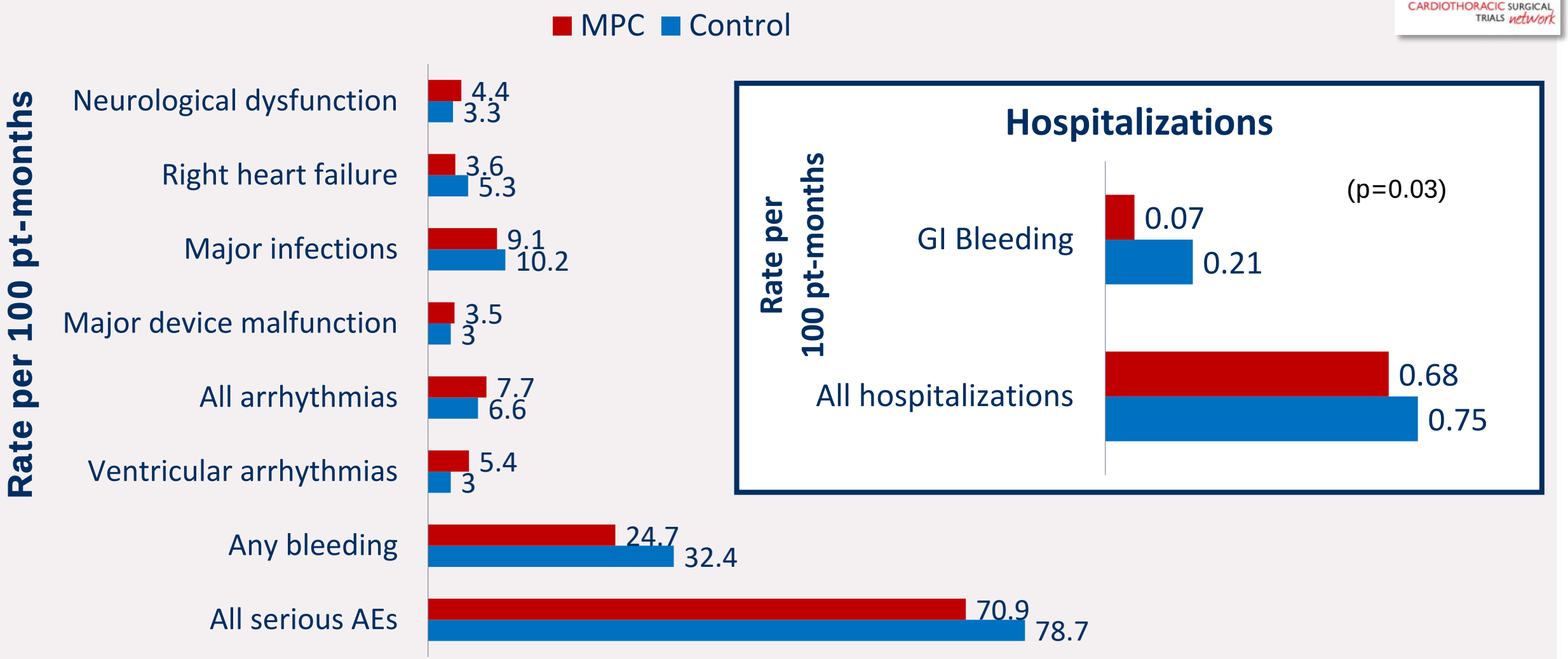
Mucosal Bleeding at 6 Months

Rate of GI/Epistaxis Bleeding

MPC (n = 106)	Control (n = 53)	P-value
Event Rate (100-Pt-Months)	Event Rate (100-Pt-Months)	
3.8	**15.9**	**<0.001**

