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65th Annual Scientific Session & Expo

The ixCELL-DCM Trial:
Transendocardial Injection of ixmyelocel-T in Patients with Ischemic Dilated Cardiomyopathy

Timothy D. Henry, MD, FACC on behalf of Arshed A. Quyyumi, Gary L. Schaer, David R. Anderson, Catalin Toma, Cara East, David P. Recker, Ann Remmers, James Goodrich, Amit N. Patel and the ixCELL-DCM Investigators

Lancet

Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double blind trial

Amit N Patel, Timothy D Henry*, Arshed A Quyyumi, Gary L Schaer, R David Anderson, Catalin Toma, Cara East, Ann E Remmers, James Goodrich, Akshay S Desai, David Recker, Anthony DeMaria, for The ixCELL-DCM Investigators*

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Disclosures

- Trial sponsored by Vericel Corporation
- Steering Committee
  - Amit N. Patel, Chair
  - Timothy D. Henry, PI
  - Gary L. Schaer
  - Anthony N. DeMaria
  - David P. Recker
- Clinical Endpoint Committee: Ashkay S. Desai, Chair, Brigham & Women's Hospital
- DSMB: David Waters, Chair, UCSF

Investigators

Principal Investigator	Study Coordinator	# Subjects Randomized
Arshed Quyyumi	Kareem Hosney	12
Amit Patel	Patty Meldrum	11
Gary Schaer	Jon Learoyd	10
David Anderson	Sara Long	8
Catalin Toma	Laurie Dennis	7
Cara East	Poupak Moshayedi	7
Timothy Henry	Michelle Domingo	6
Paul Schulze	Mary Beth Marks	6
David Schmidt	Lindsey McFarland	5
Adam Berman	Jo Williams	5
Barry Trachtenberg	Emily Taylor	5
Eugene Chung	Christine Huber	5
Richard Schatz	Heather Catchpole	5
Nabil Dib	Jennifer Vermillion	4

Principal Investigator	Study Coordinator	# Subjects Randomized
Amish Raval	Cathlyn Leitzke	3
Guy Reeder	Cindy Woltman	3
Safwan Kassas	Valerie Bitzer	3
Mark Zucker	Lily Wang	3
Rajan Patel	Monique Pellegrin	3
David Fortuin	Barbara Knight	2
Sumanth Prabhu	Patrick Frazier	2
Paul Huang	Deb Tinlin	2
Kimberly Parks	Jessica Butler	2
Frank McGrew	Susan Thomas	2
David Henderson	Lauraine Crandall	2
Jon George	Jennie Wong	1
Anthony DeMaria	Wendy Davila	1
Joshua Hare	Julio Sierra	1

Introduction

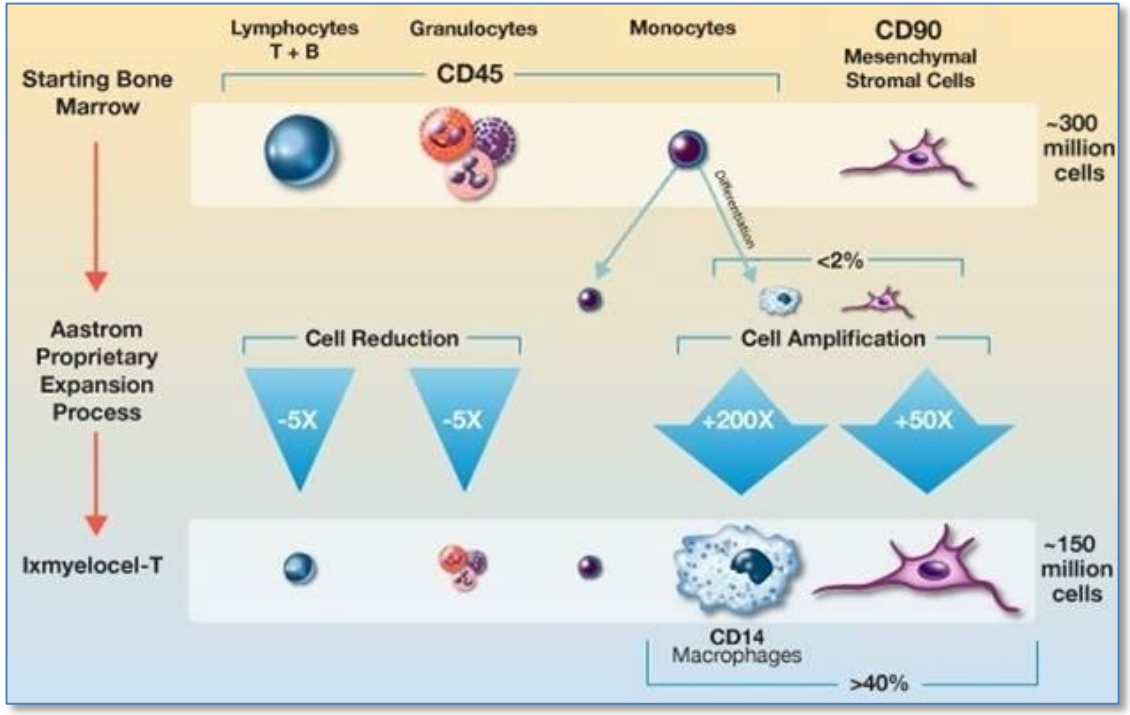
- Heart failure is a leading cause of morbidity and mortality in the U.S.
- Patients with Class III/IV heart failure, despite optimal medical and device therapy, have limited options beyond cardiac transplantation and LVAD
- Preclinical studies suggest regenerative therapies are an attractive approach
- Initial clinical trials with unselected BMMC demonstrate safety with modest efficacy due in part to variability related to the decline in the number and potency of stem cells with age and risk factors
- This has stimulated the next generation cell therapies

Background

- Ixmyelocel-T is an autologous, bone marrow derived, multicellular therapy expanded over 2 weeks to increase:
  - $CD90^+$ mesenchymal stem cells (MSC)
  - $CD45^+$ $CD14^+$ M2-like macrophages

- Phase 2a IMPACT-DCM and Catheter-DCM (n=59):
  - Improved safety with percutaneous vs. surgical delivery
  - Patients with ischemic DCM responded better than non-ischemic DCM

