

# **Safety and Feasibility of Percutaneous Autologous Skeletal Myoblast Transplantation for Ischemic Cardiomyopathy: Interim Analysis**

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# Disclosures

- Nabil Dib – Received research grants, shareholder and consultant for Mytogen, Inc.
- Edward Diethrich – Shareholder for Mytogen, Inc.
- Jonathan Dinsmore and Ann Campbell – Employees of Mytogen, Inc.
- Bee White, Susan Moravec, Zahara Mellatdoust, Katayoun Seyedmadani, Amy Rosenbaum, – Nothing to disclose

# Background

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- Ischemic heart disease is a leading cause of congestive heart failure
- Myocardial infarction results in cell death, which can eventually lead to congestive heart failure
- Progressive ventricular remodeling results in decreased cardiac function

# Background

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- Proof of concept that autologous skeletal myoblasts (ASM) survive and engraft after transplantation into infarcted myocardium in humans has been established
- We demonstrated safety and feasibility of direct injection of ASM in 24 subjects during coronary artery bypass surgery and left ventricular assist procedures
- Although these results are encouraging, a less invasive method of transplantation via a percutaneous approach may be more advantageous
- In November, 2004, we initiated a 24 patient, single center clinical trial for catheter-based delivery of ASMs

*Dib N et al. Circulation (2005); 112:1748-1755*

*Pagani FD et al. (2003) J Am Coll Cardiol 41:879-888*

# Study Design and Objective

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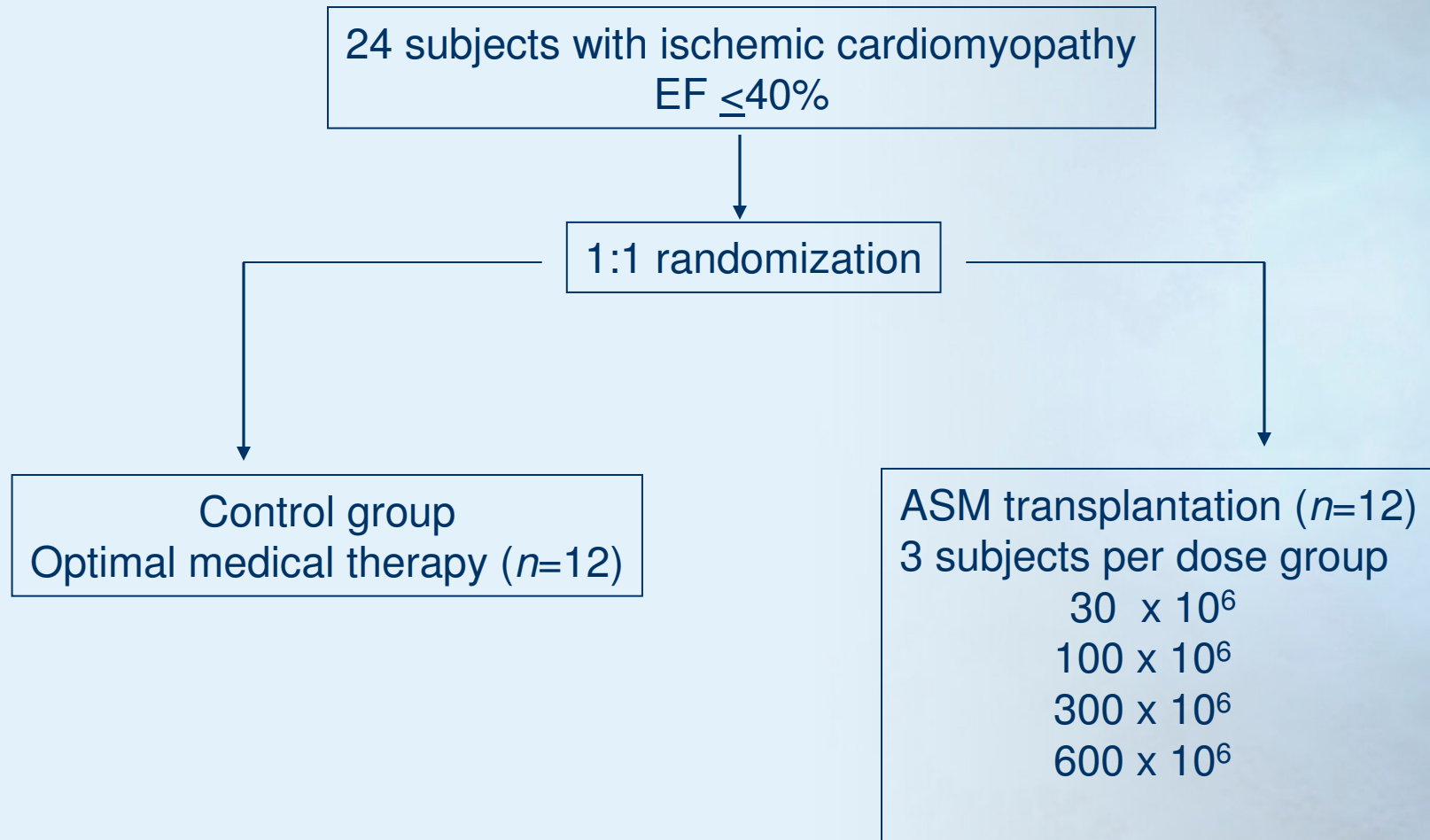
- Study design – Phase I, single center, prospective 1:1 randomized, open label, dose escalating trial
- Primary objective - to evaluate the safety, tolerability and feasibility of transplanting ASM into infarcted myocardium using a catheter-based delivery system