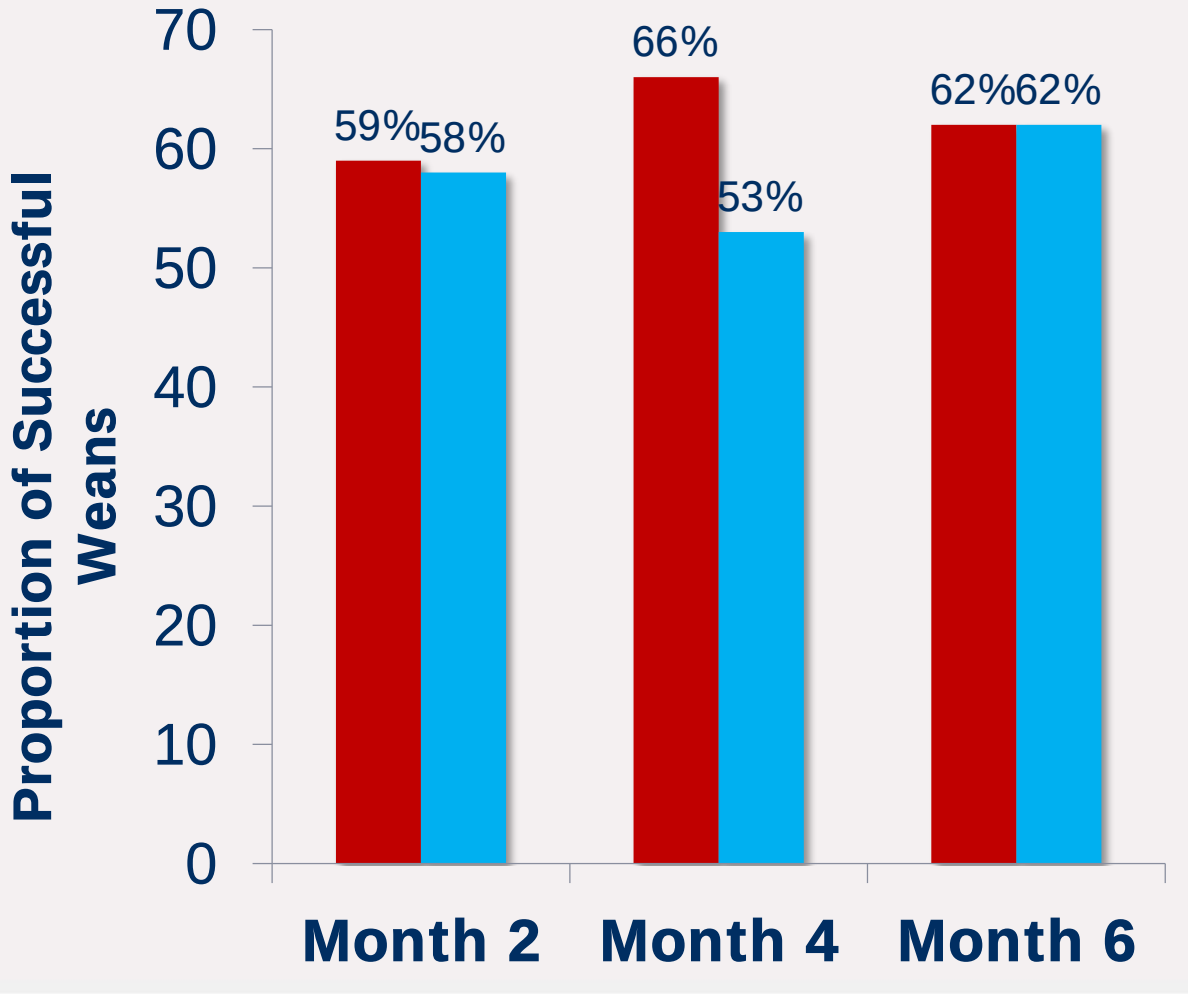


Serious AEs & Hospitalizations at 6 Months



Successful Temporary Weans from LVAD Support

- Average proportion of successful temporary weans:
  - **61% in MPC vs. 58% in control**
  - RR=1.08 (95% CI 0.83-1.41; p=0.55)
- Posterior probability that MPC increased likelihood of successful weaning:
  - **69%** (<80% pre-defined threshold)



