Randomized, Double-Blind, Placebo-Controlled Study of Intramyocardial CD34+ Cell Therapy for Refractory Angina

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on behalf of ACT34-CMI Investigators

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Presenter Disclosure Information

Douglas Losordo, M.D.

The following relationships exist related to this presentation:

- Study Sponsored by Baxter Healthcare
- Dr. Losordo was previously a paid consultant for Baxter Healthcare, receiving “modest” consulting fees by ACC definition.

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ACT34-CMI Core Labs

Exercise Treadmill Time (ETT) Core Lab

- Dr. Ernest Gervino

Cardiovascular Core Laboratories – SPECT

- James Udelson, MD

ACT34-CMI Core Labs

Magnetic Resonance Imaging / PERFUSE

- Dr. Evan Appelbaum

Quality of Life

- Dr. David Cohen

Study Logistics

Data Safety Monitoring Board

- Dr. Jeffrey Brinker, Chair
- Dr. Kenneth Ellenbogen
- Dr. Armand Keating
- Dr. George Vetrovec
- Dr. James Dziura

Brigham and Women's Hospital, Clinical Endpoint Committee

- Dr. Marc Pfeffer
- Dr. Akshay Desai
- Dr. Peter Finn

Study Logistics

Duke Clinical Research Institute (statistical analysis)

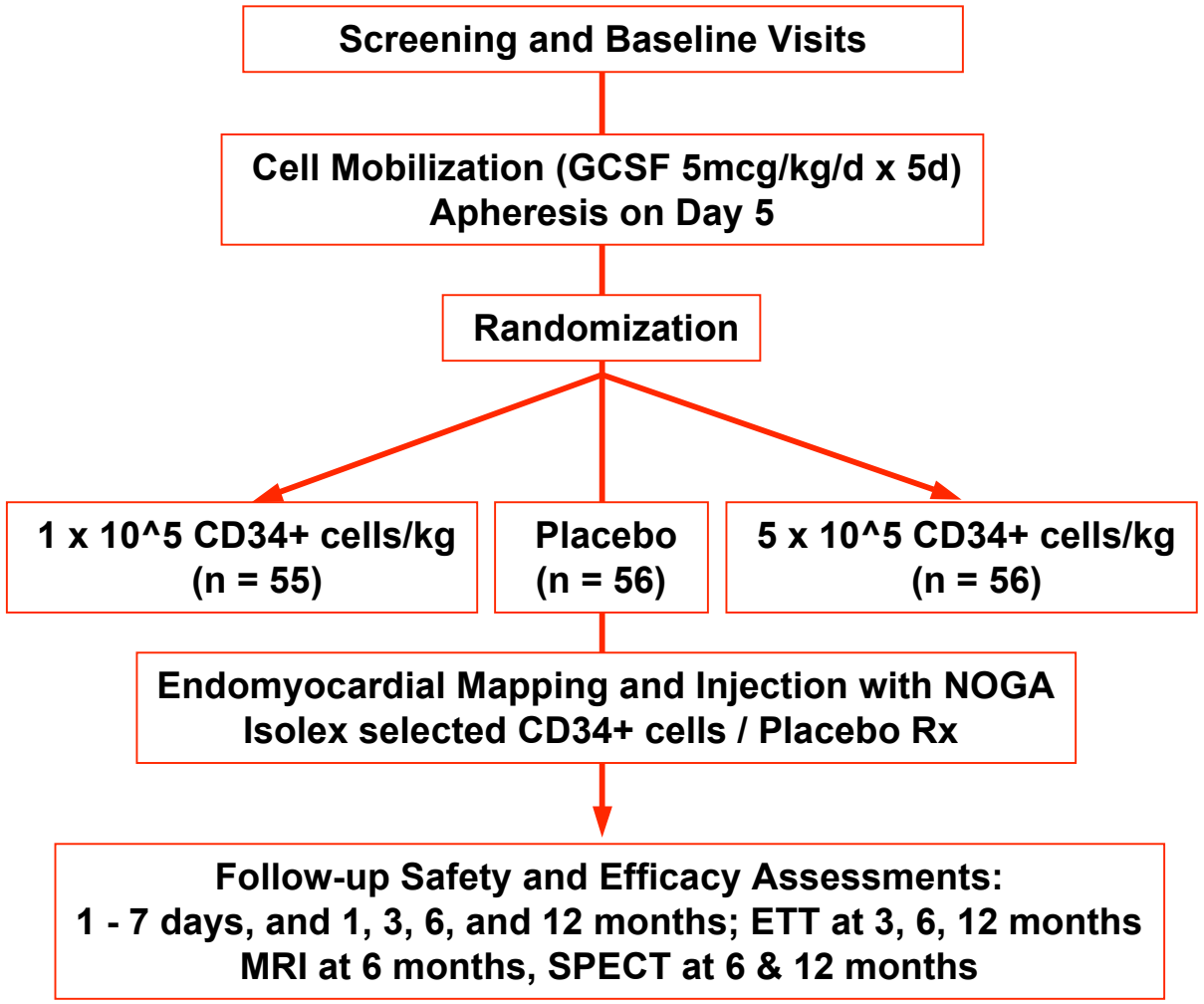
- Robert Harrington, MD
- Karen Pieper, M.S.
- Robert Clare, M.S.

