mesoblast

DREAM HF Trial: Rexlemestrocel-L (MPCs) in the Treatment of Heart Failure with Reduced Ejection Fraction (HFrEF)

Presentation at the 18th Global CardioVascular Clinical Trialists Forum (CVCT), Washington DC

DECEMBER 2021

ASX: MSB; Nasdaq: MESO

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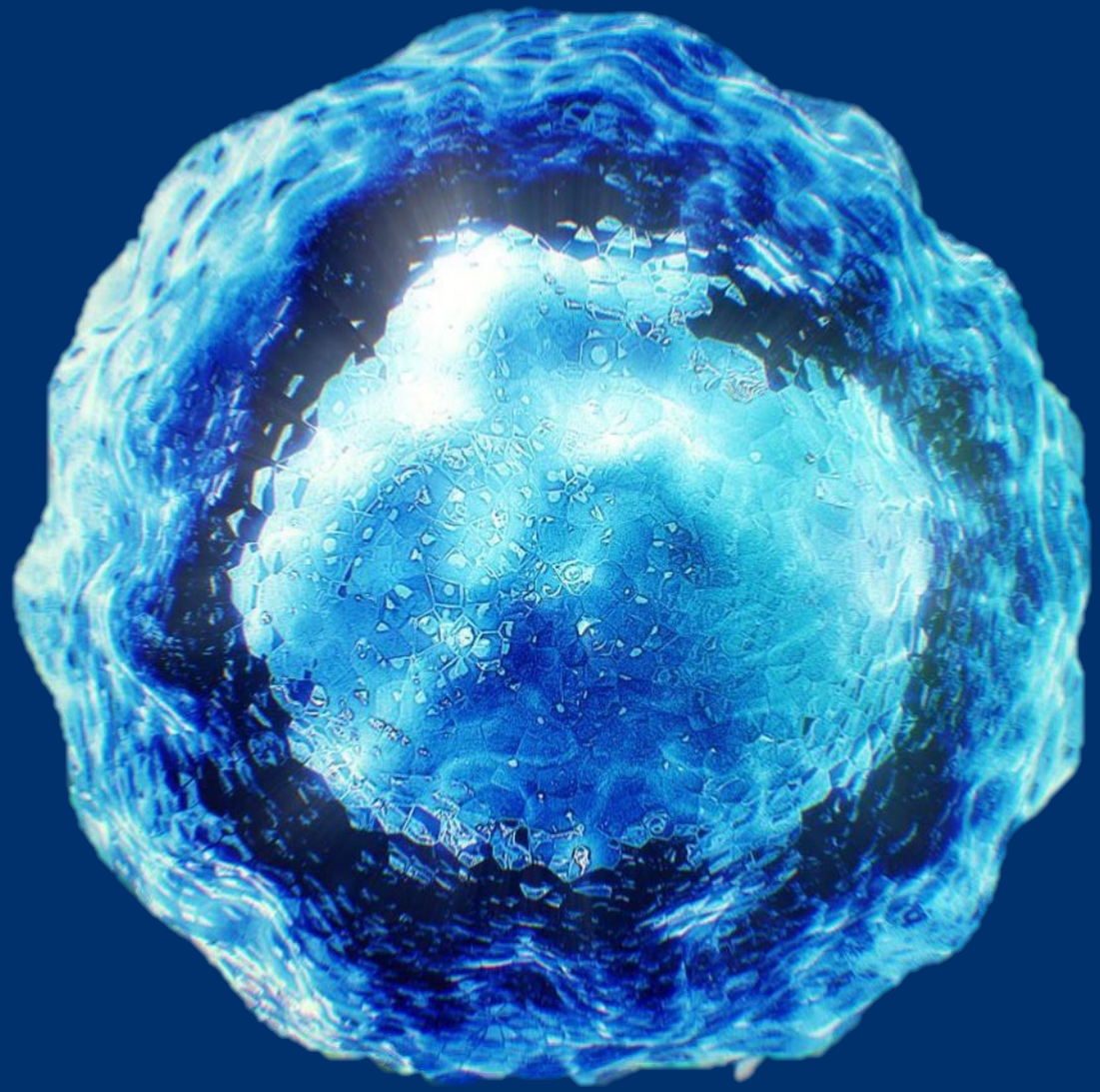
Our Mission

Mesoblast is committed to bringing to market innovative cellular medicines to treat serious and life-threatening illnesses



Chronic Heart Failure: Rising Incidence & High Mortality

- Cardiovascular disease (CVD) remains the leading cause of death in the United States[1]
- Heart failure affects 6.5 million patients in the US and 26 million patients globally. As populations age, the prevalence is increasing[2]
- Chronic heart failure is a progressive disease with a high mortality that approaches 50% at 5 years[2,3], and at least 75% after an initial hospitalization[4]
- Patients with heart failure are also at high risk of recurrent major adverse cardiac events involving large vessels (heart attacks / strokes)

New therapies for chronic heart failure reduce recurrent hospitalizations due to cardiac decompensation, however they do not materially improve cardiac mortality or major ischemic events (heart attacks/strokes)