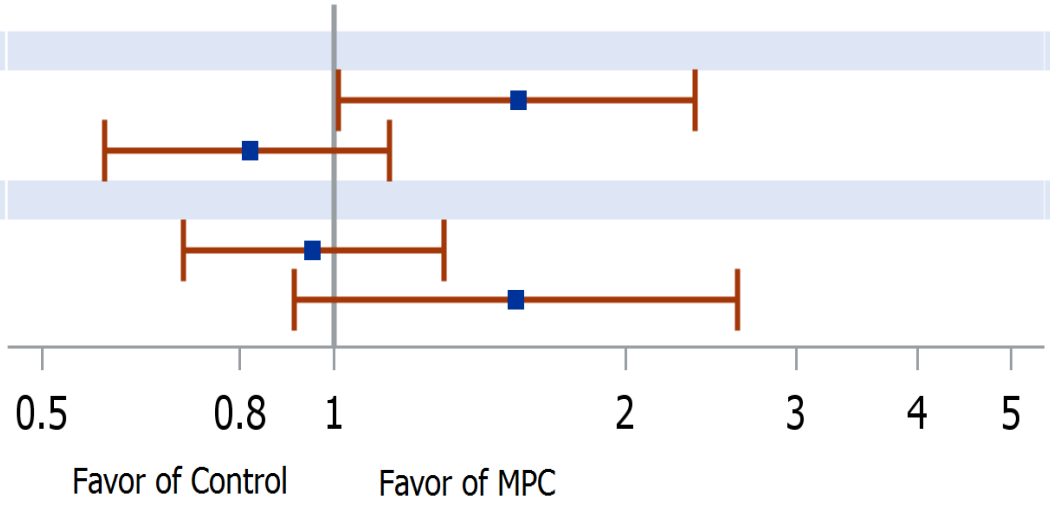
Limitations

- High rate of pump thrombosis reduced number of evaluable wean attempts
- Enrolled heterogeneous study population
  - Ischemic/non-ischemic HF, BTT/DT, 2 types of devices
  - Increased variability may have reduced likelihood of detecting Rx effect
- Although all bleeding events & transfusions were adjudicated, we did not routinely collect INR, platelets, and anticoagulation regimens

Exploratory Subgroup Analyses

Interaction of Rx and Pre-determined Subgroups on Wean Success Rate over 6 Months

Subgroup Analysis	Wean Rate Ratio (95% CI)	P-value for Interaction
Cardiomyopathy		0.02
Ischemic	1.55 (1.01, 2.36)	
Non-ischemic	0.82 (0.58, 1.14)	
Indication for LVAD		0.12
BTT	0.95 (0.70, 1.30)	
DT	1.54 (0.91, 2.61)	



Primary Safety Endpoint & Sensitization

- No patients developed a primary safety stopping event
- Allosensitization to Class I HLA antigens
  - 26% MPC vs 9.4% Control
  - Between-group difference: 16.5% (95% CI: 5 to 28%)
- Allosensitization to Class II HLA antigens
  - Similar in control and MPC patients at all time points

Conclusions

- Succeeded in achieving the FDA identified clinically meaningful outcome of reduction in GI bleeding and related hospitalization
- Results confirm the previous pilot trial, which also demonstrated significant reduction in GI bleeding and related hospitalization in MPC treated LVAD patients
- Company intends to meet with the FDA to provide full study data and discuss potential BLA filing
- While trial did not meet the overall primary endpoint of temporary weaning, MPC treatment did significantly improve weaning in ischemic patients
  - Weaning, in and of itself, is a biomarker and not a clinically meaningful outcome
- LVAD patients with ischemic heart failure closely resemble the majority of patients in DREAM-HF in terms of age and etiology; however, the LVAD patients are more advanced with end stage disease and have more severe endothelial dysfunction presenting as GI Bleeding