Biologics Delivery Systems: NOGA Mapping Support

Phase II ACT34–CMI Study Design

Subject population (n=167)

- 21-80 yrs
- CCS class III or IV Angina
- Attempted "best" medical therapy
- Non-candidate for Surgical/Perc. revasc.
- Ischemia on SPECT
- 3-10 min. mod. Bruce protocol with angina or anginal equivalent at baseline



Endpoints

Safety

- Adverse event reporting, MACE, physical examination, vital signs, ECHO, laboratory parameters, revascularization procedures, hospitalization rates for cardiac related admissions and Emergency Department/Acute Care Service visits for cardiac related admissions will assess safety.

Bioactivity

- Primary Efficacy variable is frequency of angina episodes per week, when comparing subjects receiving injection of CD34+ cells to placebo. Secondary Efficacy variables are divided into two categories, symptom relief and myocardial perfusion, and function measurement endpoints. Symptom Relief: ETT, anti-anginal medication, pedometer measurements, CCS functional class and QOL [SAQ, SF-36, Dyspnea Questionnaire, Euro 5 Questionnaire], and the combined rate of MACE events. Myocardial perfusion and function measurements: SPECT and cardiac MRI.

Enrollment/Demographics

- **Enrollment**
  - **First subject enrolled (screened): 04 April 2006**
  - First subject treated: 18 May 2006
  - Last subject screened: 15 Jan 2008
  - **Last subject treated: 13 March 2008**
  - Last subject 6 Mo follow up: 01 Oct 2008
  - Last subject 12 Mo follow up: 05 Mar 2009

- 321 subjects signed informed consent
- 167 subjects underwent injection procedure
- 162 subjects completed 6 mo follow up

Enrollment/Demographics

	Control	$1x10^5$	$5x10^5$	p-value
Age	61.8	61.3	59.8	0.471
%Female	10.7	16.4	12.5	0.668
%Diabetic	55.4	47.3	55.4	0.617
%Prior MI	73.7%	74.1%	77.6%	0.903
# of Prior PCI	2.7 (3.8)	3.2 (2.8)	2.8 (2.7)	0.668
# of Prior CABG	1.4 (0.6)	1.2 (0.6)	1.2 (0.7)	0.410
LVEF(SPECT) mean (SD)	59.8 (14.6)	58.9 (14.2)	60.6 (13.3)	0.820
ACE-I	58.9%	52.7%	57.1%	0.819
Beta Blocker	98.2%	92.7%	91.1%	0.263
Statin	91.1%	90.9%	89.3%	1.000