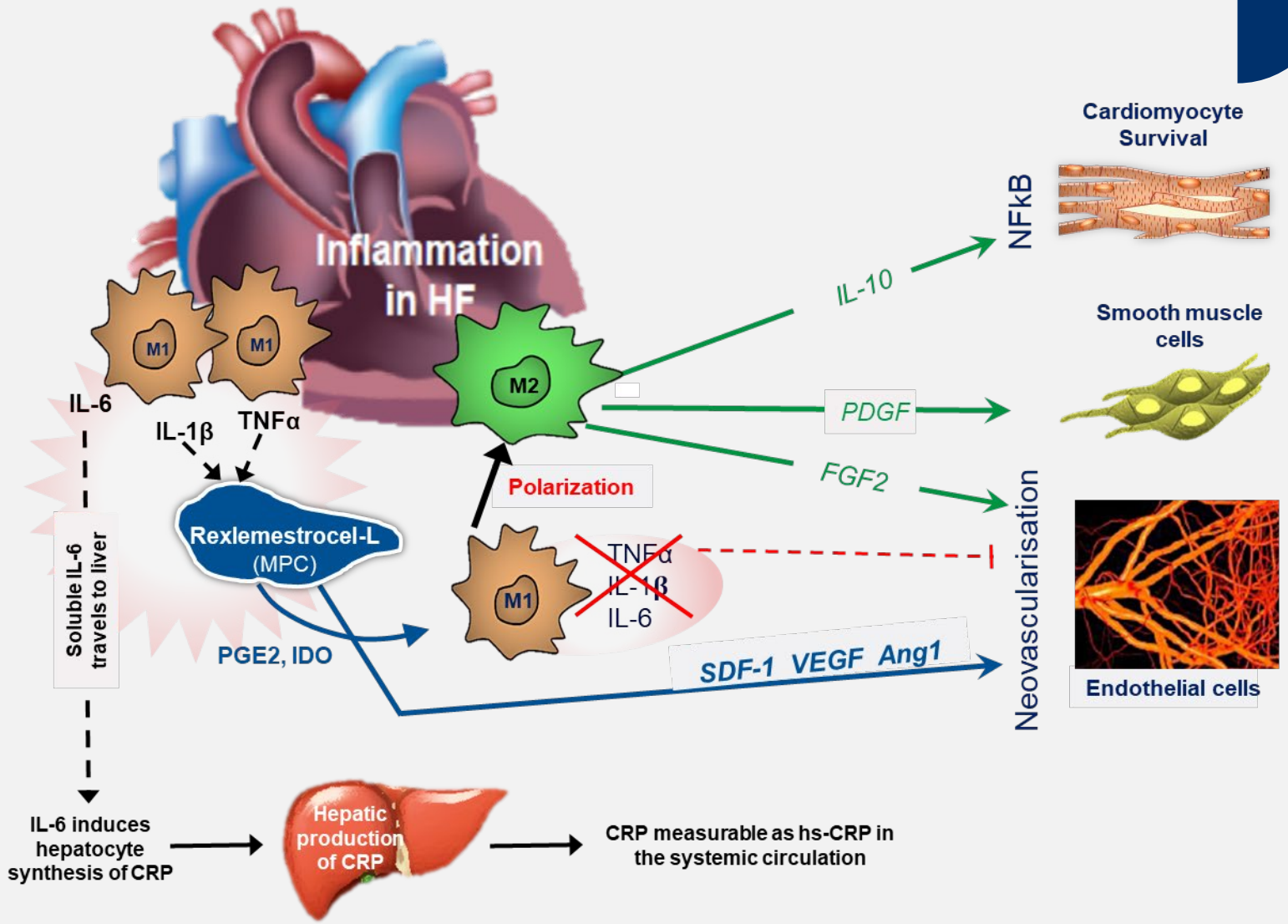
1. Muntner BEJ, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation.* Feb 19, 2019. 2. United States Food & Drug Administration. Treatment for Heart Failure: Endpoints for Drug Development. Draft Guidance. June 2019. 3. Taylor CJ, et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population-based cohort study. *BMJ.* 2019;364:l223. 4. Shah KS, et al. Heart Failure with Preserve, Borderline, and Reduced Ejection Fraction; 5-Year Outcomes. *JACC*. 2017;Nov12.

Proposed Mechanism of Action of Intra-Cardiac MPC Administration in Treatment of both Heart Failure & Large Vessel Atherosclerosis

Mesenchymal precursor cells (MPC) key mechanisms of action thought to beneficially impact the heart and the systemic vasculature:

- Reduction in cardiac and systemic inflammation
- Reversal of endothelial dysfunction
- Induction of microvascular network within viable heart muscle
- Reduction in heart muscle death

hs-CRP synthesized in the liver is the systemic consequence of intra-cardiac IL-6 production



Modified from Borow KM, Yaroshinsky A, Greenberg B, Perin E. Phase 3 DREAM-HF Trial of Mesenchymal Precursor Cells in Chronic Heart Failure: A Review of Biological Plausibility and Implementation of Flexible Clinical Trial Design. *Circ Res.* 2019;125:265-281

DREAM-HF Trial: Overview

Key Inclusion Criteria

- 18 to ≤80 years of age
- **NYHA class II / III, LVEF ≤ 40%**
- Receiving **optimal medical therapies for heart failure** at stable and tolerated doses for at least 1 month before study intervention
- No option for percutaneous coronary intervention or coronary artery bypass graft surgery
- Enrichment criteria:
  - **At least 1 heart failure hospitalization** or **outpatient visit** requiring intravenous diuretic, vasodilator, and/or positive inotropic therapy >1 month but ≤9 months before initiation of screening procedures and/or
  - Plasma levels of **NT-pro-BNP** >1000 pg/mL (>1200 pg/mL for patients with atrial fibrillation)

Trial Design

- Prospective, randomized, double-blind, sham controlled
- 1:1 randomization: Single administration procedure of 150 million allogeneic MPC delivered by transendocardial image-guided injection vs sham-control procedure
- All medical therapies for heart failure continued for all patients
- 565 randomized patients; 537 received treatment
- Mean patient follow-up 30 months
- Prospective adjudication by treatment-blinded independent Clinical Endpoints Committee (CEC) of all Major Adverse Cardiovascular Events (MACE) including potential Cardiovascular death, cardiac deaths or non-cardiac vascular deaths

Clinically Significant Endpoints in Persistent HFrEF

Pre-Specified Endpoints

1. Mortality (cardiovascular death, all-cause cardiac death, cardiac death from pump failure)

2. Irreversible Morbidity (non-fatal myocardial infarction, non-fatal cerebrovascular accident)

3. Non-fatal Decompensated HFrEF Morbidity Events (non-fatal hospitalization or urgent care treatment for decompensated HFrEF &/or successfully resuscitated cardiac death associated with high-grade ventricular arrythmias)