# Secondary Objectives

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- Efficacy of ASM transplantation assessed by changes at 3, 6 and 12 months follow-up:
  - quality of life assessment
  - NYHA classification
  - 6-minute walk test
- Myocardial viability assessments performed:
  - electromechanical mapping (NOGA™)
  - left and right heart catheterization
  - Echocardiography
  - nuclear SPECT
- Assessed by changes at 3 months:
  - left ventricular volumes
  - ejection fraction
  - systolic left ventricular pressure

# Study Design



# Methods

## *ASM Transplant*

## *Control*

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- 5 gm skeletal muscle biopsy obtained 4-6 weeks prior transplant was processed and expanded *in vitro*
  - Percutaneous endocardial ASM injections using a needle injection catheter guided by a 3-D electromechanical mapping system
  - Escalating doses of 30-600 x 10<sup>6</sup> ASMs, in 3-24 injections, of 0.25 ml were delivered over 20 sec.
- Continue optimal medical therapy

# Inclusion/Exclusion Summary

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## *Inclusion*

- Congestive heart failure (NYHA Class II -IV) on optimal medical therapy for a minimum of 2 months and confirmed by an independent medical monitor
- Previous MI documented by gated SPECT imaging demonstrating fixed defect
- Ejection fraction  $\leq 40\%$  as measured by stress nuclear/viability assessment with gated imaging

## *Exclusion*

- Hospitalization within 4 weeks for ACS, MI, unstable angina or CVA
- Contraindications for left ventricular mapping, i.e. thrombus, severe peripheral arterial disease, uncontrolled atrial and ventricular arrhythmias
- Mechanical valve replacement
- Cardiac resynchronization therapy (CRT) within 6 months
- Idiopathic cardiomyopathy
- Left ventricular wall thickness  $< 5\text{mm}$
- Severe renal insufficiency or liver disease

# Baseline Demographics

	<i>ASM Treated</i>	<i>Control</i>
Number Patients	12	11
Gender (%)		
Male	91	82
Female	9	18
Age (yr)	65.1	62.0
NYHA	2.7	2.5
Ejection fraction nuclear SPECT(%)	25	30
Previous MI (%)	100	100
Dyslipidemia (%)	75	72
Diabetes (%)	25	27
Hypercholesterolemia (%)	100	90
Previous PCI (%)	75	63
Previous CABG (%)	66	72
Ventricular arrhythmias (%)	67	64
Atrial arrhythmias (%)	42	55
Implantable cardioverter-defibrillator (%)	92	82
Cardiac resynchronization therapy (%)	58	0