Safety

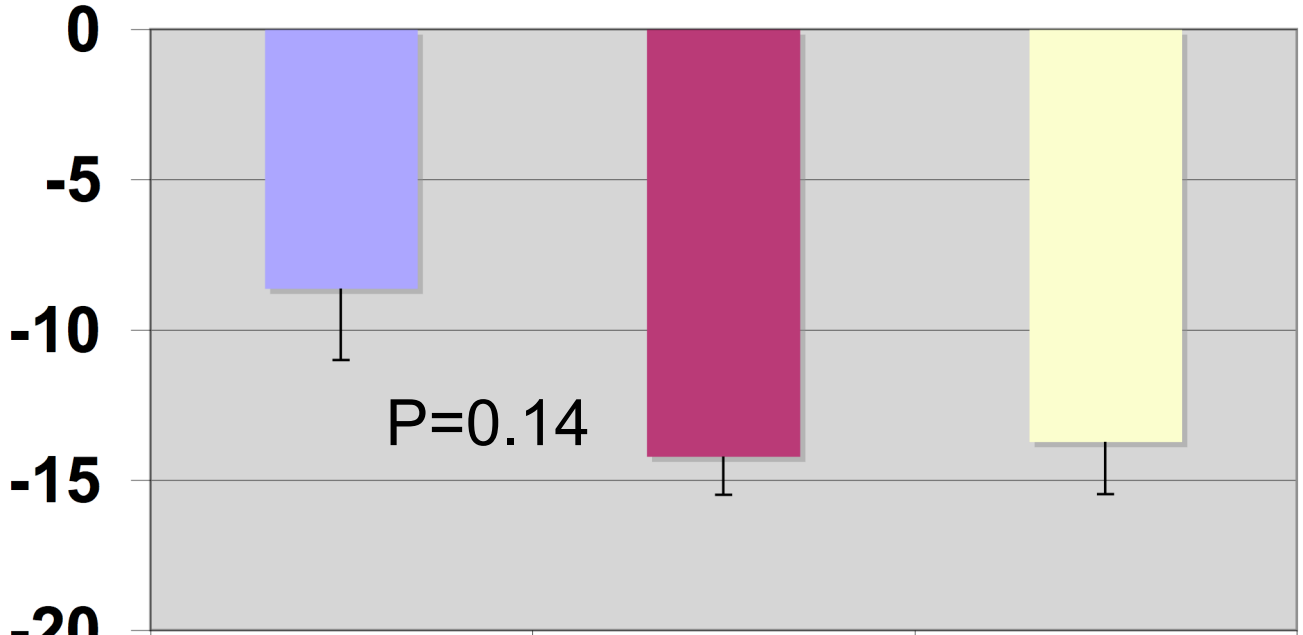
- **Procedural Events**
  - 2 Perforations (1.2%)
  - 1 Death (0.6%)

Major Adverse Cardiac Events (12 Months)

	Control	$1x10^5$	$5x10^5$	p-value
Any MACE	25.0%	12.7%	14.3%	0.194
Death, MI, Urgent Revasc	10.7%	7.3%	5.4%	0.594
Death, MI, Post-PCI MI, Urgent Revasc	12.5%	7.3%	5.4%	0.416
Any MI	7.1%	9.1%	5.4%	.707
MI pre/injection	3.6%	1.8%	1.8%	1.000
Death, MI, Urgent Revasc, Worse CHF, ACS	21.4%	9.1%	8.9%	0.123