Ixmyelocel-T: Expanded Multicellular Therapy



Two-Week Expansion Increases:

1. $CD45^+$ $CD14^+$ M2-like macrophages
2. $CD90^+$ MSCs

Potential Mechanisms:

1. Anti-Inflammatory
2. Tissue Remodeling
3. Endothelial Protection
4. Angiogenesis

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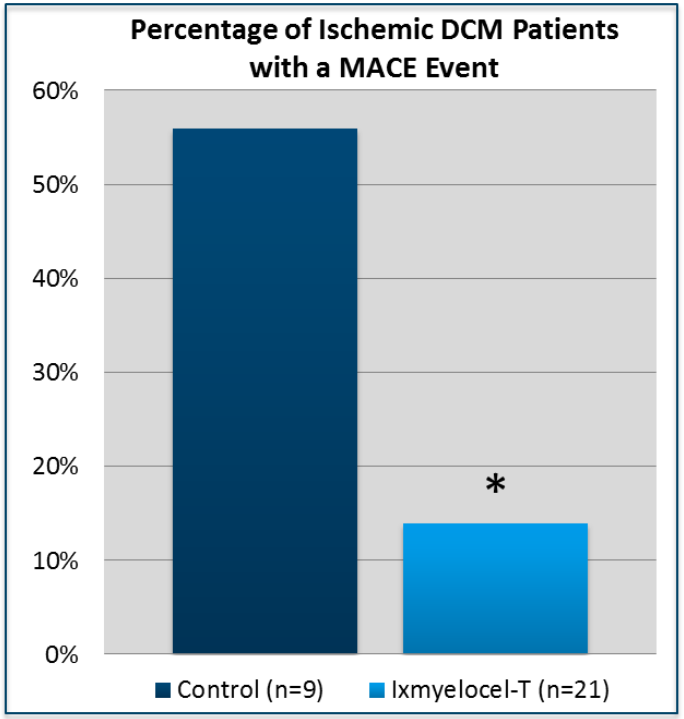
Phase 2a Results



Henry TD, et al. Circ Res 2014;115:730-737.

IMPACT-DCM (n=39)
Catheter-DCM (n=22)

75% fewer patients treated with ixmyelocel-T experienced a MACE (* p < 0.05)

MACE = cardiac death, cardiac arrest, MI, HF hospitalization, or major bleeding

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ixCELL-DCM Study Objective

- The ixCELL-DCM clinical trial is a multicenter, prospective, randomized, double-blind, placebo-controlled Phase 2b study designed to evaluate the efficacy, safety, and tolerability of ixmyelocel-T compared to placebo when injected transendocardially in patients with Class III/IV heart failure due to ischemic cardiomyopathy

ixCELL–DCM Eligibility

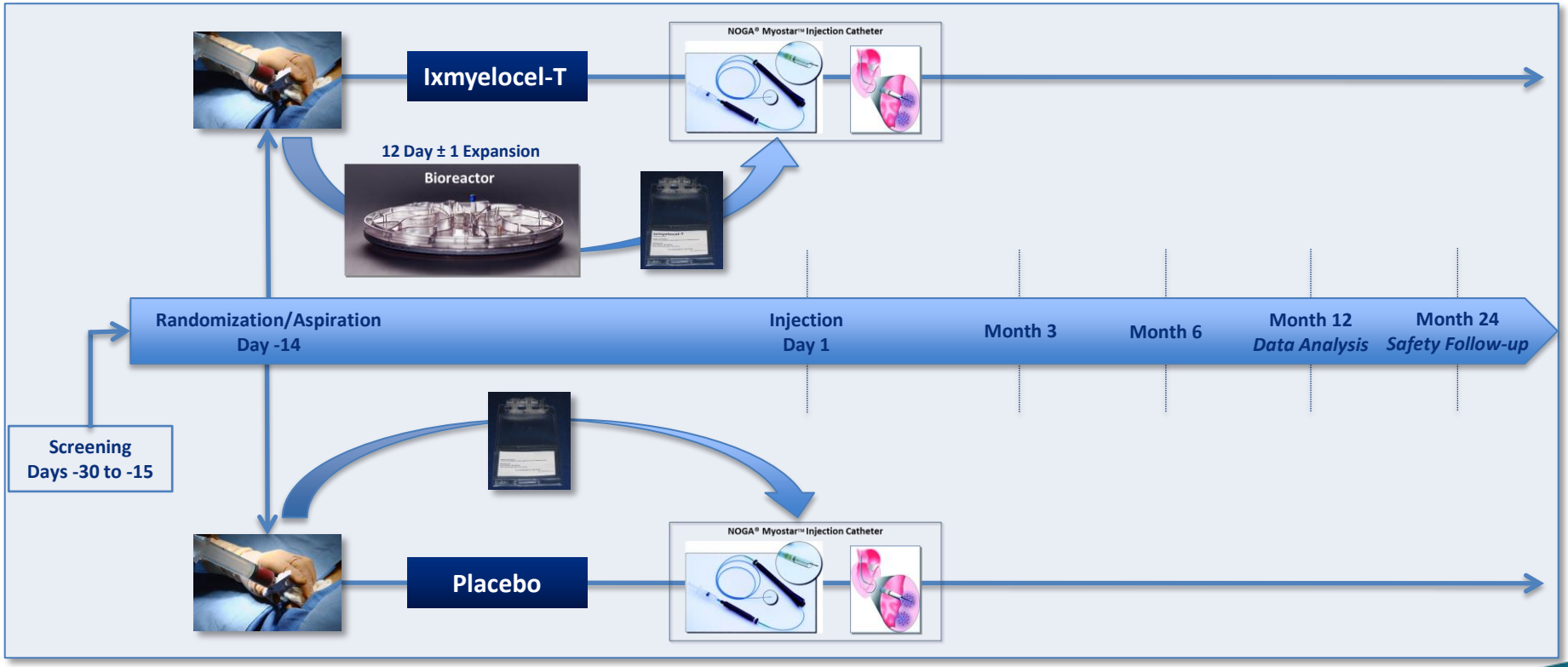
Inclusion Criteria

- Age 30 to 86
- NYHA Class III/IV heart failure
- Diagnosis of ischemic cardiomyopathy
- LVEF ≤35%
- ICD in place
- Heart failure hospitalization within 6 months **or**
- BNP ≥400 pg/mL or NT-pro BNP ≥2000 pg/mL **or**
- 6 MWT ≤400 meters