# Baseline and Follow-up Procedures

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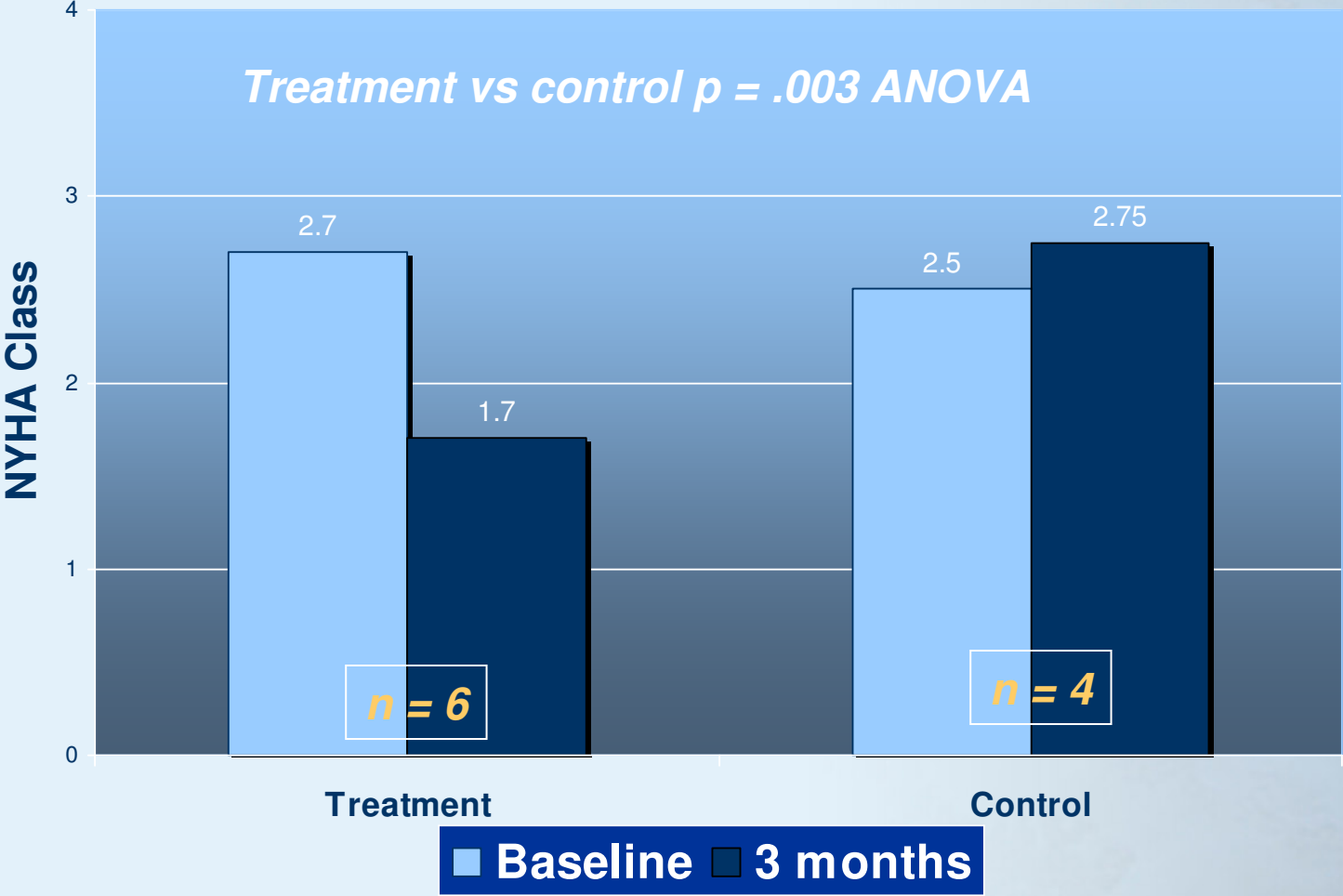
- Physical exam with vital signs (all visits)
- NYHA Classification (baseline, months 1, 3, 6, 12)
- ECG (baseline, week 1, months 1, 3, 6,12)
- Contrast enhanced echocardiography (baseline, week 1, months 1, 3, 6,12)
- 48 hour Holter Monitor or device interrogation (baseline, 24 hour, week 1, months 1, 3, 6, 12)
- Nuclear gated SPECT imaging (baseline, months 3, 6, 12)
- Cardiac enzymes (baseline, immediately post injection, 8, 16, 24 hours and 7 days)
- Routine Blood Testing (baseline, week 1, months 1, 3, 6, 12)
- T-wave alternans testing (baseline and 6 months)
- Chest X-ray (baseline, 24 hours, 7 days, month 3)
- Minnesota Living With Heart Failure Questionnaire (baseline, months 1, 3, 6, 12)
- 6-minute walk test (baseline, months 1, 3, 6, 12)
- ASM group - 3-D electromechanical mapping (NOGA™), right and left heart catheterization (3 months)