ACT-34 CMI: Reduction in Angina

Anginal Episodes per Week
Change from baseline at 6 months

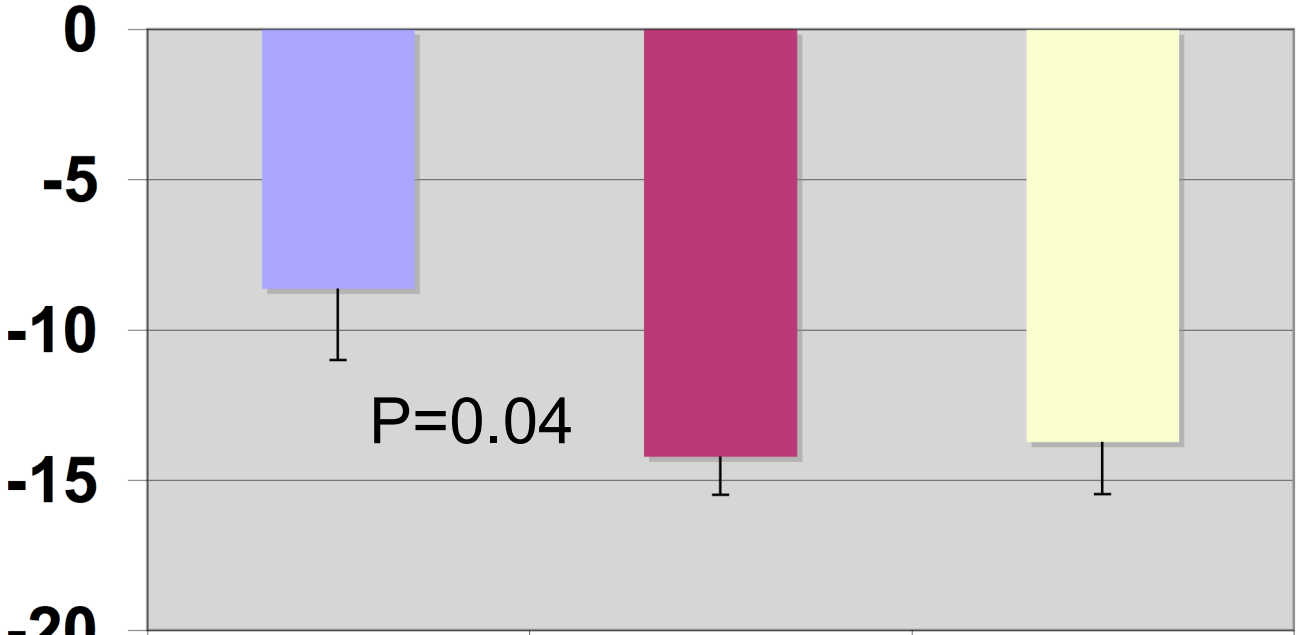


Placebo	Low	High
-8.6	-14.2	-13.7

Poisson Regression with Extra Variability

ACT-34 CMI: Reduction in Angina

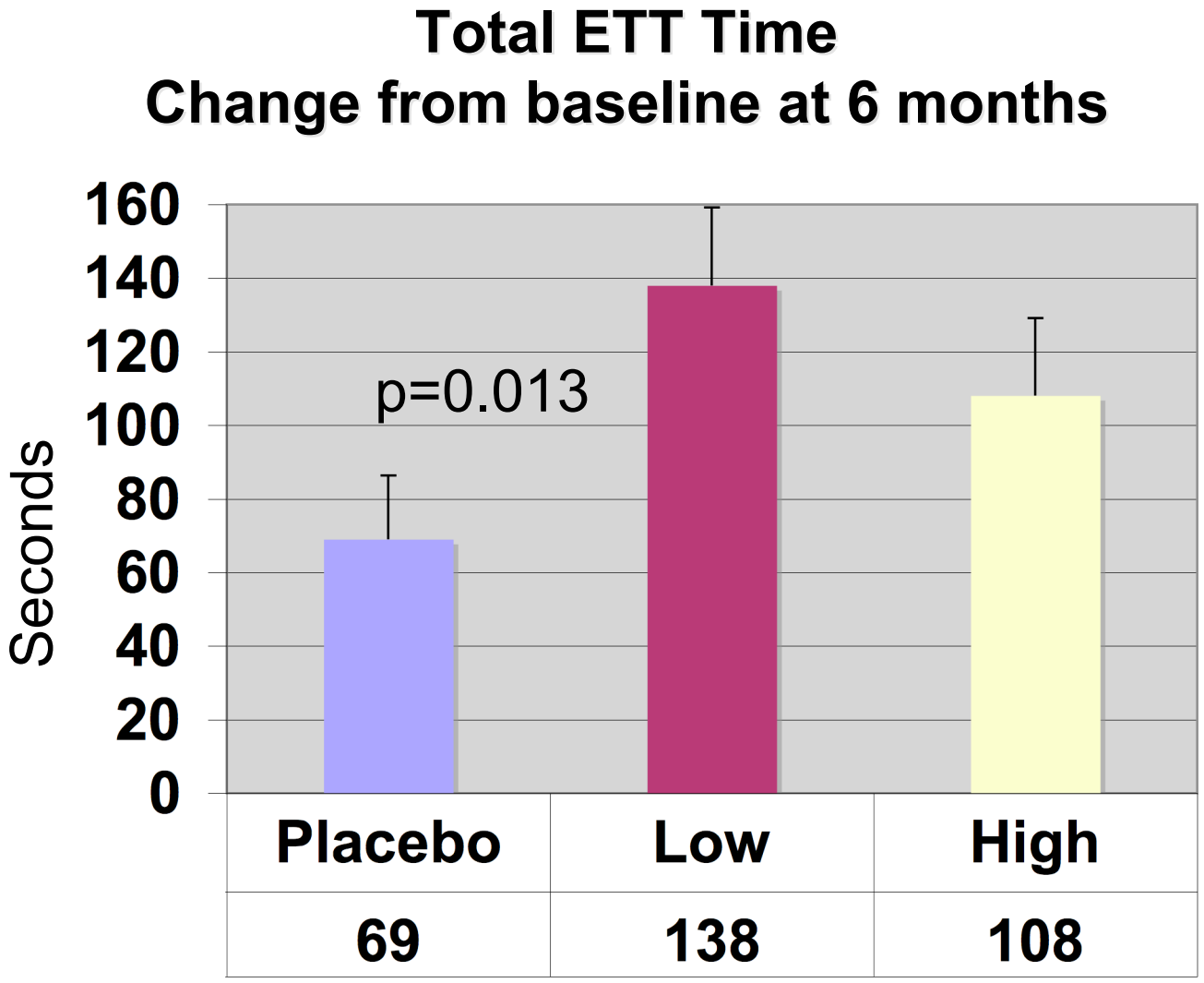
Anginal Episodes per Week
Change from baseline at 6 months