3-Point Composite MACE Endpoint

4. Irreversible Morbidity or Mortality: IMM (cardiovascular/cardiac death, or non-fatal MI, or non-fatal stroke)

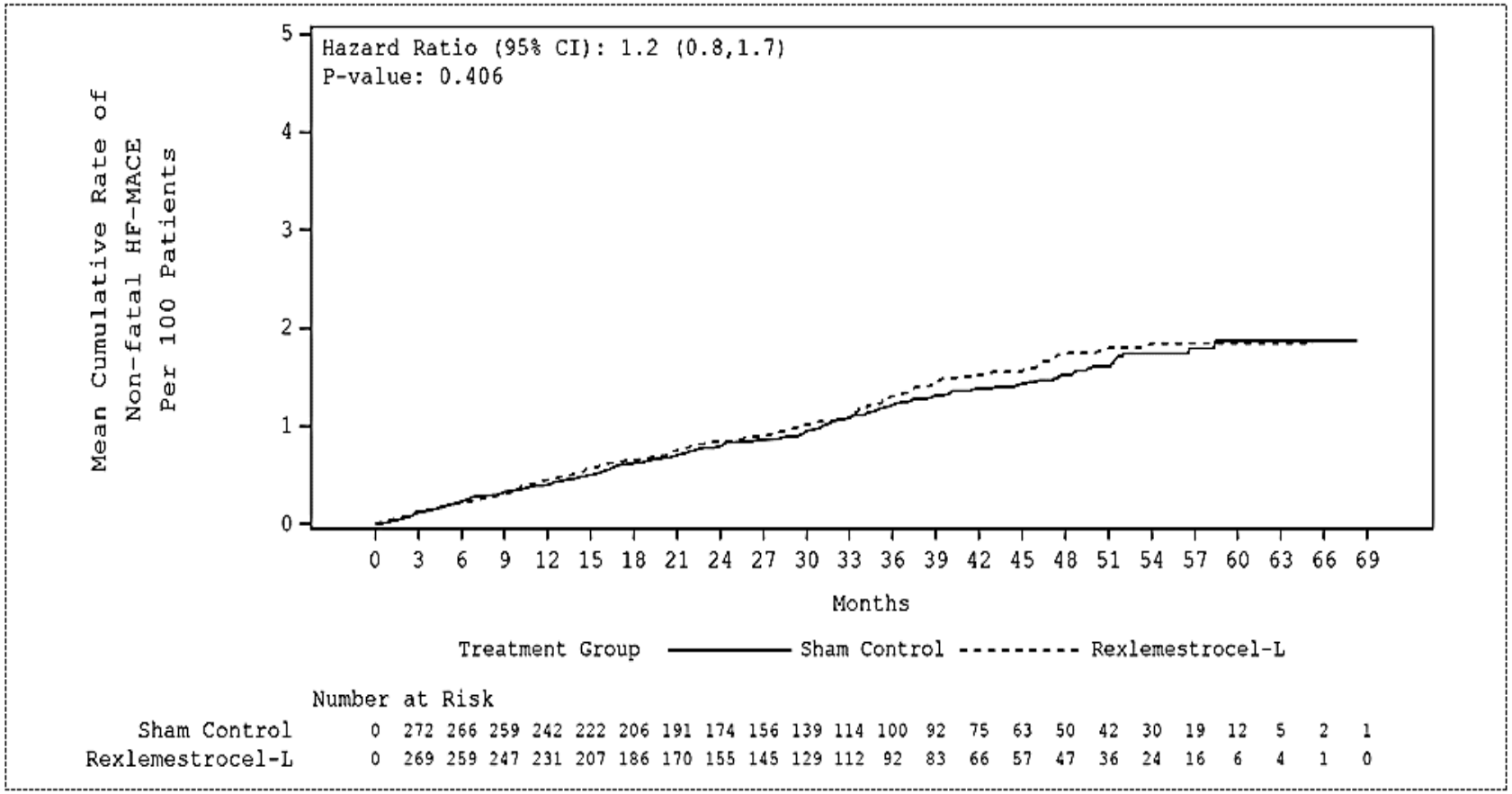
NOTE: Adjudication of all deaths in DREAM-HF trial (including CV, all-cause cardiac, or non-cardiac) was prospectively performed by the treatment-blinded independent Clinical Endpoints Committee (CEC) at the Brigham & Women's Hospital using pre-specified causal categories, defined in the study's Adjudication Operations Manual.

Rexlemestrocel-L Did Not Further Reduce Frequency of Hospitalization for Worsening HF Symptoms Over Maximal Standard of Care

All Patients (n=537)