Acknowledgements

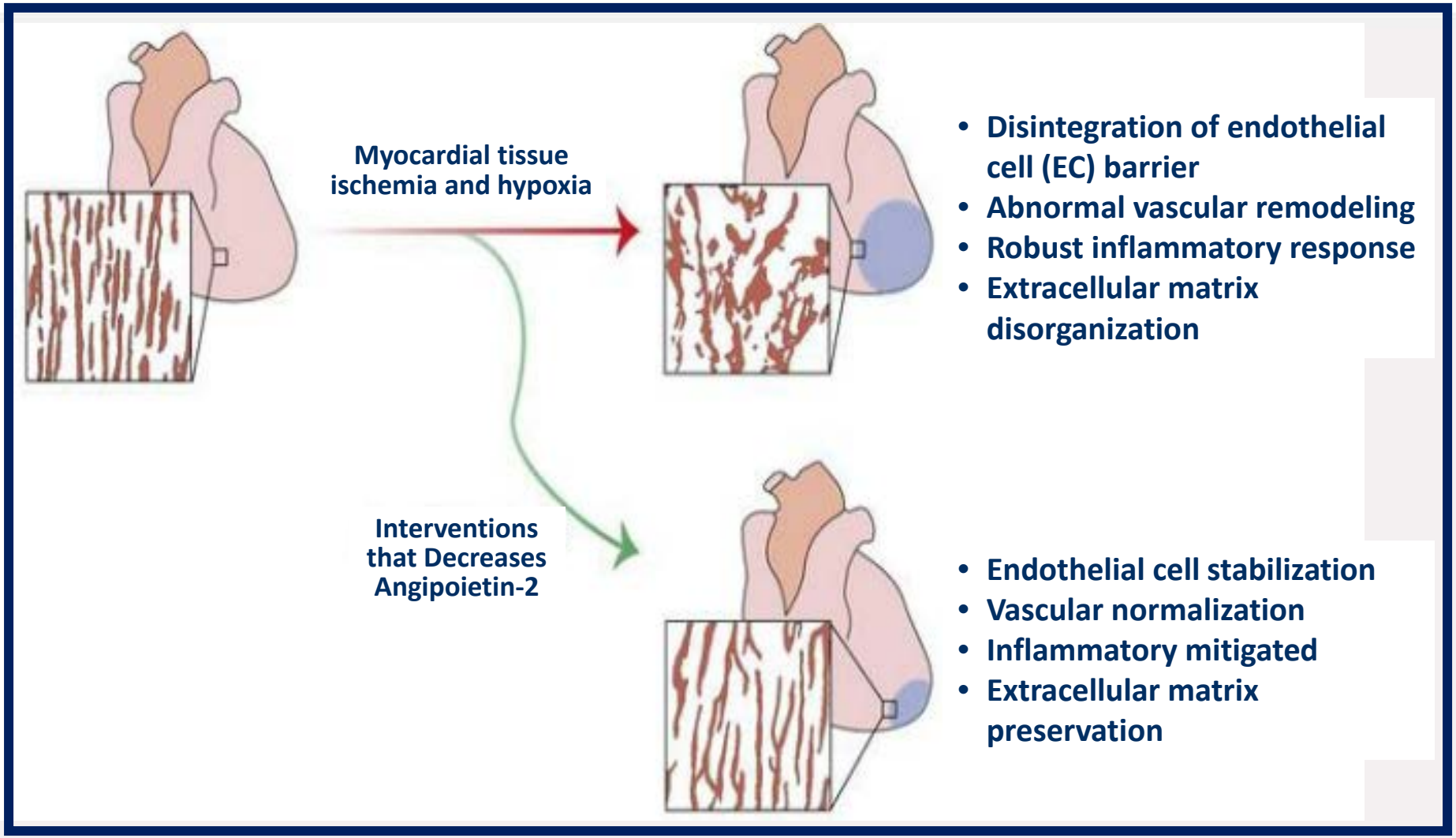
- This trial was supported by a cooperative agreement (U01-HL088942) funded by NHLBI and NINDS, of the National Institutes of Health (NIH), and the Canadian Institutes for Health Research (CIHR)
- Mesoblast provided MPCs and cryoprotective medium
- We would like to thank the patients, their families, doctors, nurses and research personnel for participating in this trial

Questions & Answers


Dublin
Zurich
New York
San Francisco
Hong Kong
Melbourne
ASX
Nasdaq

Appendix

Roles of Angiopoietin-2 in Exacerbating Cardiac Hypoxia and Inflammation in Association with Myocardial Ischemia

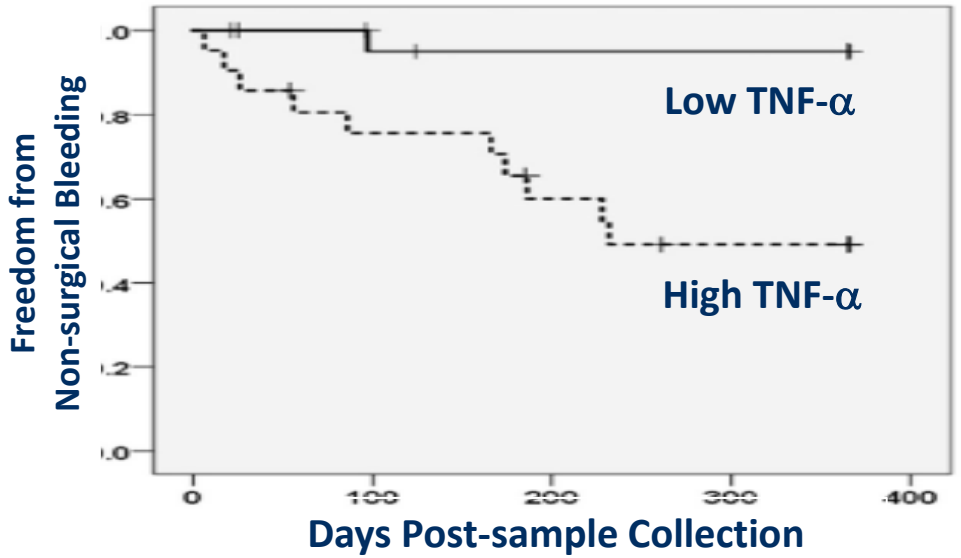


Source: Modified from Lee SJ, et al. Angiopoietin-2 exacerbates cardiac hypoxia and inflammation after myocardial infarction. J Clin Invest 2018:128:5018-5033