Placebo	Low	High
-8.6	-14.2	-13.7

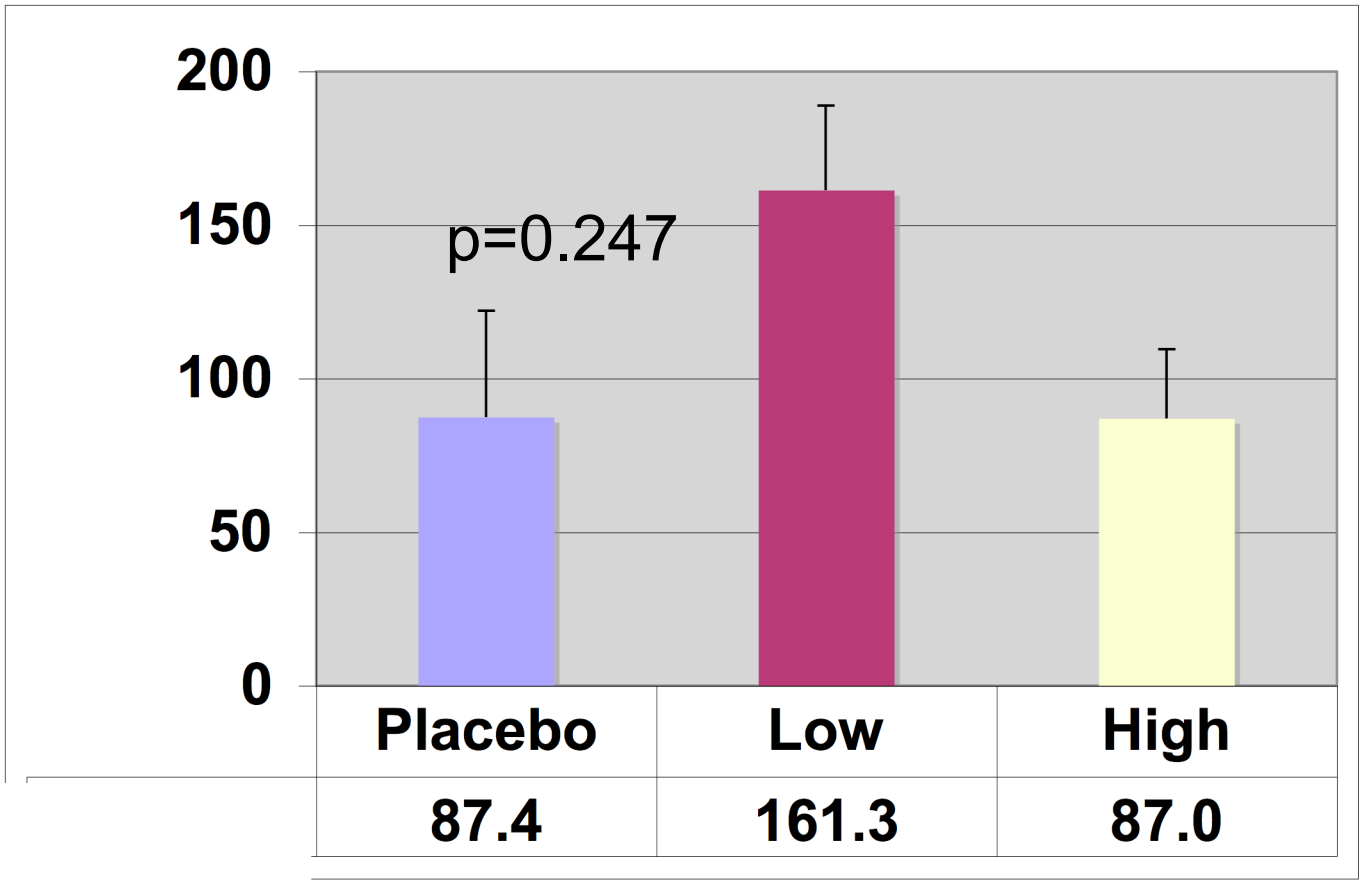
Analysis of Variance (ANOVA)