Exclusion Criteria

- MI, Stroke, TIA within 3 months
- LV thrombus/ineligible for NOGA
- PCI, CABG within 30 days
- Status 1A or 1B on heart transplant list
- Severe valvular disease
- Malignancy within 12 months
- CKD or creatinine clearance <15 mL/min
- Hg <9 g/dL or HbA1c ≥9%

Protocol



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Primary Endpoint

- The Primary Endpoint was a composite of:
  - All-cause death
  - Cardiovascular hospitalization
  - Unplanned clinical visits to treat acute decompensated HF
    - ❖ Excluding procedure-related events within 7 days of injection (sensitivity analysis)
    - ❖ All events adjudicated by independent Clinical Endpoint Committee

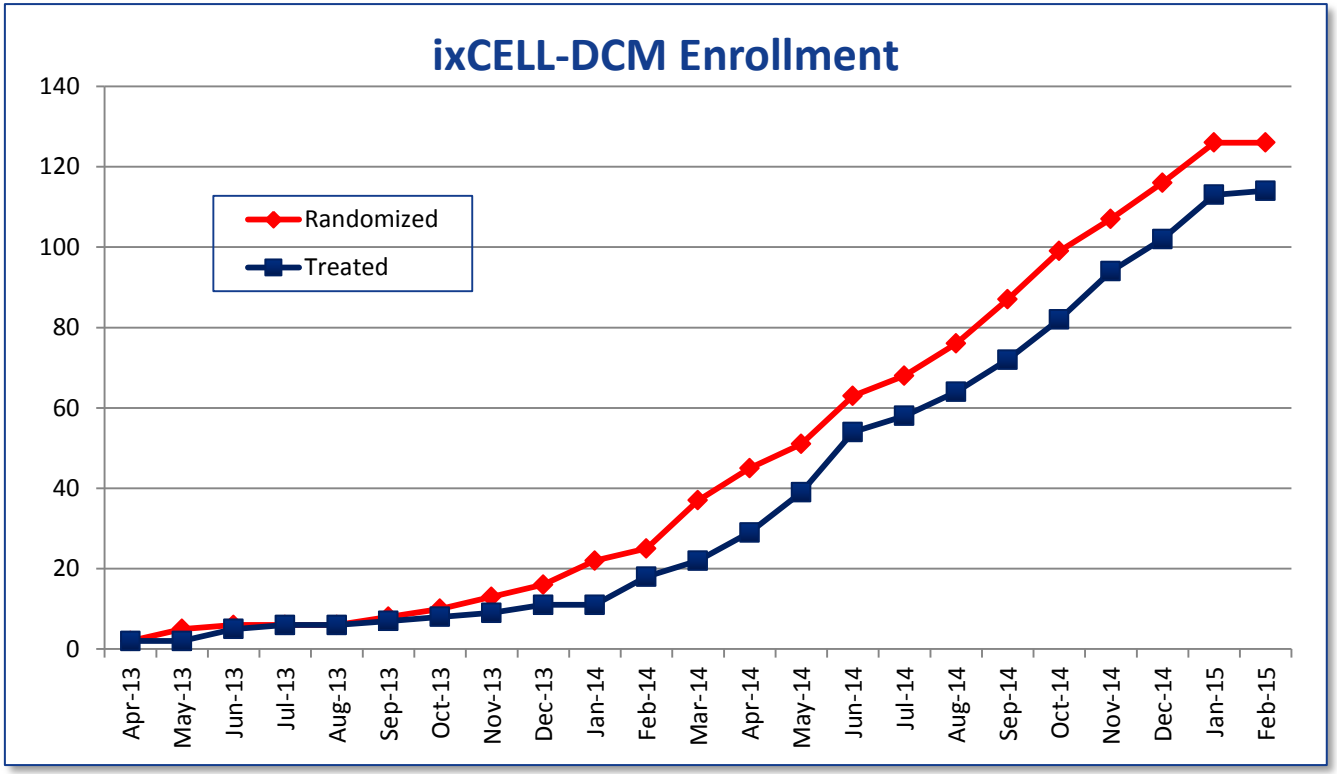
Secondary Endpoints

- Time to First Event
- LVEF, LVESV, and LVEDV measured by echocardiogram
- NYHA class
- Six-minute walk distance
- Win ratio