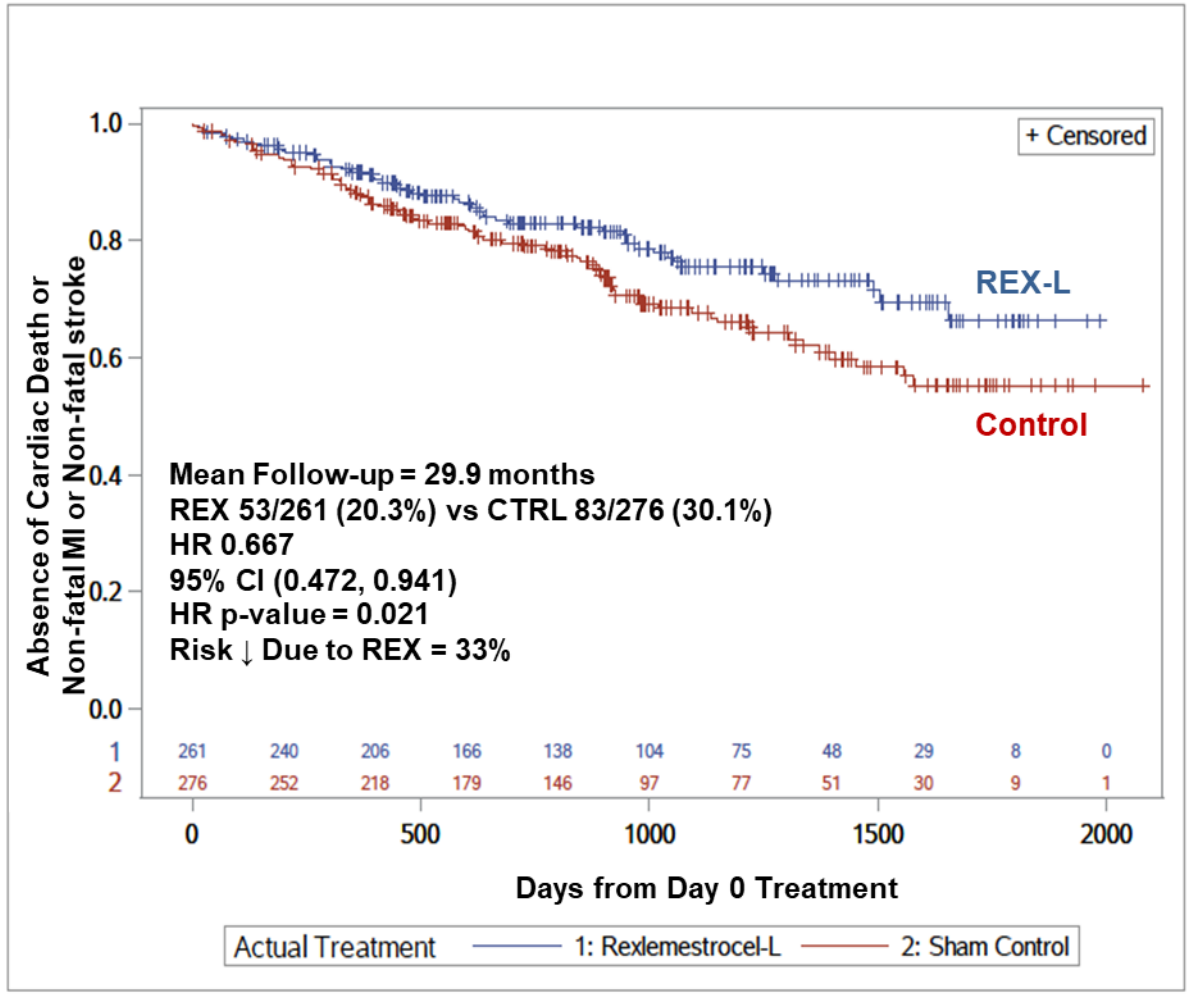
HR: 1.2

p=0.4



Rexlemestrocel-L Reduced Incidence of 3-Point Composite MACE (CV Death, MI or Stroke) Compared to Controls Across All 537 Treated Patients

Time-to-First-Event for Cardiovascular Death or Non-fatal MI or Non-fatal Stroke



Evaluation of Rexlemestrocel-L on 3-Point IMM MACE in Pre-Specified Patient Populations With Reproducibly High-Risk for Poor Outcomes:

72% of total treated population (n=537)

Greatest Treatment Effect in Patients with Micro- or Macro- Vascular Disease (Myocardial Ischemia and/or Diabetes)

Pre-Specified Patient Subset	Number of Patients	Hazard Ratio	95% Confidence Interval	
Myocardial Ischemia &/or Diabetes	**385**	**0.63**	**0.434, 0.928**	***P = 0.019***
Myocardial Ischemia[1]	303	0.66	0.436, 0.988	*P = 0.044*
Diabetes[2]	231	0.66	0.400, 1.094	*P = 0.108*
HF hospitalization within prior 1-9 months	330	0.66	0.414, 1.048	
Prior Myocardial Infarction	280	0.70	0,452, 1.069	
NT-proBNP >1000	365	0.74	0.505, 1.083	
LVESV >100 mL	431	0.75	0.517, 1.073	
LVEF <30%	299	0.77	0.508, 1.116	