ACT-34 CMI: Increase in Exercise Time



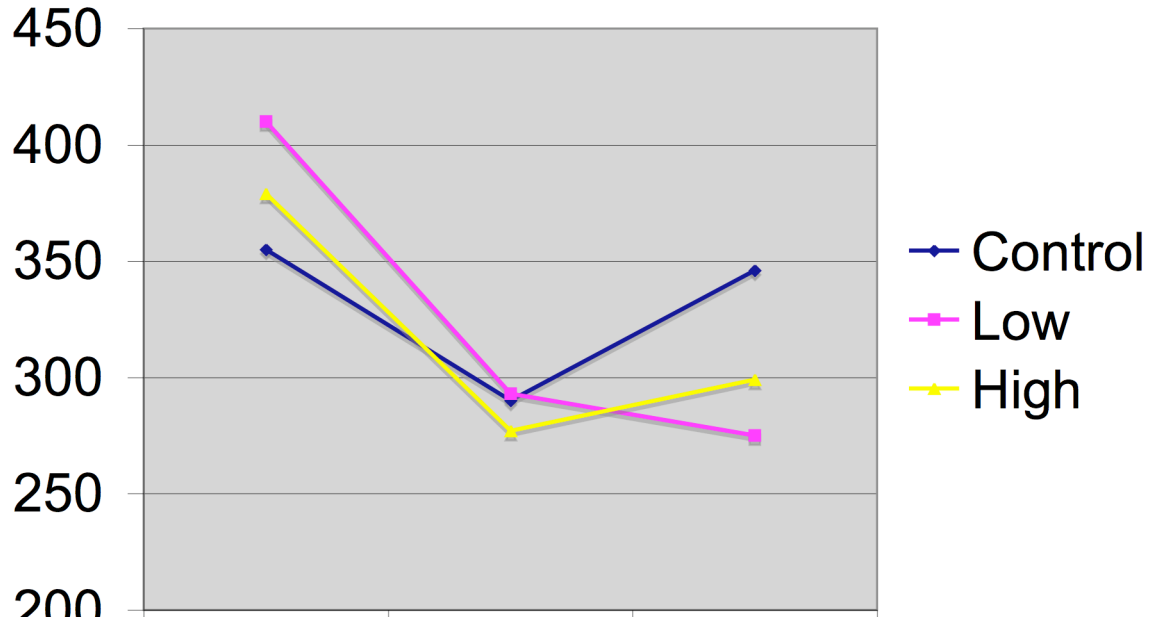
ACT-34 CMI: Increase in Time to Angina

Time to Angina
Change from baseline at 6 months



ACT-34 CMI: Reduction in Time to Resolution of Angina

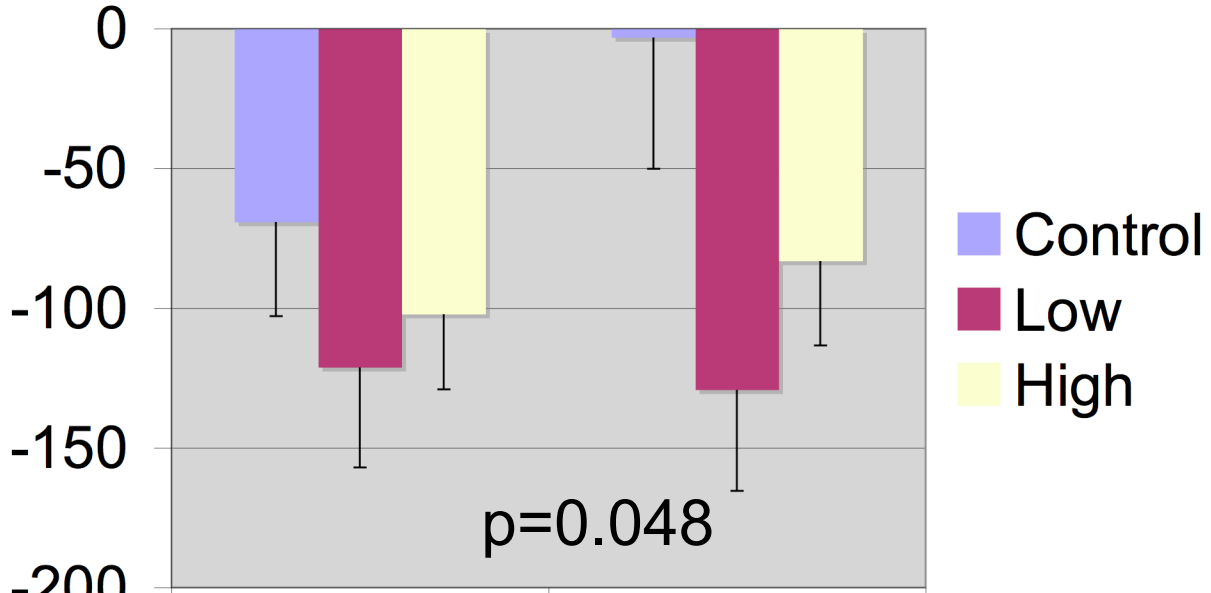
Time to Resolution of Angina



	Baseline	3 Mo	6 Mo
Control	355	290	346
Low	410	293	275
High	379	277	299

ACT-34 CMI: More Rapid Resolution of Angina

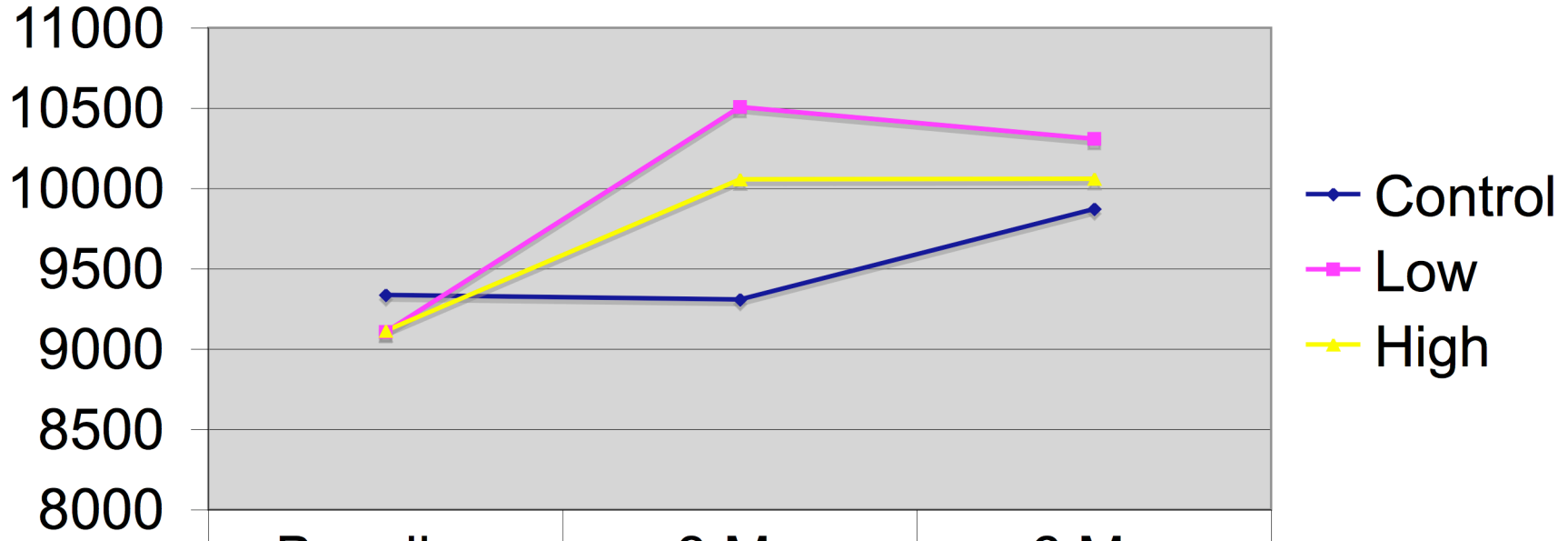
Change in Time to Resolution of Angina



	3 Mo	6 Mo
Control	-69	-3
Low	-121	-129
High	-102	-83

ACT-34 CMI: Increased RPP at Resolution of Angina

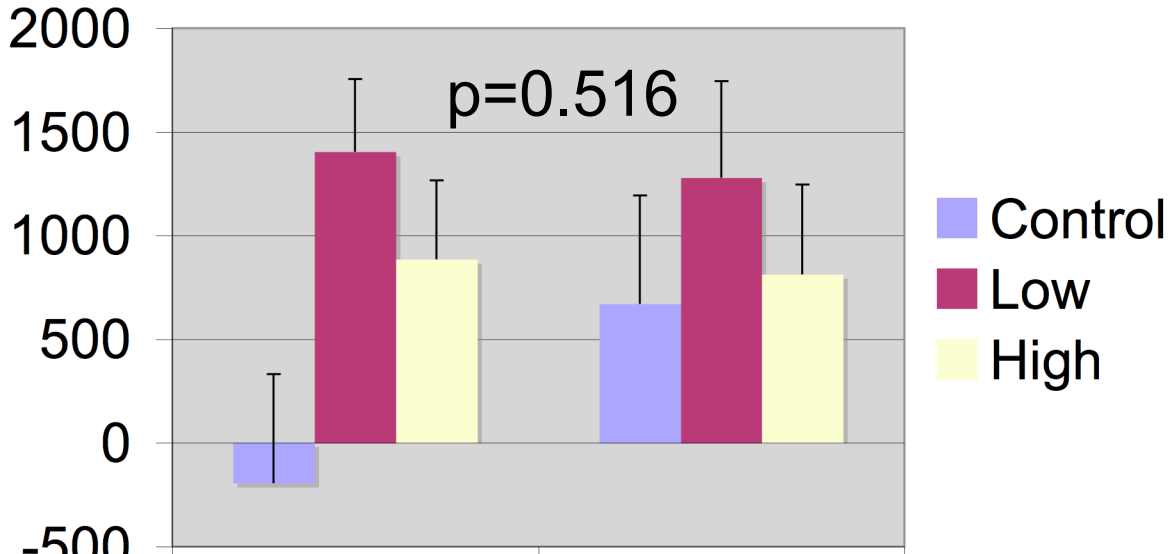