Safety Endpoints

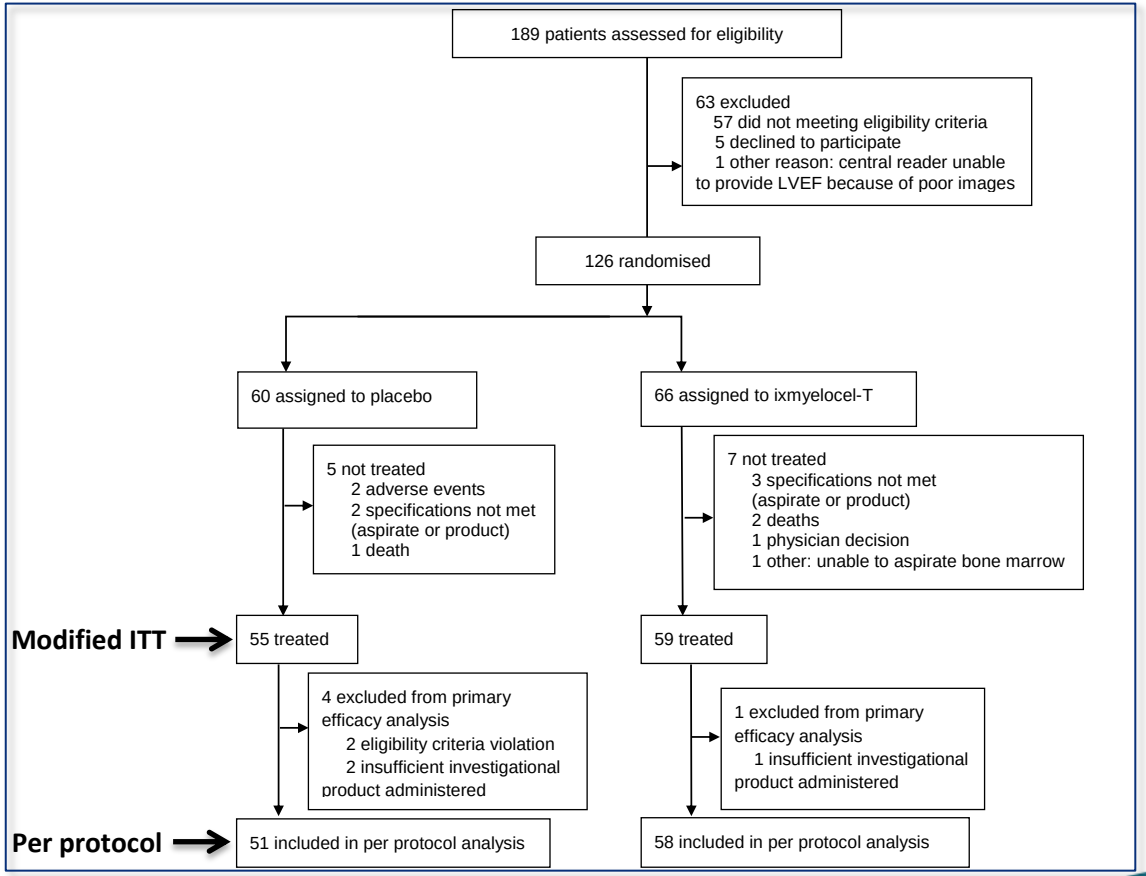
- Serious Adverse Events – MACE
  - Cardiovascular death
  - MI
  - CVA
  - HF requiring hospitalization
  - UA requiring hospitalization
  - Resuscitated sudden death
  - LVAD
  - Heart transplantation

Enrollment Curve



Month	Subjects Randomized	Subjects Treated
Feb-14	3	7
Mar-14	12	4
Apr-14	8	7
May-14	6	10
Jun-14	12	15
Jul-14	5	4
Aug-14	8	6
Sep-14	11	8
Oct-14	12	9
Nov-14	8	11
Dec-14	9	8
Jan-15	10	11
Feb-15	0	1

Patient Enrollment



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Patient Demographics

Category		Placebo (N=51)	Ixmyelocel-T (N=58)	P value
Demographics				
Sex (%)	Male	88%	95%	0.30
Age (years)	Mean	64.7	65.3	0.69
Race (%)	White	88%	91%	0.75*
Risk Factors				
Hypertension	%	90%	81%	0.28
Hyperlipidemia	%	96%	97%	1.00
Diabetes	%	51%	41%	0.34
CV Medical History				
Previous CABG	%	63%	55%	0.44
Previous PCI	%	82%	85%	0.80
Previous MI	%	96%	88%	0.17
AICD	%	96%	93%	0.68
CRT	%	39%	50%	0.33

* White vs Non-White

Baseline Data & Medications

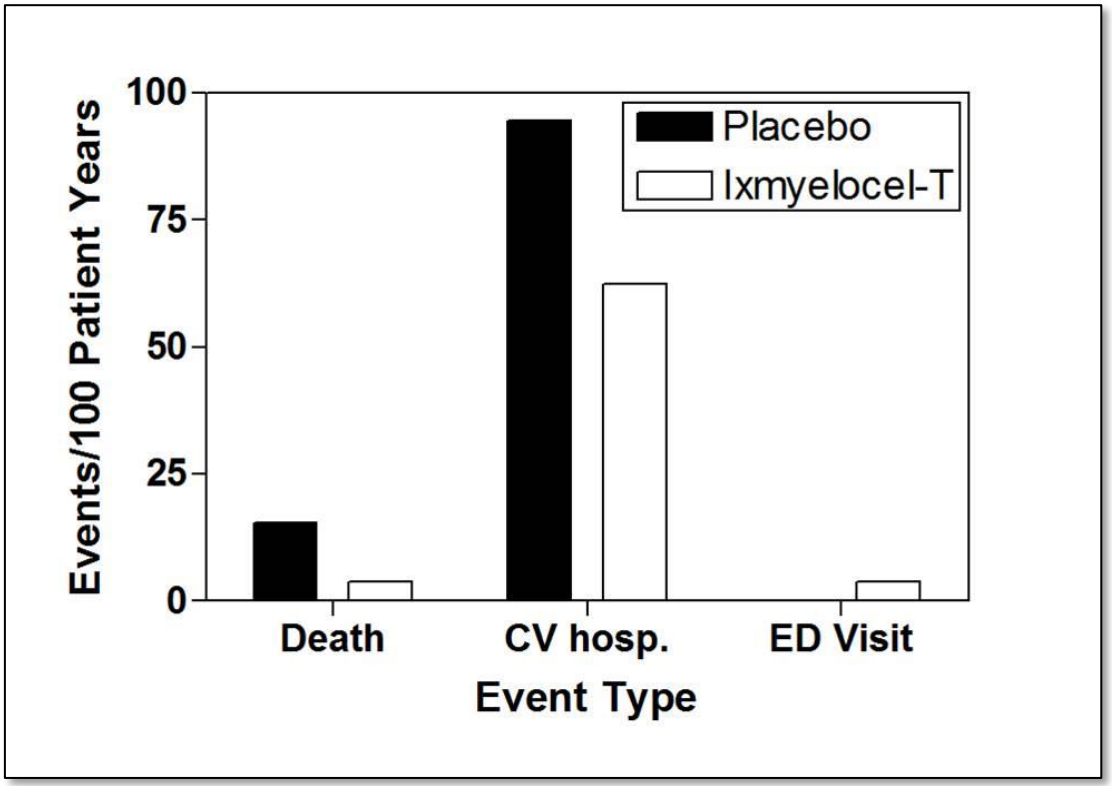
Category		Placebo (N=51)	Ixmyelocel-T (N=58)	P value
Baseline				
NYHA Class III	%	92%	90%	0.88*
LVEF (%)	Mean	24.4% (+/-6.0)	26.5% (+/-5.1)	0.05
Creatinine Clearance (mL/min)	Mean	61.9 (+/-19.0)	61.8 (+/-21.4)	0.83
Six Minute Walk Test (meters)	Mean	301.6 (+/-104.8)	313.4 (+/-100.1)	0.76
NT-ProBNP (ng/L)	Mean	2132 (+/-2021)	1755 (+/-1842)	0.29
Medications				
Beta Blockers	%	94%	100%	0.10
Ace Inhibitors	%	67%	55%	0.24
Diuretics	%	98%	94%	0.62
Warfarin	%	27%	28%	1.00
Antiplatelet	%	94%	91%	0.72
Statin	%	90%	97%	0.25