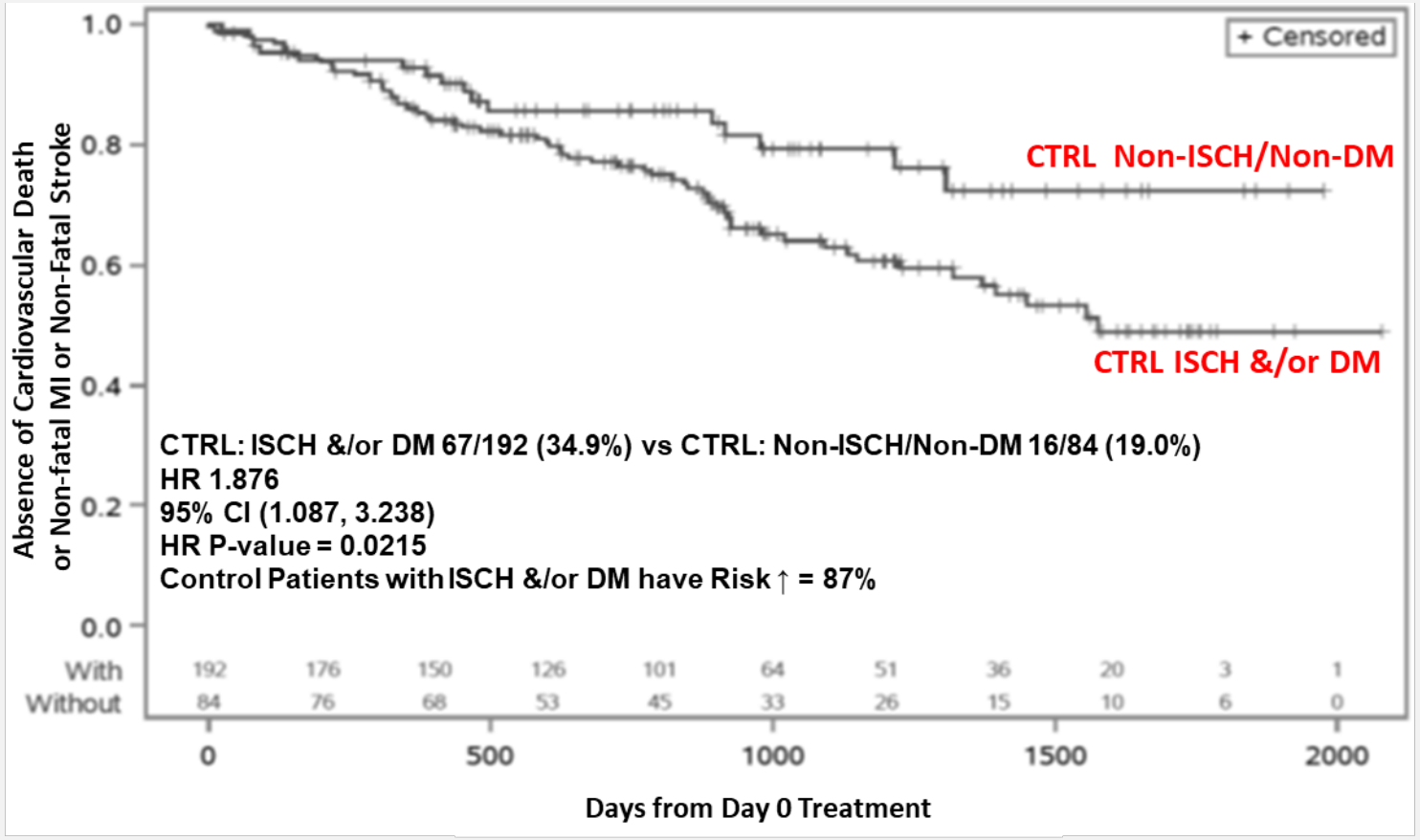
[1] Chronic HF of ischemic etiology includes epicardial CAD, defined as documented stenosis of at least 50% in one or more major epicardial coronary arteries, documented prior coronary artery revascularization, and/or documented prior MI

[2] Diabetes includes patients with end-organ involvement due to microvascular disease

Myocardial Ischemia &/or Diabetes in Control Patients in DREAM-HF Trial Identifies Subgroup with Worse Outcomes, as Measured by 3-Point IMM MACE, than other HFrEF Controls

3-Point TTFE Composite IMM MACE (n=276 Control Patients)

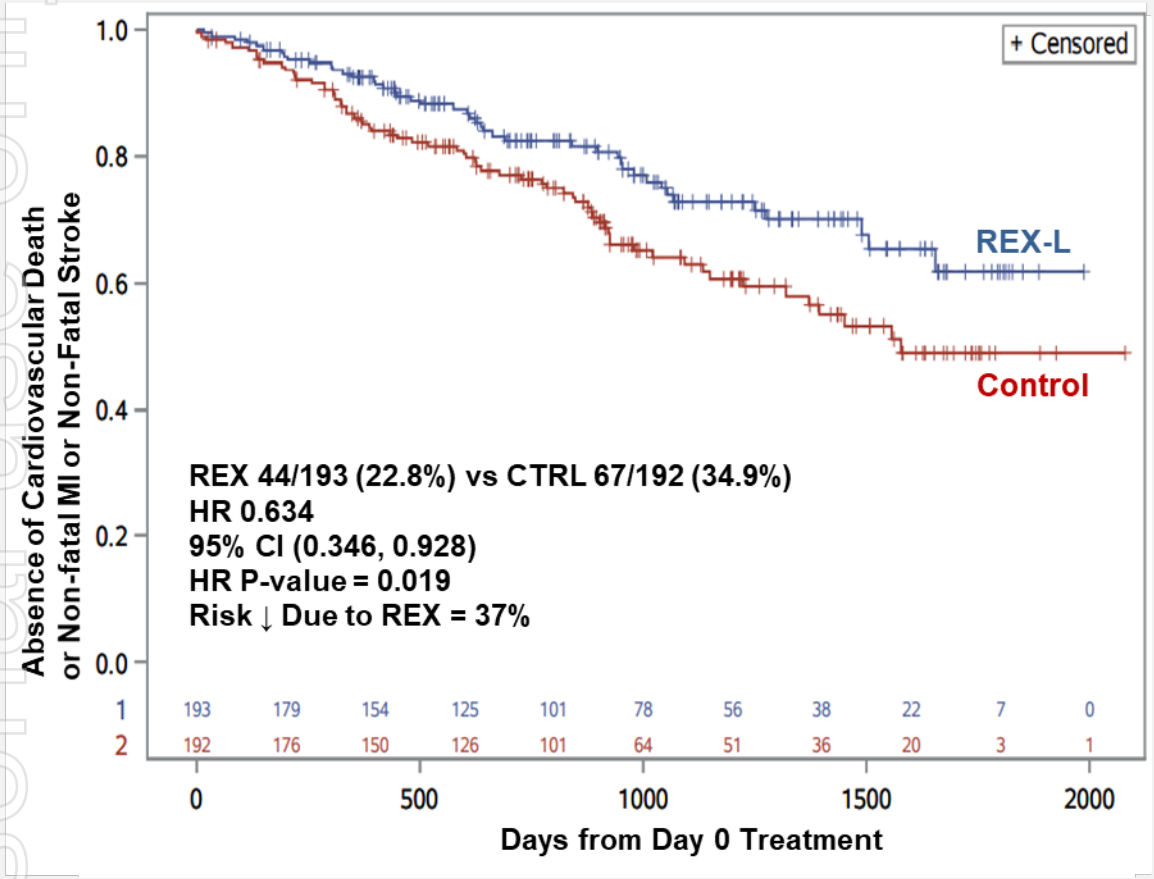
Myocardial Ischemia &/or Diabetes (n=192) vs. Non-Ischemia/Non-Diabetes (n=84)