Effects of CF-LVAD on TNF-α, ANG-2 and ANG-1 on GI Bleeding

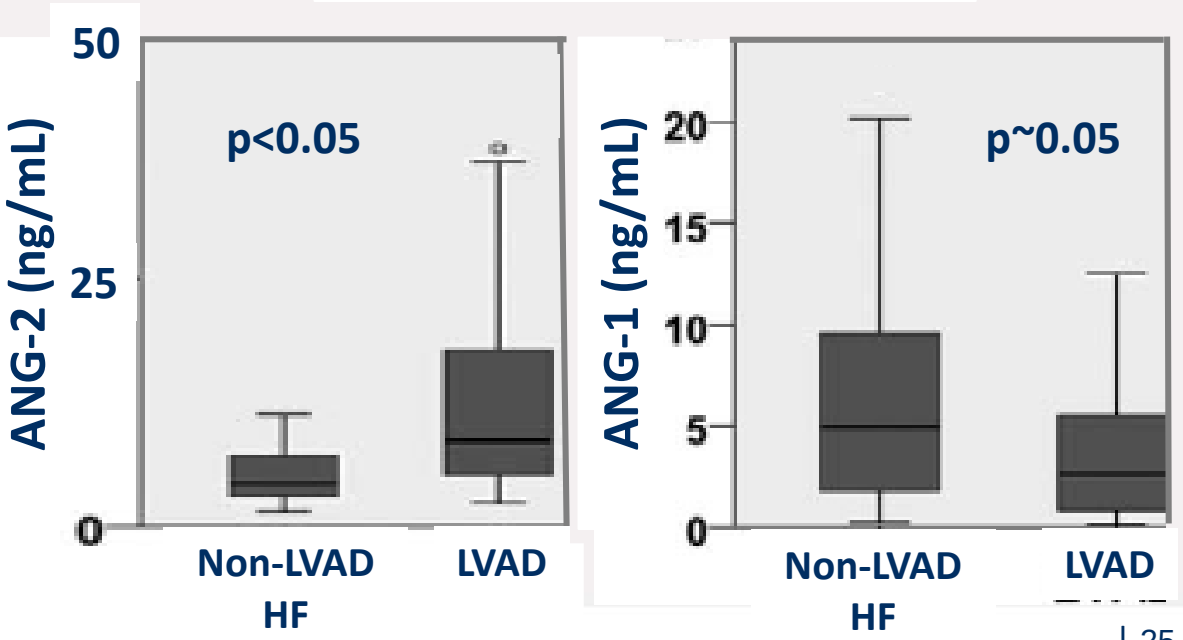
TNF-α in CF-LVAD Patients[1]

- Elevated TNF-α level is a key regulator of altered angiogenesis, pericyte apoptosis and expression of tissue factor
- High TNF-α levels are associated with increased risk of non-surgical bleeding, predominantly GI in origin



ANG-2 and ANG-1 In CF-LVAD Patients[2]

- ↑ANG-2 and ↓ANG-1 levels occur compared to non-LVAD HF patients
- ↑ANG-2 level is associated with higher rate of non-surgical bleeding, predominantly GI in origin



1. Tabit CE, et al. J Heart Lung Transplant 2018;37-107-115
2. Tabit CE, et al. Circulation 2016;134:141-152

MPCs Improve Coronary Artery Endothelial Dysfunction In A Sheep Model of Systemic Inflammation