* Test compares 3 categories (II, III & IV)

Primary Endpoint: Per Protocol (n=109)

	Primary Endpoint Without IP Procedure Related Events		Sensitivity Endpoint With IP Procedure Related Events	
	Placebo (N=51)	Ixmyelocel-T (N=58)	Placebo (N=51)	Ixmyelocel-T (N=58)
P-Value		0.0344		0.0267
Rate Ratio [95% CI]		0.63 [0.42, 0.97]		0.62 [0.41, 0.95]
Events/100 patient years	109.97	69.76	112.17	69.76
Patient years Exposed	45.5	54.5	45.5	54.5
Total Events	50	38	51	38
Distribution of Events by Patient, n (%)				
0	26 (51.0)	36 (62.1)	25 (49.0)	36 (62.1)
>=1	25 (49.0)	22 (37.9)	26 (51.0)	22 (37.9)
1	9 (17.6)	13 (22.4)	10 (19.6)	13 (22.4)
2	11 (21.6)	3 (5.2)	11 (21.6)	3 (5.2)
3	2 (3.9)	5 (8.6)	2 (3.9)	5 (8.6)
4	2 (3.9)	1 (1.7)	2 (3.9)	1 (1.7)
5	1 (2.0)	0 (0.0)	1 (2.0)	0 (0.0)
Death	7 (13.7)	2 (3.4)		
LVAD Insertion	0 (0.0)	3 (5.2)		
Heart Transplant	1(2.0)	1(1.7)		
Cardiovascular Hospitalization	24 (47.1)	22(37.9)		
Unplanned Outpatient/ED Visit	0 (0.0)	2 (3.4)		

Primary Endpoint Components: Per Protocol (n=109)



P=0.0344
Rate Ratio [95% CI]: 0.63 [0.42-0.97]

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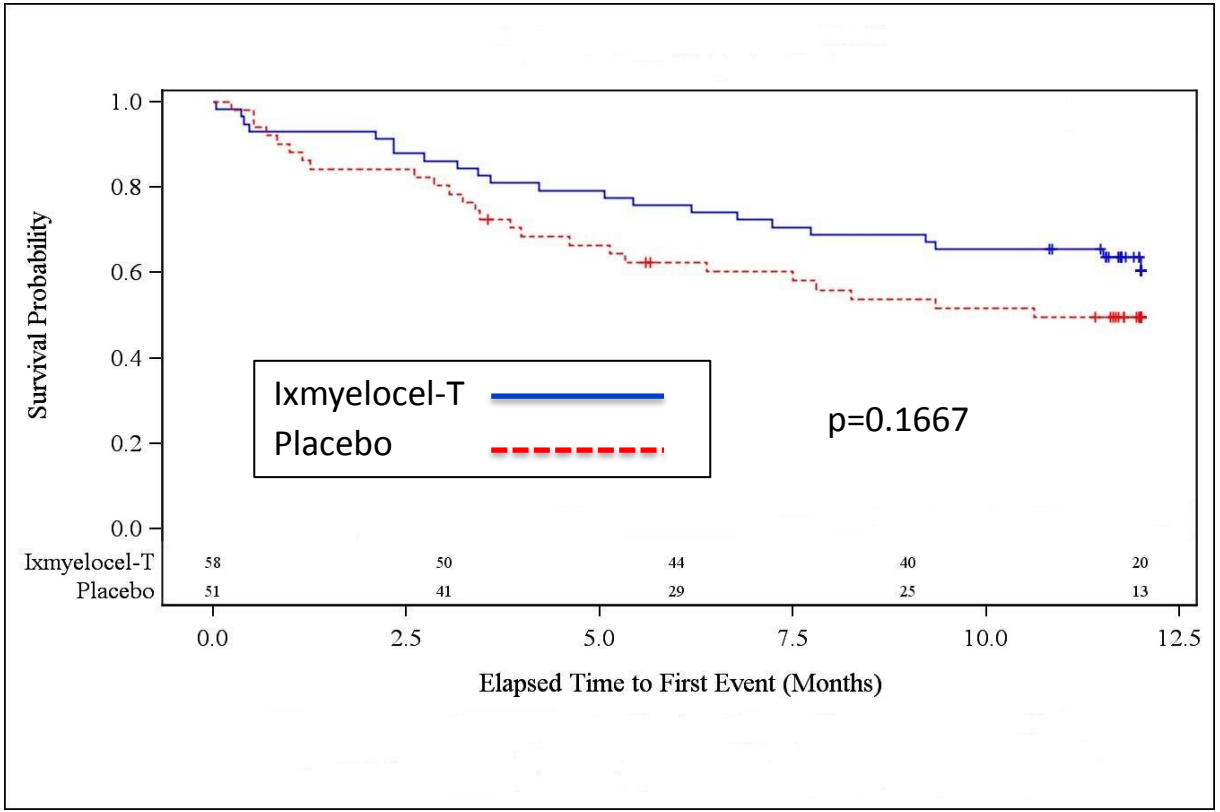
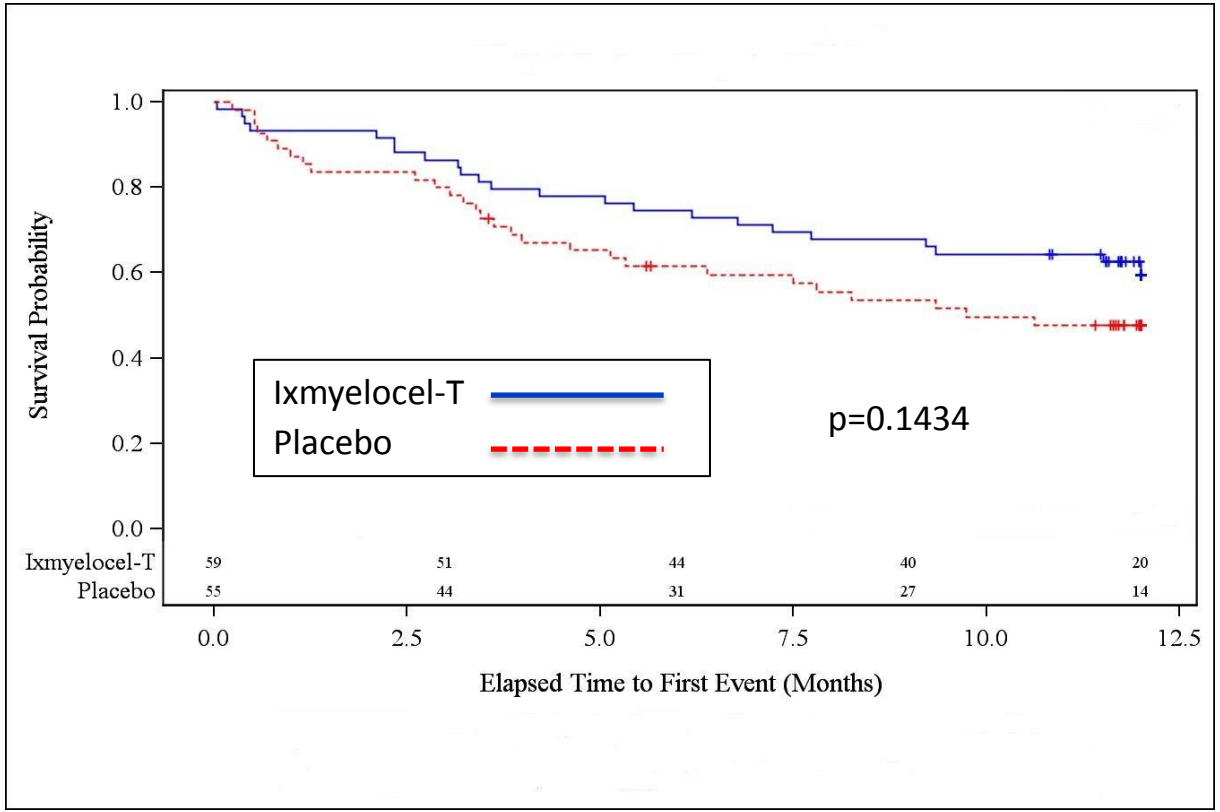
Primary Endpoint: Modified ITT (n=114)