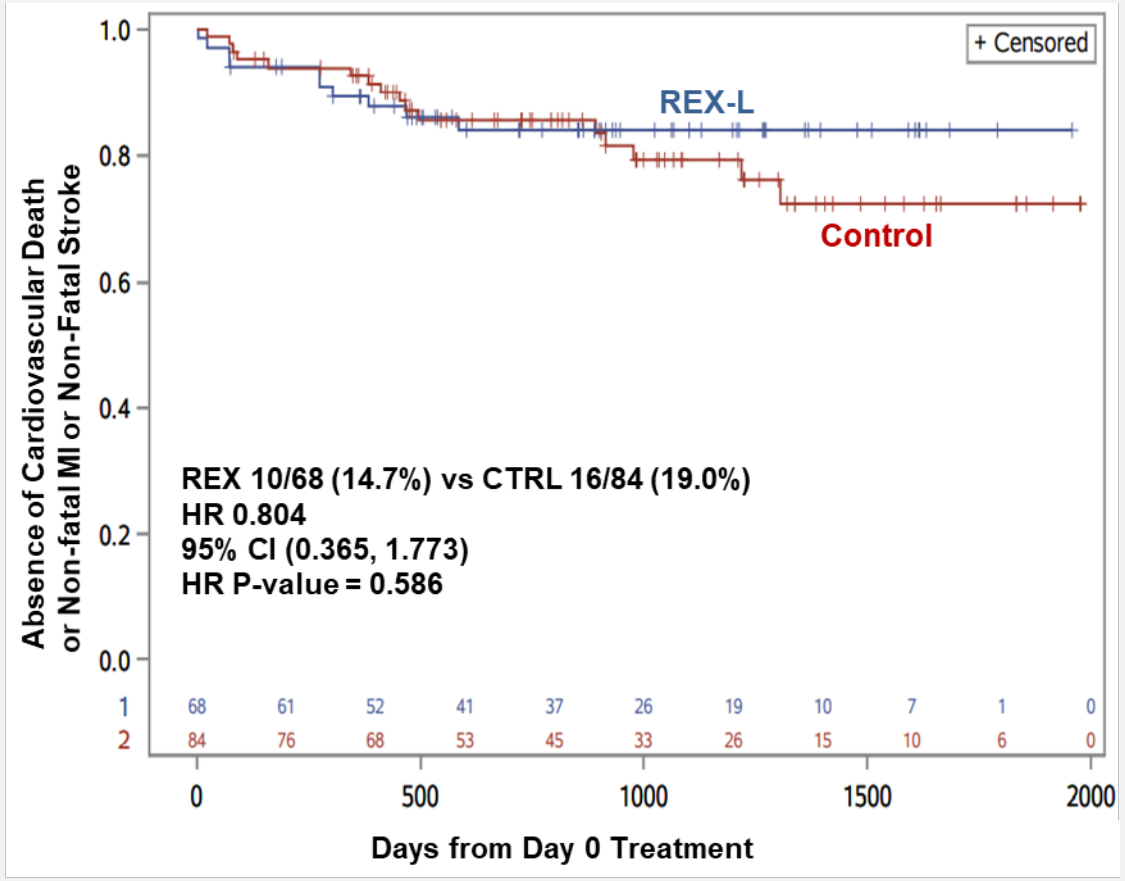
Kaplan-Meier log rank statistics

Rexlemestrocel-L Reduced Risk of 3-Point TTFE Composite IMM MACE in High-Risk Patients with Myocardial Ischemia &/or Diabetes by 36%

Ischemic &/or Diabetic Patients (n=385)



Non-Ischemic/Non-Diabetic Patients (n=152)



Kaplan-Meier log rank statistics

Pre-Specified Hypotheses

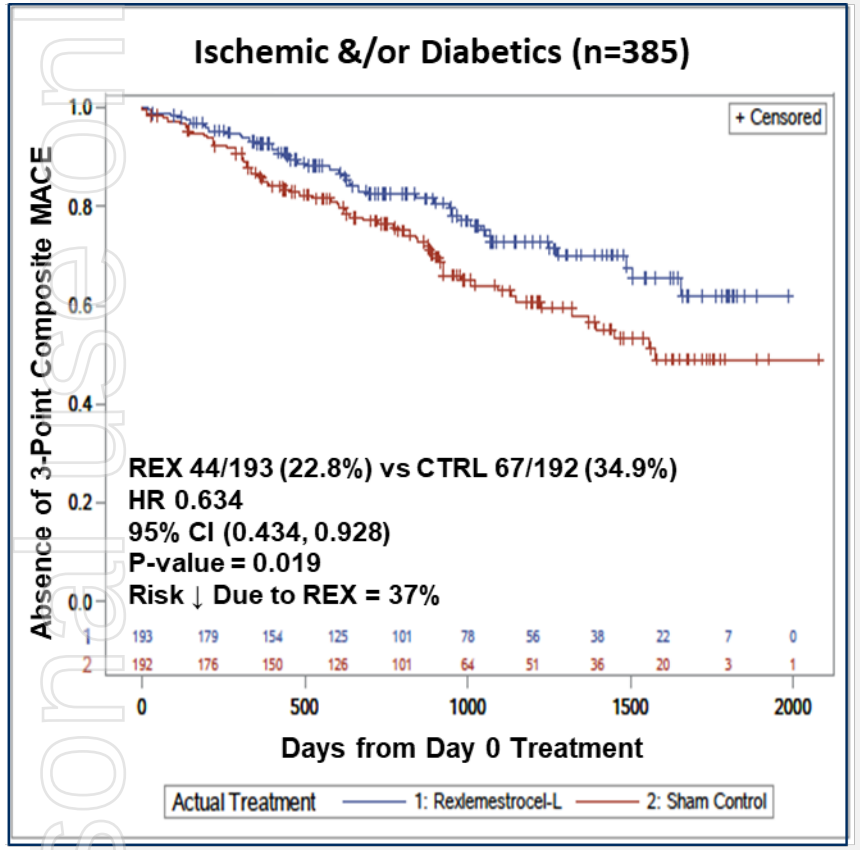
- **hs-CRP** is a validated biomarker for risk of vascular disease, accelerated atherosclerosis, myocardial infarction, and heart failure severity
  - Cut-points of <2mg/L, ≥ 2 mg/L, ≥ 3mg/l, and ≥ 4mg/L were pre-specified for sensitivity analyses in the DREAM-HF SAP
  - Values for hsCRP ≥2 mg/L have previously been used as a threshold for systemic inflammation in cardiovascular disease patient populations, including heart failure[1]