Rate-Pressure Product at Resolution of Angina



	Baseline	3 Mo	6 Mo
Control	9336	9307	9873
Low	9107	10506	10308
High	9115	10057	10062

ACT-34 CMI: Increase in RPP at Resolution of Angina

Change in Rate-Pressure Product at Resolution of Angina



	3 Mo	6 Mo
Control	-191	671
Low	1403	1279
High	886	813

Other Outcomes

- Seattle Angina Questionnaire
- SPECT
- CCS Angina Classification
- SF36

Summary

- **Feasibility**
  - Phase 2 study successfully enrolled 167 pts at 26 centers across US
- **Safety**
  - No evidence of harm by injection of autologous CD34+ cells; Net trends toward decreased MACE

Summary (2)

- **Bioactivity**
  - Angina frequency
  - ETT
    - Total Time increased
    - Time to Resolution of Angina
    - Time to Angina
    - Change in RPP at resolution of Angina
  - SPECT CCS Class, SAQ, SF36

Conclusions

- 167 “no-option” refractory angina pts enrolled in RCT of intramyocardial autologous $CD34^+$ stem cell therapy
- Safety profile appears acceptable
- Significant improvement in ETT - first in this population
- Reduced angina; trend vs. significant

Ongoing

- Awaiting 12 month data
- 2nd year follow up study

Limitations

- Phase 2 study - not conclusive
- 12 mo data pending

Questions

- Effects of GCSF
- Non-linear dose response

Thank you for your attention

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