	Primary Endpoint Without IP Procedure Related Events		Sensitivity Endpoint With IP Procedure Related Events	
	Placebo (N=55)	Ixmyelocel-T (N=59)	Placebo (N=55)	Ixmyelocel-T (N=59)
P-Value[a]		0.0107		0.0082
Rate Ratio [95% CI]		0.59 [0.40, 0.89]		0.58 [0.39, 0.87]
Events/100 patient years	121.73	72.16	123.79	72.16
Patient years Exposed	48.5	55.4	48.5	55.4
Total Events	59	40	60	40
Distribution of Events by Patient, n (%)				
0	27 (49.1)	36 (61.0)	26 (47.3)	36 (61.0)
>=1	28 (50.9)	23 (39.0)	29 (52.7)	23 (39.0)
1	11 (20.0)	13 (22.0)	12 (21.8)	13 (22.0)
2	11 (20.0)	4 (6.8)	11 (20.0)	4 (6.8)
3	2 (3.6)	5 (8.5)	2 (3.6)	5 (8.5)
4	2 (3.6)	1 (1.7)	2 (3.6)	1 (1.7)
5	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)
7	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)

Time to First Event: Per Protocol (n=109)



Time to First Event: Modified ITT (n=114)



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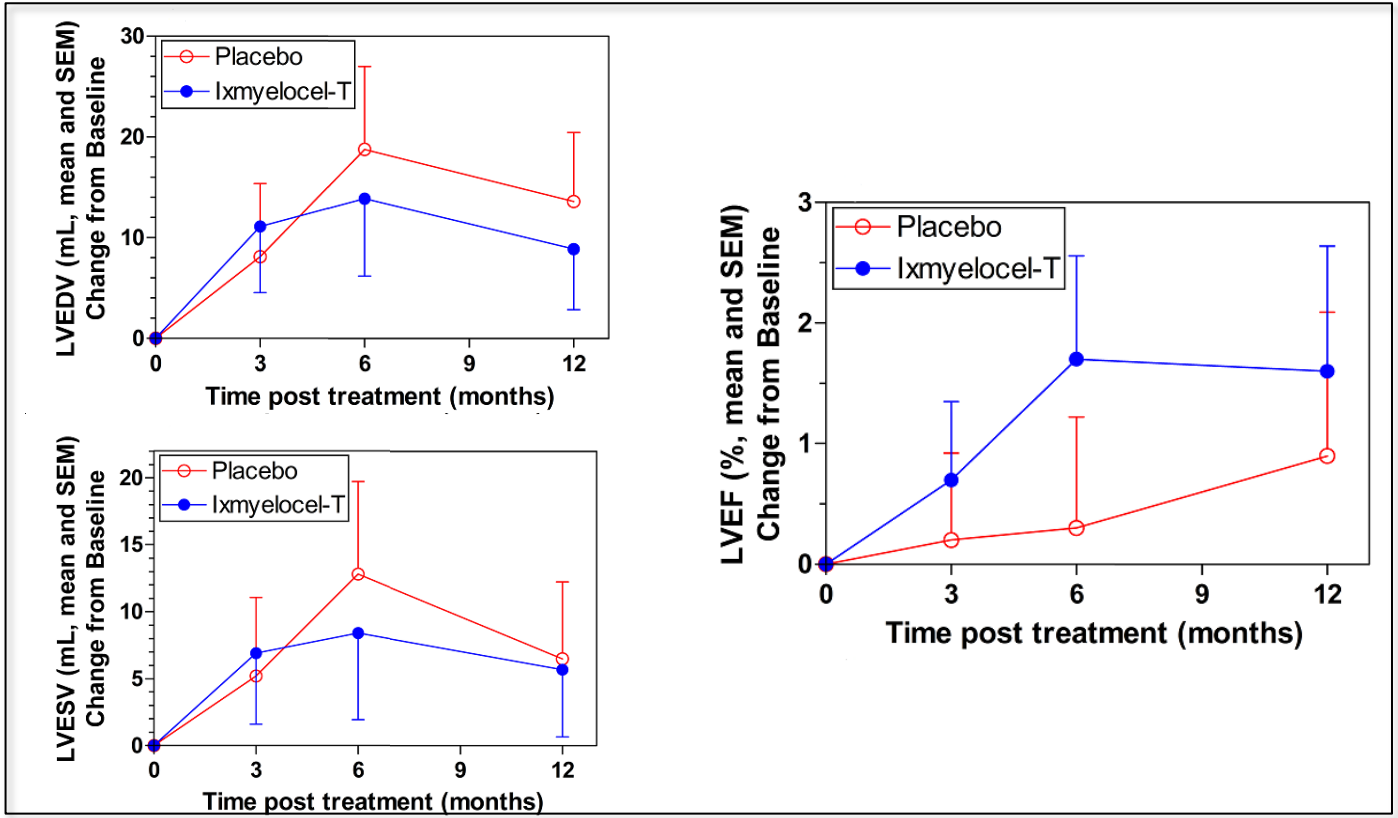
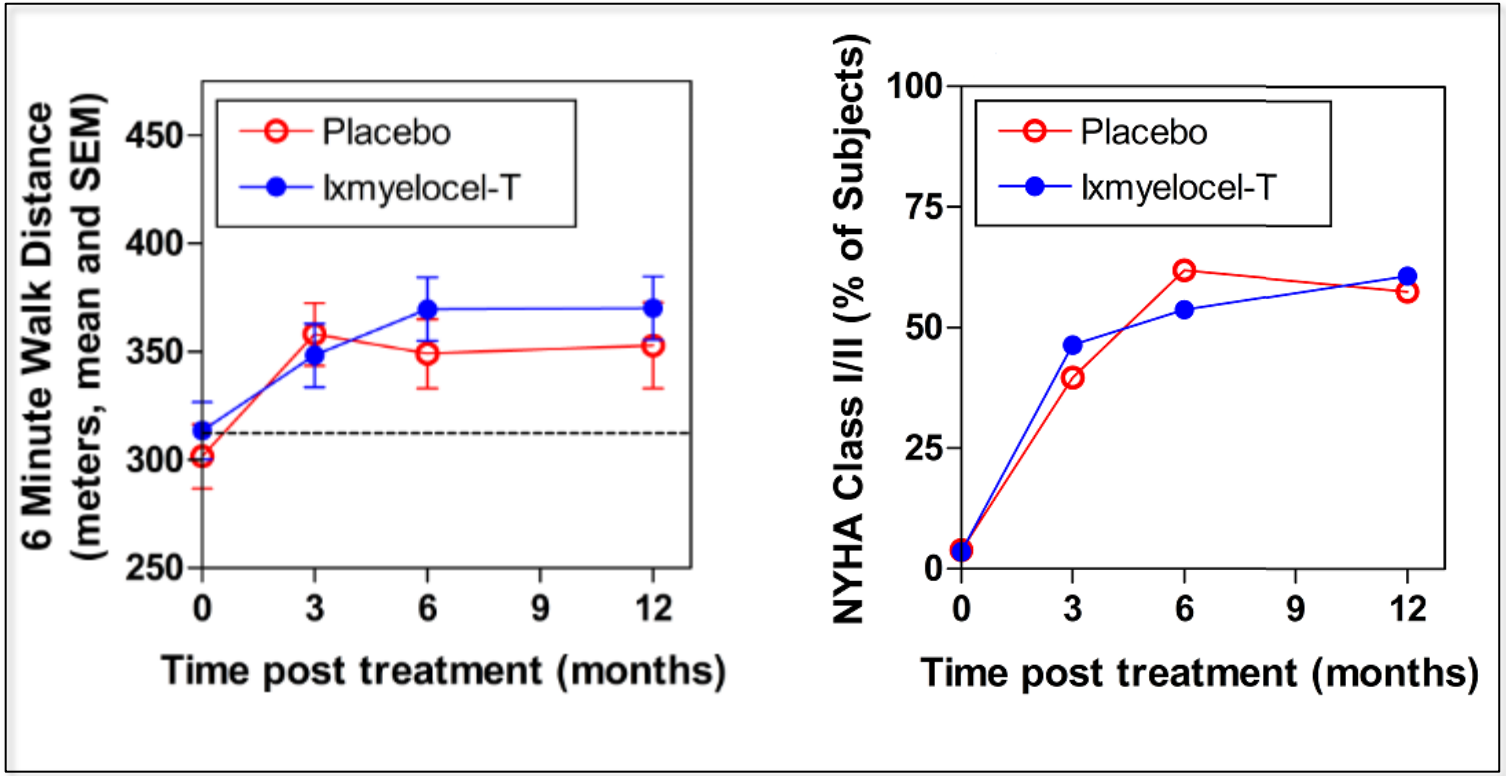
Safety Analysis

	Placebo (N=55)	Ixmyelocel-T (N=59)	P-Value
Adverse Events (% patients)	51 (92.7%)	52 (88.1%)	0.75
Total #	344	323	
Serious Adverse Events (% patients)	41 (74.5%)	31 (52.5%)	0.0197
Total #	124	73	
Major Adverse Cardiovascular Events (% patients)	23 (41.8%)	16 (27.1%)	0.12
Total #	38	31	

LVEF and Volumes



Six-Minute Walk Test & NYHA



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Summary

- Patients treated with ixmyelocel-T had a significant reduction in the primary endpoint on both per protocol and modified ITT analysis
- 37% to 41% reduction in cardiac events compared to placebo; similar to the Phase 2a clinical trials
- Driven by a reduction in mortality and cardiac hospitalizations
- Fewer patients with SAEs observed in the ixmyelocel-T group compared to the placebo group
- No significant changes in LVEF or LV volumes, NYHA or 6-minute-walk

Conclusions

- The transendocardial delivery of ixmyelocel-T resulted in a significant reduction in cardiac events driven by both mortality and cardiac hospitalizations at 12 months compared to placebo