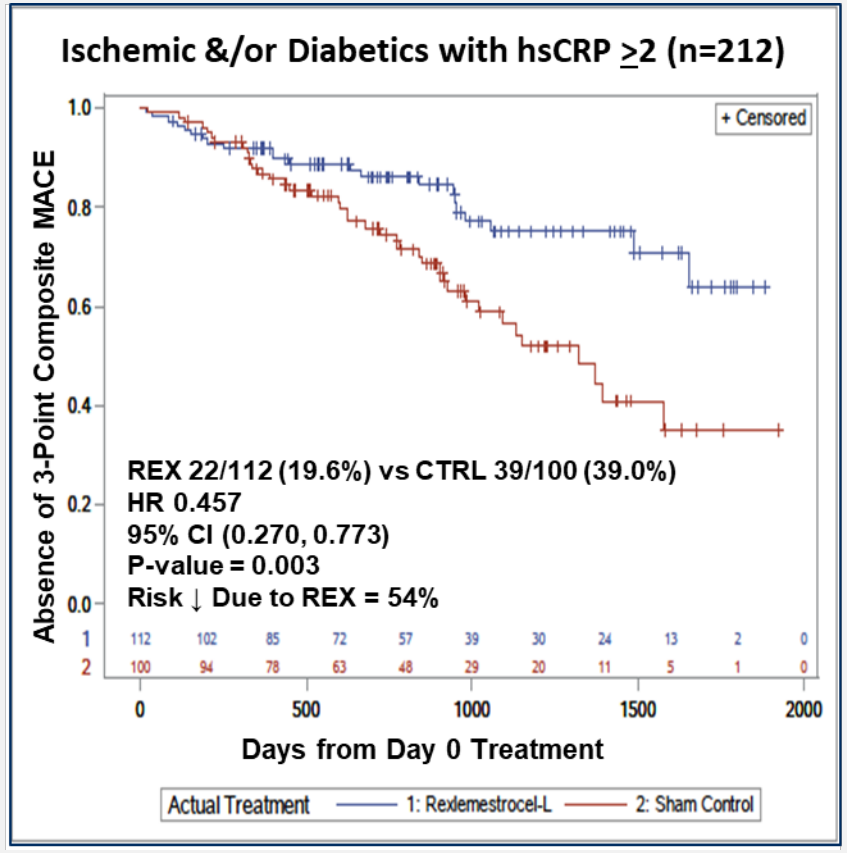
- **High levels of hs-CRP may:**
  - Be circulating biomarkers to identify those patients with evidence of inflammatory etiology to their HFrEF
  - Identify those HFrEF patients most likely to respond to the anti-inflammatory effects of rexlemestrocel-L treatment
  - Identify those HFrEF patients with micro- or macro-vascular disease who may be most likely to benefit from rexlemestrocel-L therapy

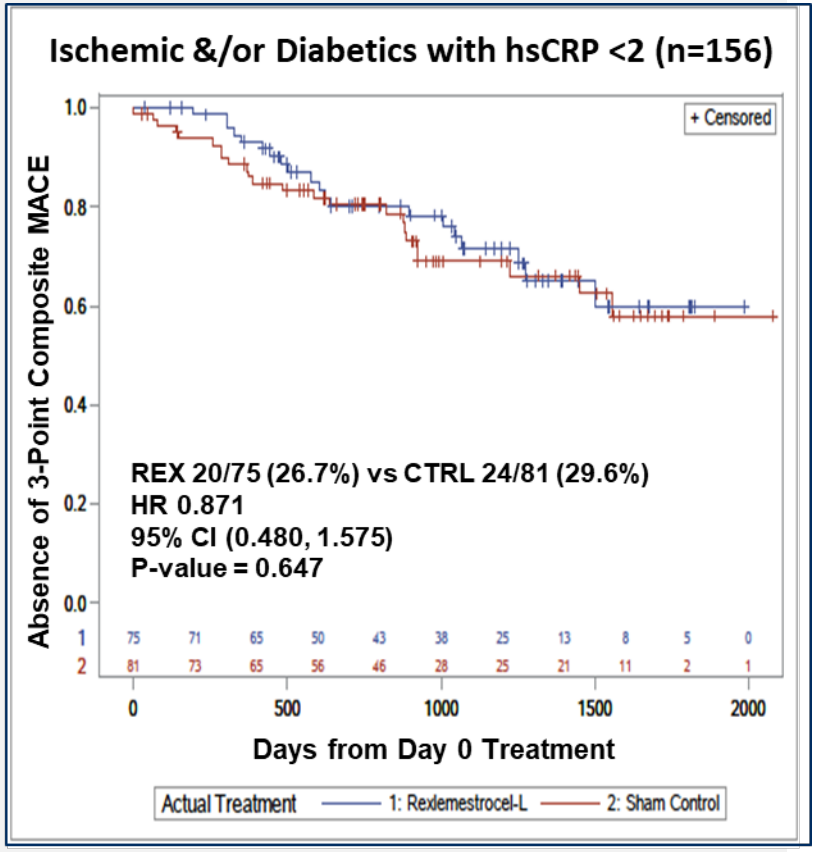
[1]Pellicori P, Zhang J, Cuthert J, et.al. High sensitivity C-reactive protein in chronic heart failure: patient characteristics, phenotypes, and mode of death. Cardiovasc Res 2020;116:91-100