# Results

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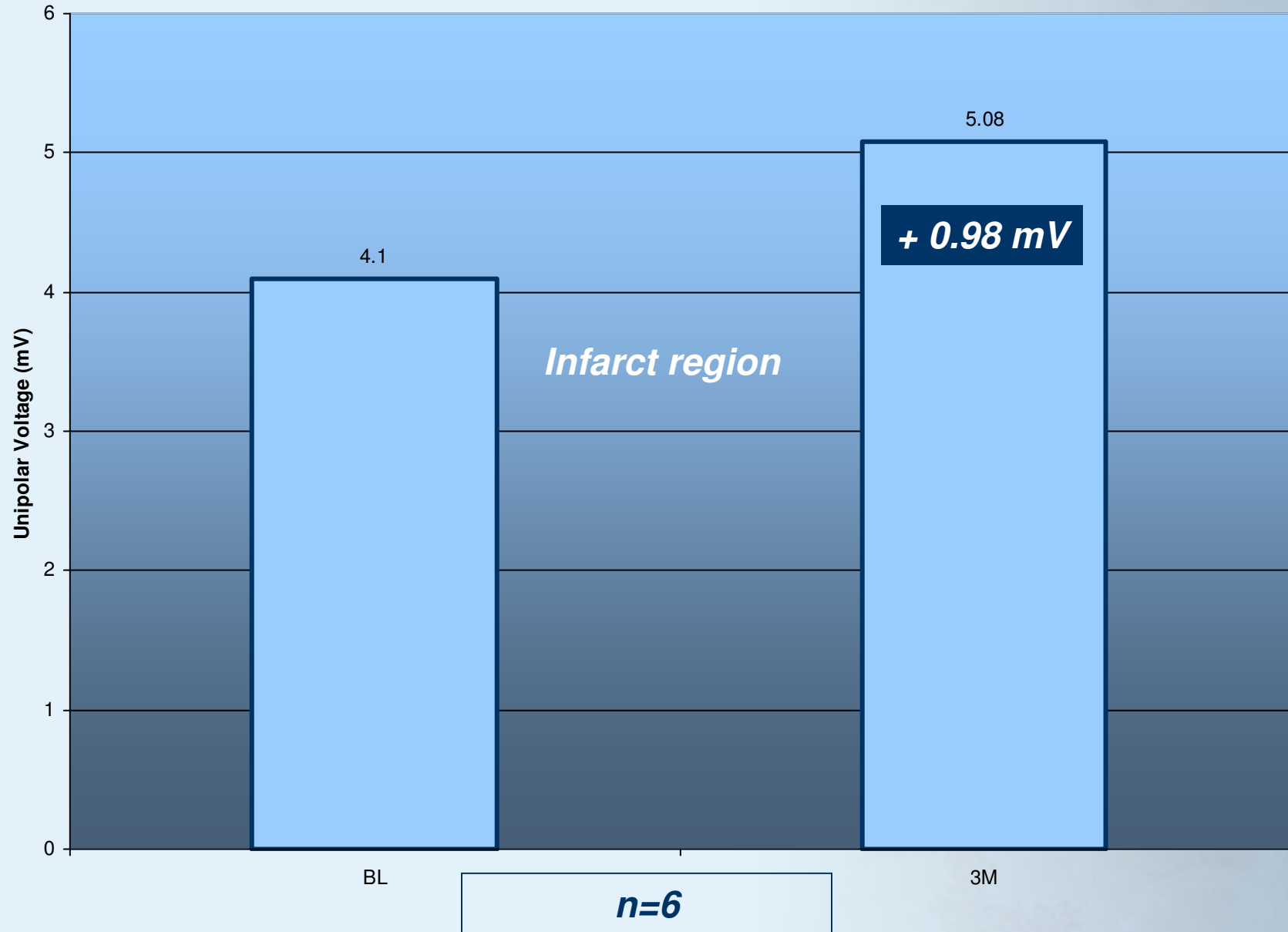
- 1 control subject received an upgrade of a single chamber ICD to a biventricular ICD approximately 10 weeks after randomization and was not included in the follow-up data analysis
- 1 subject in the ASM group who received  $30 \times 10^6$  ASM was not included in the analysis of the electromechanical mapping (NOGA™) due to cardioversion performed the previous day for termination of atrial fibrillation
- All ASM transplant procedures were performed successfully without injection-related complications
- During mapping of the left ventricle 2 subjects experienced sustained ventricular tachycardia requiring cardioversion prior to performing the ASM injections
- 1 subject in the ASM group who received  $300 \times 10^6$  ASM experienced 2 ICD shocks on day 9 post transplant and was treated with amiodarone and procainamide. At 3 months follow-up, no further arrhythmic events were recorded by the ICD
- 1 subject in the ASM group who received  $30 \times 10^6$  ASM required PCI of RCA at 12 months follow-up
- No deaths, MI, heart failure hospitalizations, or cerebrovascular events were observed in either group