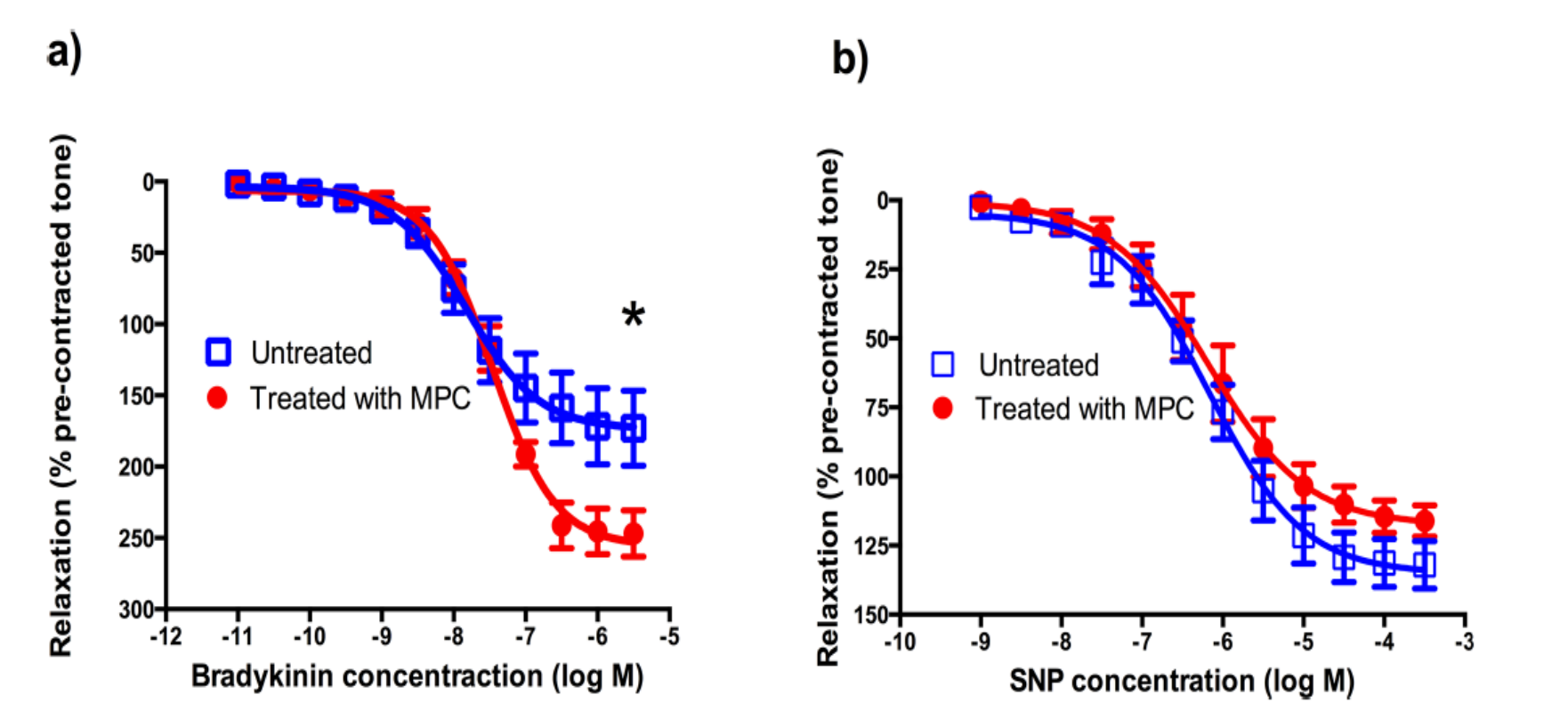
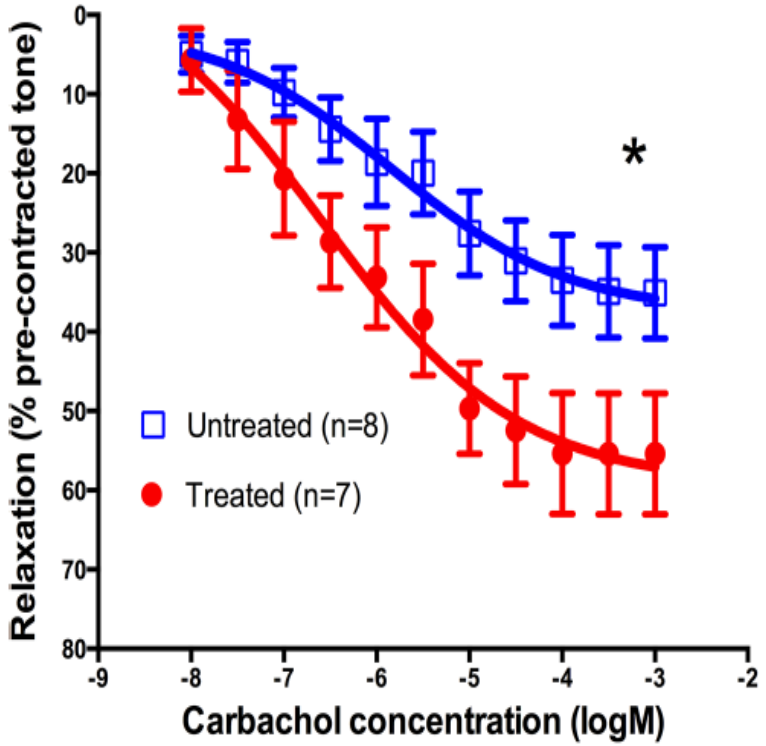