Composite 3-Point MACE and Inflammation

In Patients with Myocardial Ischemia and/or Diabetes with hsCRP≥2 mg/L Rexlemestrocel-L Reduced Risk of TTFE for 3-Point MACE by 54%







Kaplan-Meier log rank statistics

Investigational Agents Evaluated for Cardiovascular Risk Reduction Using 3-Point IMM MACE*: Comparison With Rexlemestrocel-L in Patients With Myocardial Ischemia &/or Diabetes

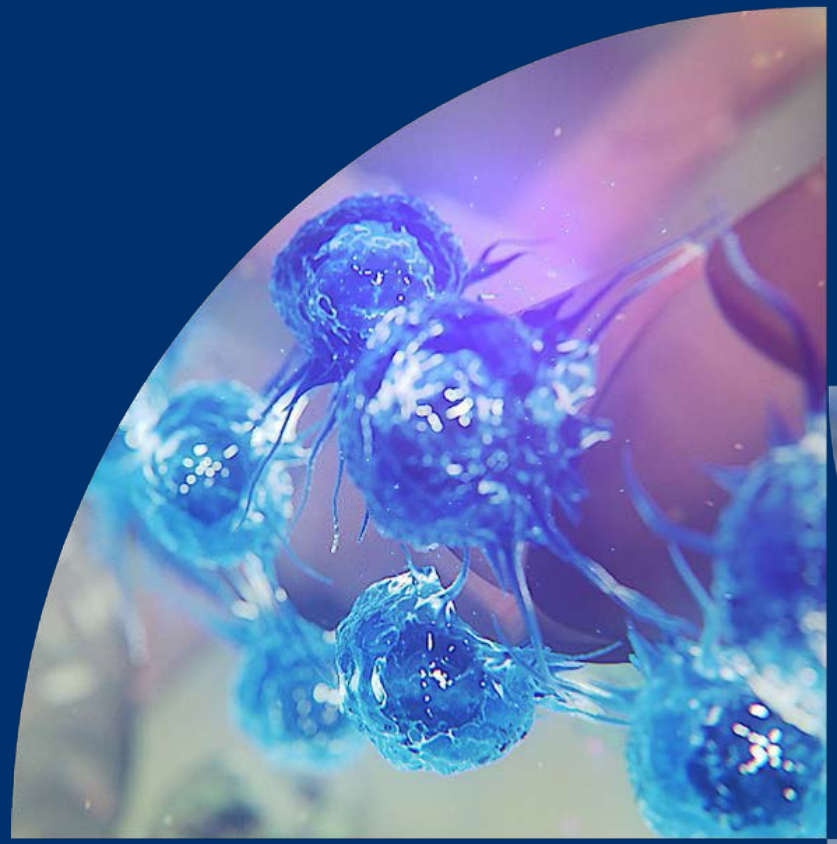
Medication	Drug Class	Clinical Trial	Hazard Ratio	Risk Reduction	95% CI	P-value	# Randomized Patients
Liraglutide	GLP-1 Receptor Agonist (RA)	LEADER	0.87	13%	0.78, 0.97	0.01	9,340
		Heart Failure Sub-group	0.94	6%	0.72, 1.21	-------	1,305
Dulaglutide	GLP-1 Receptor Agonist (RA)	REWIND	0.88	12%	0.79, 0.99	0.03	9,901
Empagliflozin	SGLT-2 Inhibitor	EMPA-REG	0.86	14%	0.74, 0.99	0.04	7,020
Canagliflozin	SGLT-2 Inhibitor	CANVAS + CANVAS-R	0.86	14%	0.75, 0.97	0.02	10,142
		Heart Failure Sub-group	0.80	20%	0.61, 1.05	-------	1,461
Dapagliflozin	SGLT-2 Inhibitor	DECLARE Timi 58	0.93	7%	0.84, 1.03	-------	17,160
		Heart Failure Sub-group	1.01	0%	0.81, 1.27	-------	1,724
Ertugliflozin	SGLT-2 Inhibitor	VERTIS CV	0.99	1%	0.88, 1.12	-------	8,246
Rexlemestrocel-L	**Mesenchymal Precursor Cells**	**DREAM HF Ischemics &/or Diabetics**	**0.63**	**37%**	**0.43, 0.93**	**0.019**	**385**
		Ischemics &/or Diabetics With Baseline hsCRP≥2mg/L	**0.46**	**54%**	**0.27, 0.77**	**0.003**	**212**

* TTFE Composite for Cardiovascular Death or Non-fatal MI or Non-fatal Stroke

Wang CCL et al. Circulation 2019; 139: 1741-1743. McGuire DK et al. JAMA Cardiol. 2021; 6:148-158.

Conclusion & Key Next Steps

1. Transendocardial delivery of 150 million allogeneic MPCs (rexlemestrocel-L) was safe and did not elicit any clinically meaningful immune-related responses
2. Over a mean follow-up of 30 months, a single rexlemestrocel-L dose on top of maximal standard of care significantly reduced:
   - Composite of cardiovascular death or non-fatal MI or non-fatal stroke in all 537 patients
   - Composite of cardiovascular death or non-fatal MI or non-fatal stroke in all 537 patients
   - A hierarchical analysis of pre-specified risk stratification showed greatest benefit in patients with myocardial ischemia and/or diabetes (72% of total treated population)
   - In controls (treated with maximal current therapies for heart failure), the presence of myocardial ischemia and/or diabetes resulted in 1.9-fold greater risk of 3-Point MACE versus other control patients with heart failure
   - Rexlemestrocel-L reduced 3-Point MACE in myocardial ischemics and/or diabetics by 37%
   - Greatest benefit in patients with elevated CRP at baseline with reduction in 3-Point MACE of 54% (n = 212)
3. Mesoblast to formally submit to FDA its new analyses of outcomes in high-risk HFrEF patients with diabetes and/or myocardial ischemia to agree on a potential pathway to approval



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