# NYHA Class



# LV mapping

## Average unipolar voltage

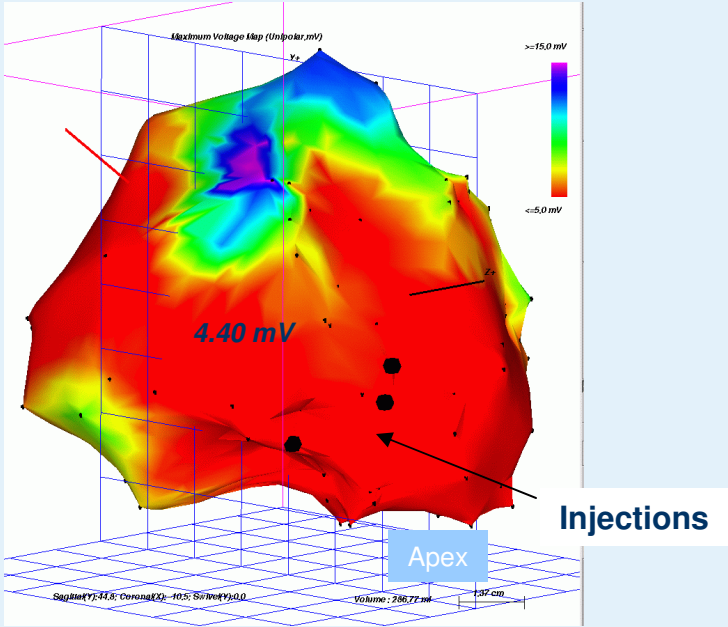


# 3-D NOGA MAPPING AND INTRACARDIAC INJECTIONS

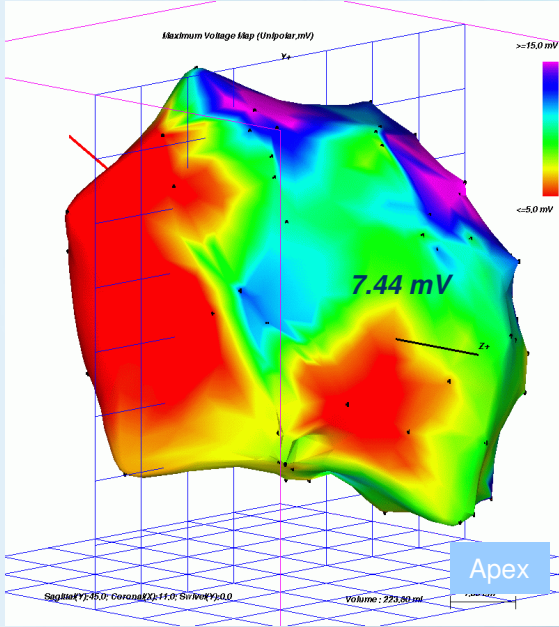
## Unipolar Voltage Map

*Injections of 100 million cells into infarct region shown in red*