Fig 3. Comparison of vasorelaxation in ovine coronary arteries in arthritic sheep treated and untreated with mesenchymal precursor cells (MPC). Arterial rings were contracted with endothelin-1, and relaxation responses to cumulatively increasing concentrations of (A) Bradykinin (BK), (B) Sodium nitroprusside (SNP), were expressed as a percentage relaxation of pre-contracted tone. Each point represents the mean ±SEM from 8 animals. * Indicates statistically significant difference ($p < 0.05$) in the maximum response for the dilation to bradykinin between treated and untreated animals (see Table 1).

Source: Dooley et al. Effect of MPCs on the systemic inflammatory response and endothelial dysfunction in an ovine model of collagen-induced arthritis. PLOS One, May 7, 2015.

MPCs Improve Digital Artery Endothelial Dysfunction In A Sheep Model of Systemic Inflammation



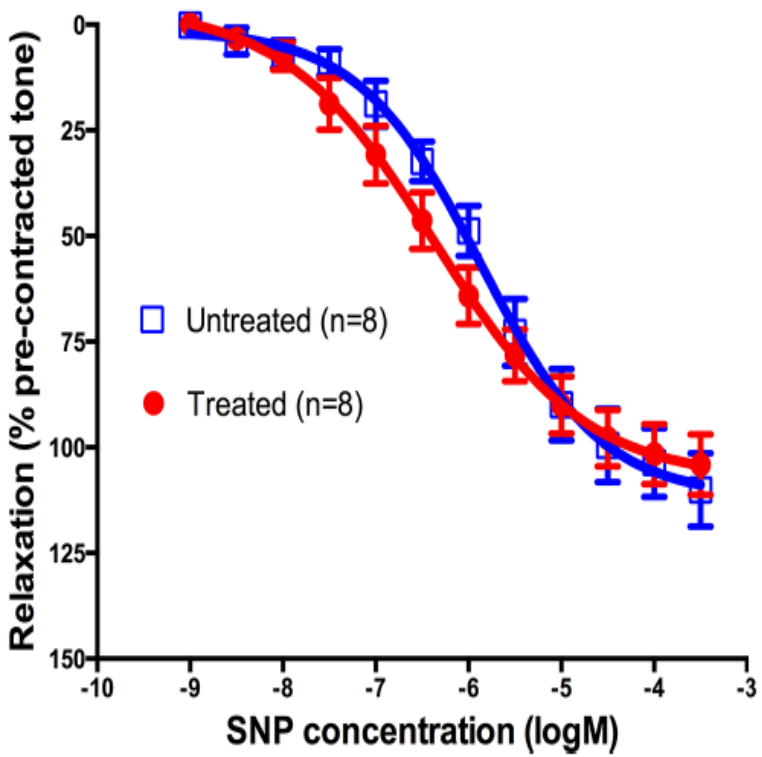


Fig 4. Comparison of vasorelaxation in ovine digital arteries in arthritic sheep treated and untreated with mesenchymal precursor cells (MPC). Arterial rings were contracted with 5-hydroxytryptamine (5-HT), and relaxation responses to cumulatively increasing concentrations of (A) Carbachol and (B) Sodium Nitroprusside (SNP) were expressed as a percentage relaxation of pre-contracted tone. Each point represents the mean ±SEM from 7–8 animals. * Indicates statistically significant difference ($p < 0.05$) in the maximum response for the dilation to carbachol between treated and untreated animals (See Table 2).

Source: Dooley et al. Effect of MPCs on the systemic inflammatory response and endothelial dysfunction in an ovine model of collagen-induced arthritis. PLOS One, May 7, 2015.