- Results suggest that ixmyelocel-T may be an attractive option for NYHA Class III/IV patients with ischemic heart failure who have exhausted optimal medical and device therapy

Appendix

Win Ratio: Per Protocol (n=109)

	Placebo n/N (%)	Ixmyelocel-T n/N (%)
Incidence of Individual Components*:		
All-cause Deaths/LVAD/Heart Transplants	8/51(15.7)	6/58(10.3)
Death	7/51(13.7)	2/58(3.4)
LVAD Insertion	0/51	3/58(5.2)
Heart Transplant	1/51(2.0)	1/58(1.7)
CV Hospitalization	24/51(47.1)	22/58(37.9)
Unplanned Outpatient/ED Visits to Treat ADHF	0/51	2/58(3.4)

Pair Categorization and Win Ratio:	All Pairs: Control to Ixmyelocel-T (N=2958)
Death / LVAD Implant / Heart Transplant on Ixmyelocel-T First (a)	271
Death / LVAD Implant / Heart Transplant on placebo First (b)	438
Cardiovascular Hospitalization on Ixmyelocel-T First (c)	504
Cardiovascular Hospitalization on placebo First (d)	770
Unplanned Outpatient or ED Intervention for ADHF on Ixmyelocel-T First (e)	0
Unplanned Outpatient or ED Intervention for ADHF on placebo First (f)	0
None of the Above (g)	975
N_W: Pairs where ixmyelocel-T wins (b + d + f)	1208
N_L: Pairs where placebo wins (a + c + e)	775
Win Ratio (N_W/N_L)	1.56
[95% Confidence Interval]	[0.87 – 2.81]
P-Value	0.1391

Irrespective of the timing, a single event in the primary endpoint analysis may have multiple components for comparison in this analysis. For example, a patient first hospitalized for a CV reason who dies while in the hospital. The primary analysis counts this a single event (death) but for the win ratio both the date of death and the date of CV hospitalization are used as components for pair categorization.

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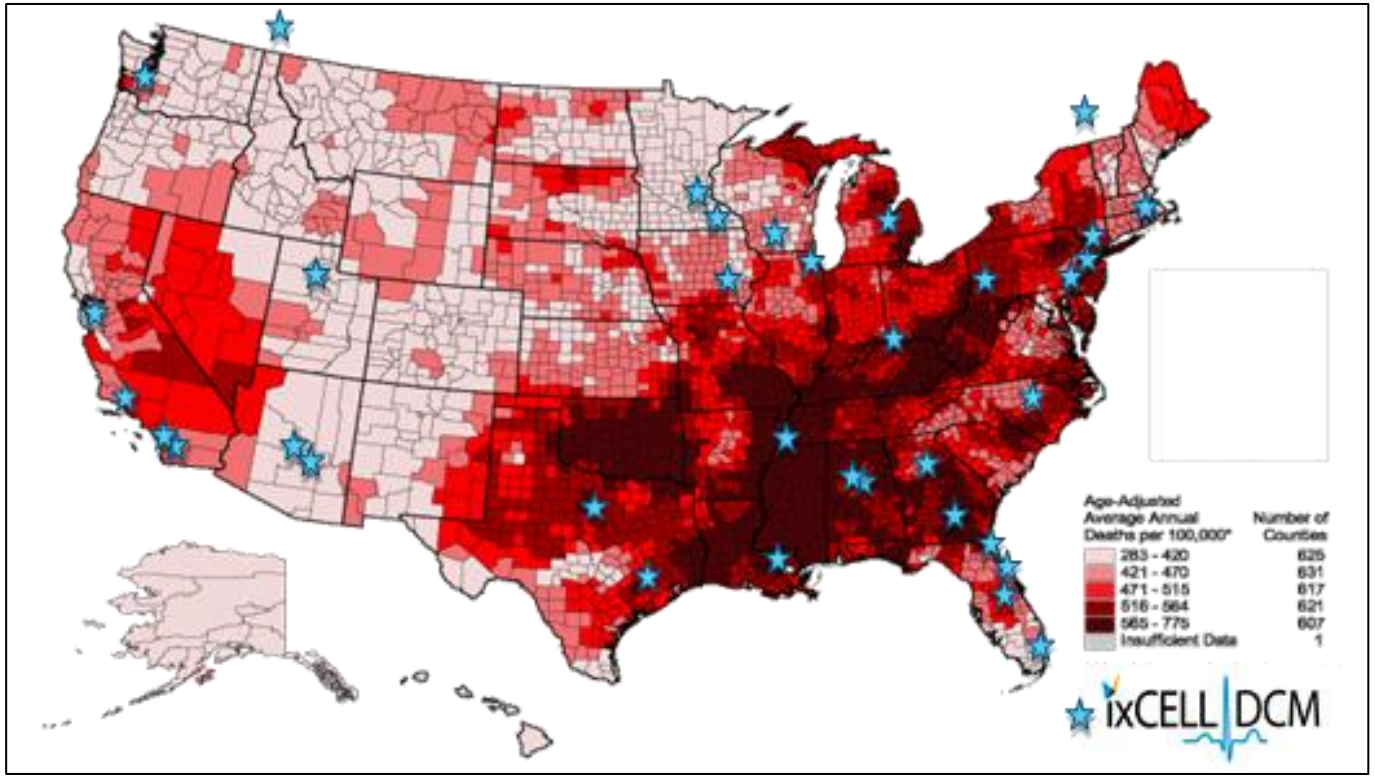
Clinical Sites



Steering Committee

- Amit N. Patel (Chair)
- Timothy D. Henry (PI)
- Gary L. Schaer
- Anthony N. DeMaria
- David P. Recker

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ixCELL-DCM Study Design

Phase 2b ixCELL–DCM Study Design	
Design	• Multicenter, randomized (1:1), double-blind, placebo-controlled phase 2b trial
Patient Population	• NYHA Class III/IV ischemic dilated cardiomyopathy
Treatment	• Intramyocardial ixmyelocel-T vs. placebo
Study Size	• 126 patients randomized • 114 patients treated at 28 centers in the United States
Primary Endpoints	• Composite of all-cause death, CV hospitalization or outpatient treatment of acute decompensated heart failure over 12 months
Key Secondary Endpoints	• Win ratio • LVEF and volumes by echo • NYHA class • Six-minute walk test