*3 months post reveals significant improvement in viability of the heart*



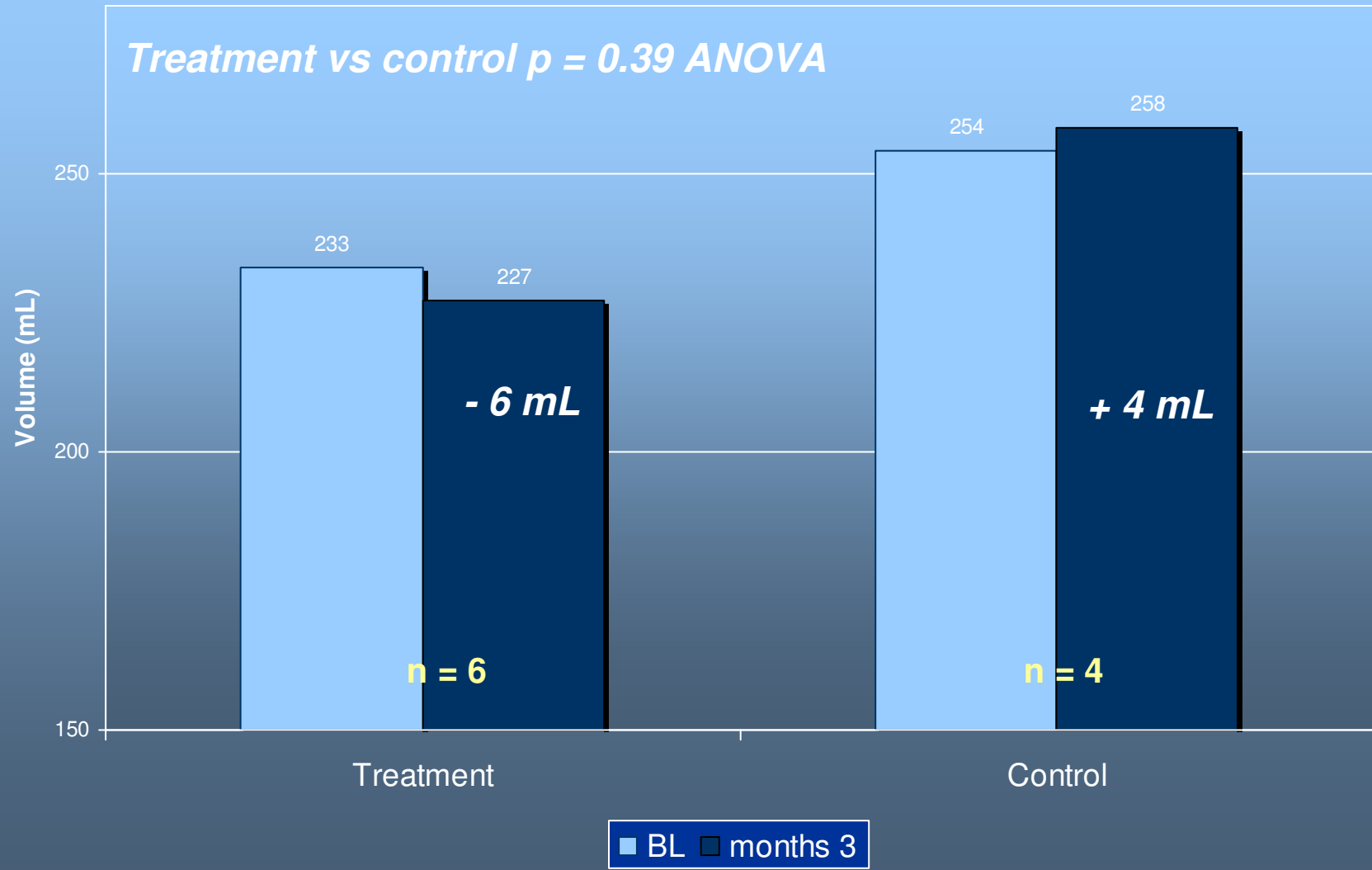
Inferior view



Inferior view

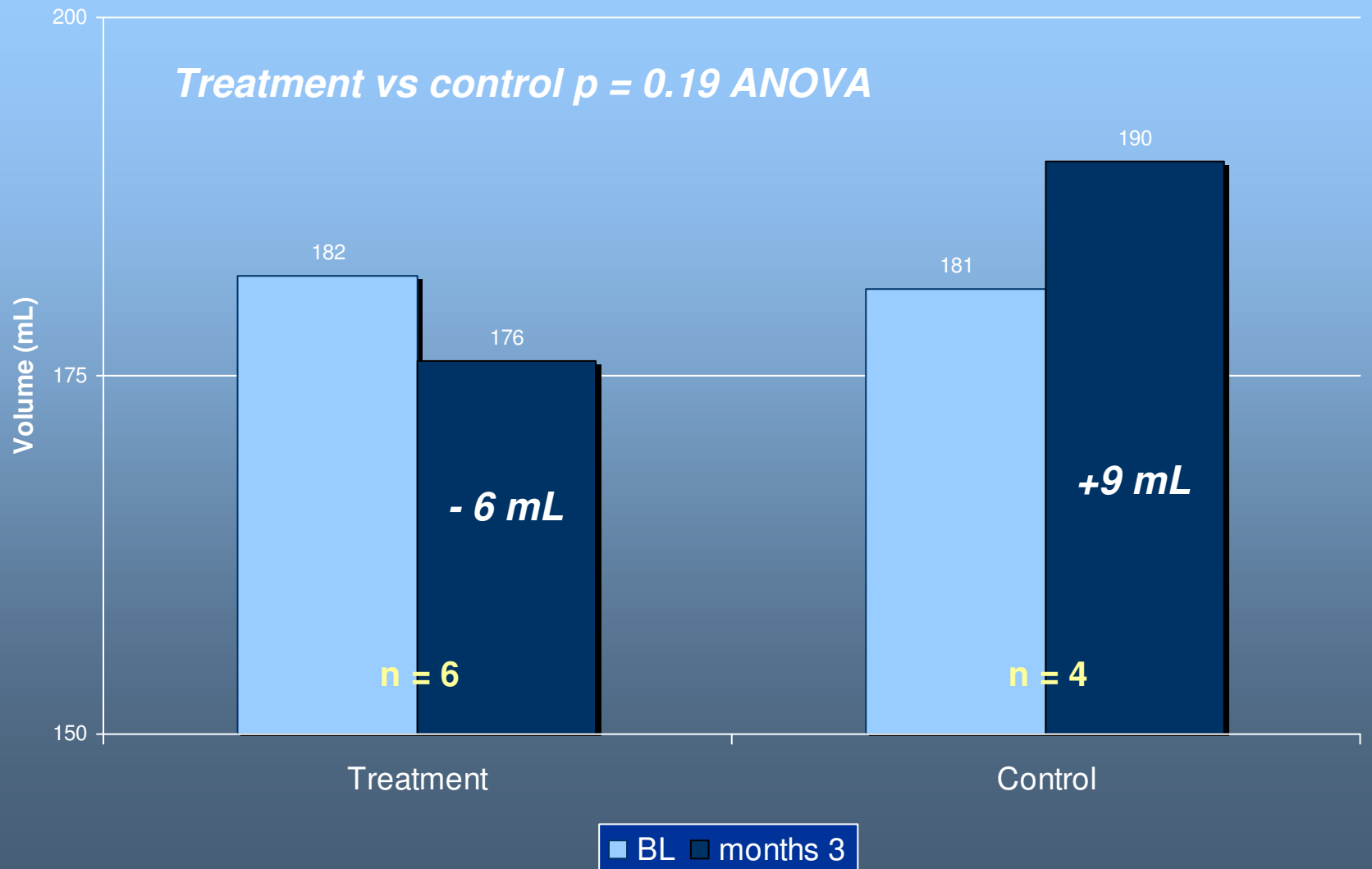
# Nuclear SPECT

End Diastolic Volume

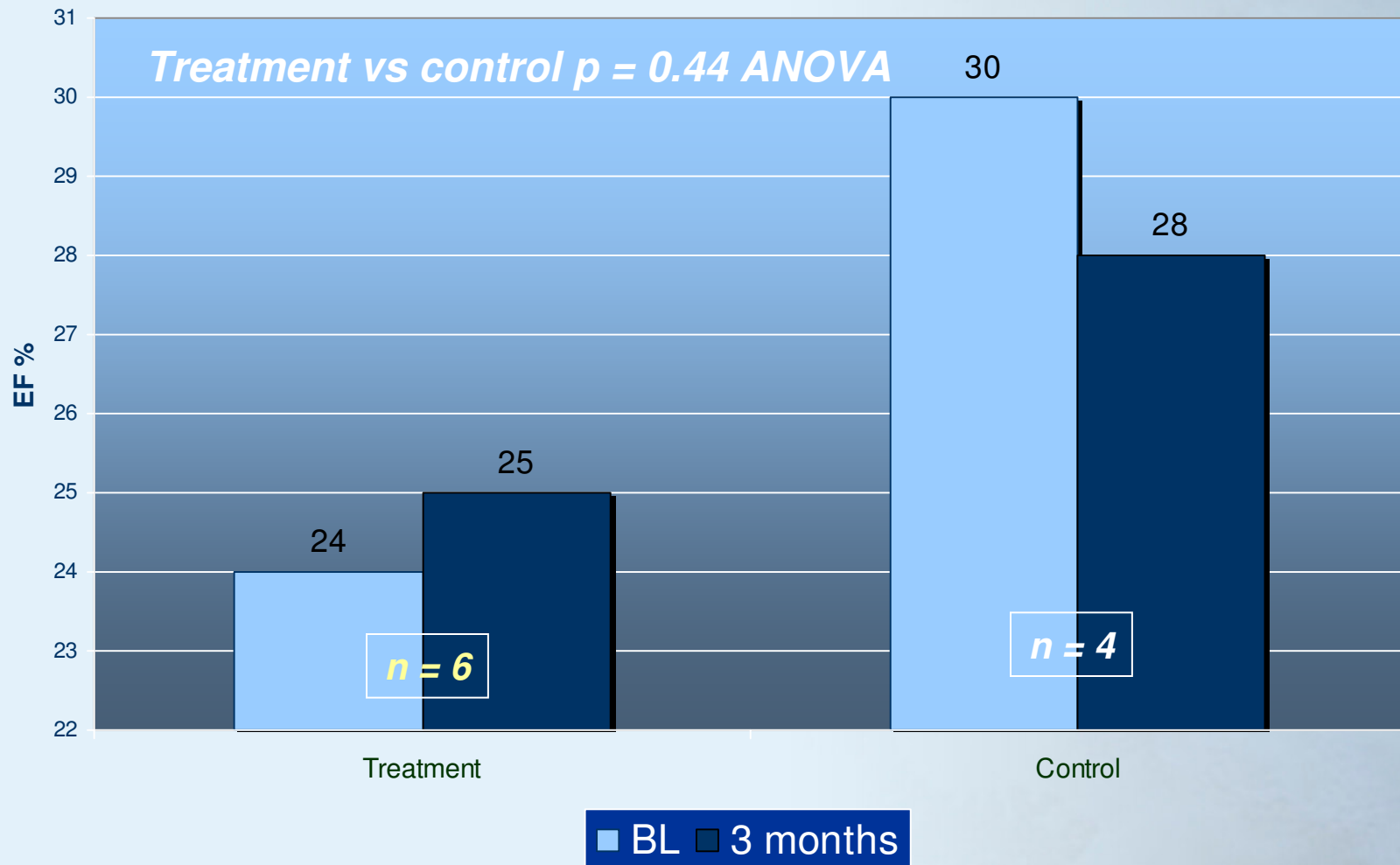


# Nuclear SPECT

End Systolic Volume



Ejection Fraction  
Gated SPECT



# Conclusion

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- These findings confirm that endomyocardial delivery of ASM is feasible and safe
- Highly significant improvement in patient heart failure symptoms (NYHA)
- Improvement in viability by 3-D electromechanical mapping verified correct and accurate targeting
- There was trend toward improvement in heart function
- In this small sample size there was a trend toward improvement in the ASM group, while a slight worsening was observed in the control group
- Further larger scale placebo controlled trials are warranted