
**Discussion of Results of OBA Protocol
#0610-809: A Phase 1/2
Randomized, Double-Blinded, Placebo-
Controlled Dose Escalation trial
of Intracoronary Administration of
MYDICAR® (AAV1/SÉRCA2a) in Subjects with
Heart Failure**

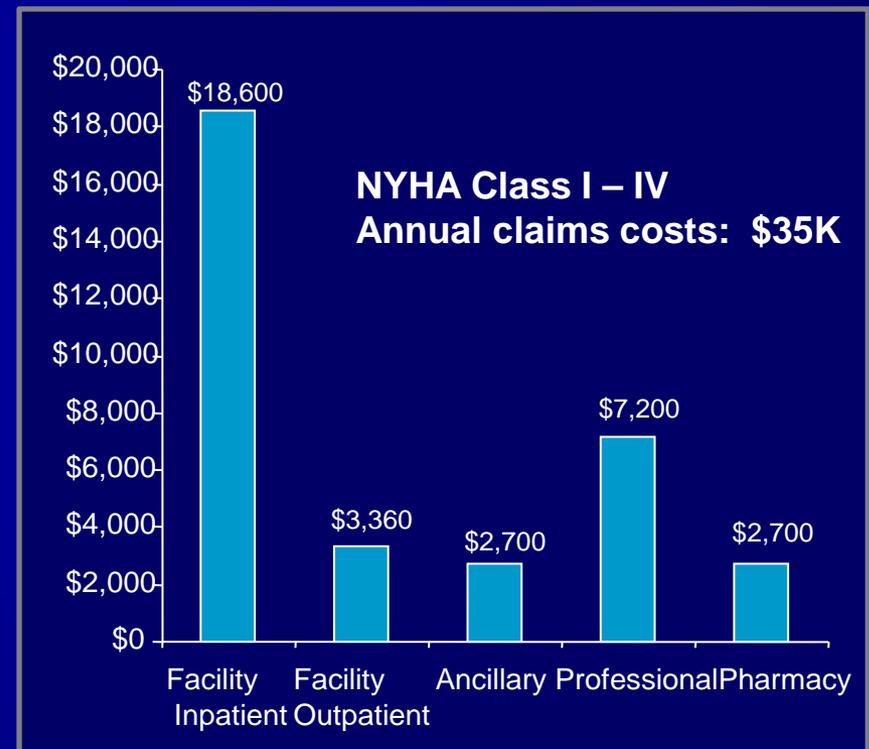
Presenter: Dr. Krisztina Zsebo, Ph.D.
Celladon Corporation, La Jolla, CA

MYDICAR® Targets End-Stage Heart Failure: A Significant Healthcare Burden

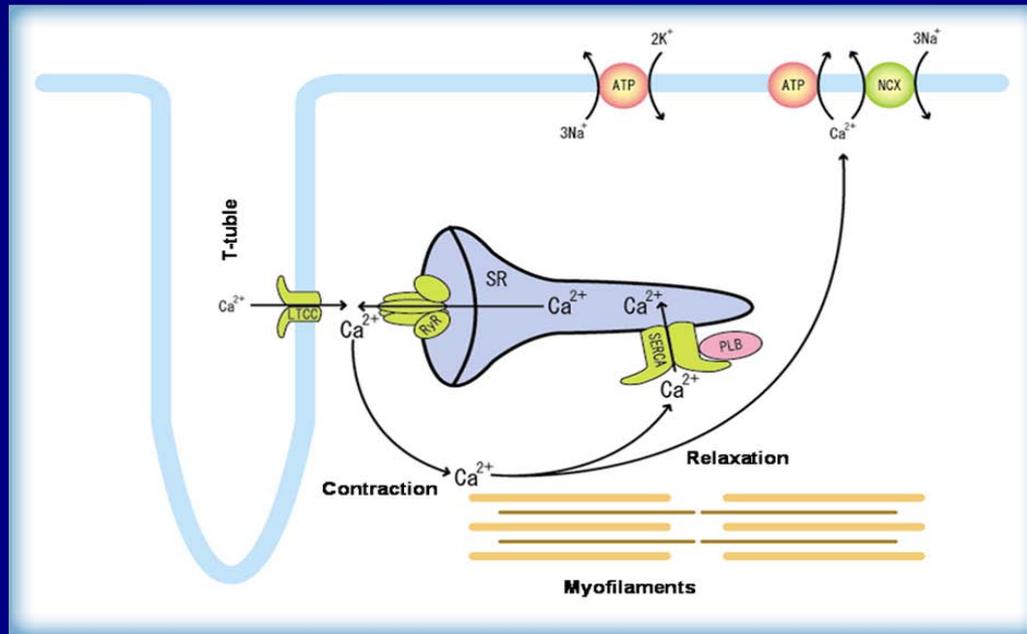
Current Treatment Options:

- Heart Transplant
 - Limited by available donor hearts (~2100 per year); 100,000 patients on waiting list
 - >\$169 K
- Left Ventricular Assist Device (LVAD)
 - Limited by invasive surgical procedure and patient co-morbidities; provides ~two year survival benefit (~1000 per year)
 - >\$169K

Heart failure: ~ 300,000 deaths annually in U.S. and \$39 B Annual Cost



SERCA2a Deficiency is Central to Progression of Heart Failure



- SERCA2a transfers 75% of Ca^{2+} from cytosol to SR lumen
- In both experimental models and human HF, SERCA2a deficiency results in abnormal Ca^{2+} handling and a deficient contractile state
- In animal models, restoration of SERCA2a activity via gene transfer rescues contractile deficit

– J Am Coll Cardiol. 2008;51:1112-1119; J Mol Cell Cardiol. 2007;42:852-861; Byrne M, et.al. Gene Ther. (24 Jul 2008);[DOI: 10.1038/gt.2008.120]

MYDICAR[®]: AAV Based Genetic Enzyme Replacement Therapy



- Recombinant AAV delivering the human SERCA2a cDNA
- AAV2 ITR & AAV1 Capsid proteins
- Pharmacological effects in heart failure:
 - SERCA2a protein expressed in cardiomyocytes increases contractility and relaxation
 - Transduction of coronary endothelial cells increases coronary blood flow



Current MYDICAR[®] Administration: Direct Intracoronary Infusion

- Simple outpatient procedure in cardiac catheterization lab
- Percutaneous catheterization through femoral artery using off the shelf components
- One time intracoronary infusion over 10 minutes-
 - *No balloon occlusion*
 - *No injection or local tissue trauma*
- Used in pivotal large animal pharmacology-safety studies and CUPID Phase 1 and 2 trials



MYDICAR®

**PHARMACOLOGY &
TOXICOLOGY**

Pivotal Pharmacology & Safety Study Swine Model of Systolic Heart Failure

Study Title

A 16-Week, Single Dose, Pharmacology Study of AAV1/SERCA2a Delivered via Intracoronary Infusion in a Swine Mitral Regurgitation Model of Heart Failure

Design

- Day 0: Heart failure created by surgical disruption of mitral valve
- Day 56: Dose with MYDICAR[®] (1×10^{12} DRP) or placebo (Between Cohorts 2 and 3 in CUPID)
- Day 112: Invasive hemodynamics, functional studies, molecular studies, safety assessment (clinical chemistry, histopathology, hematology)

Cardiac Function Improved vs. Placebo

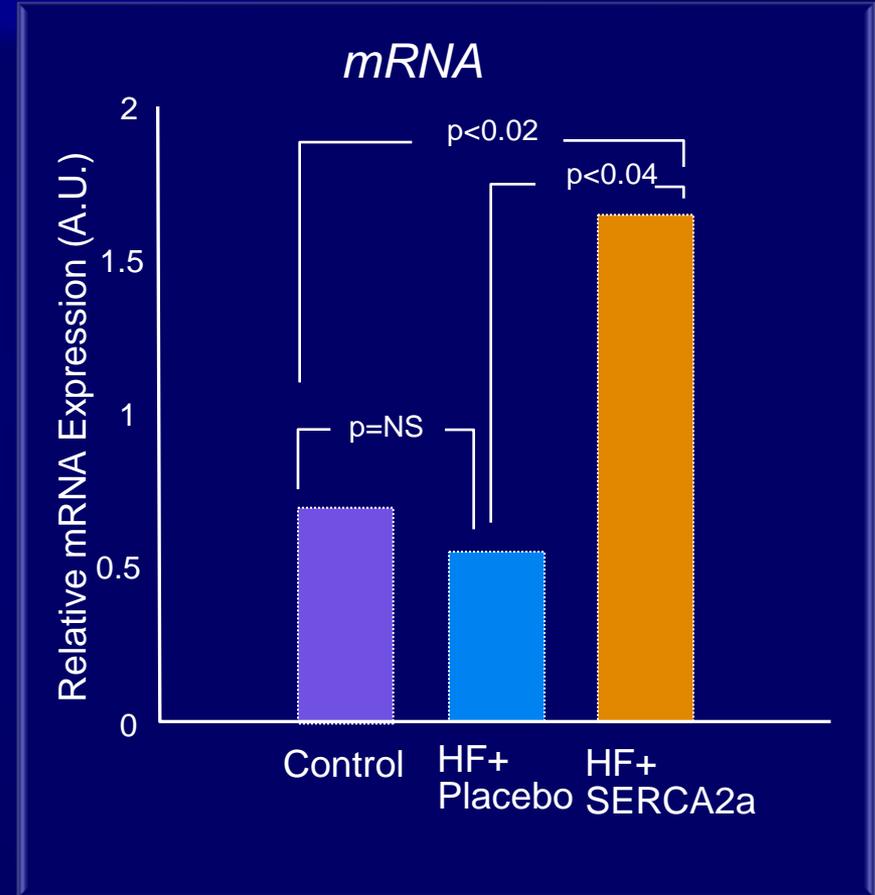
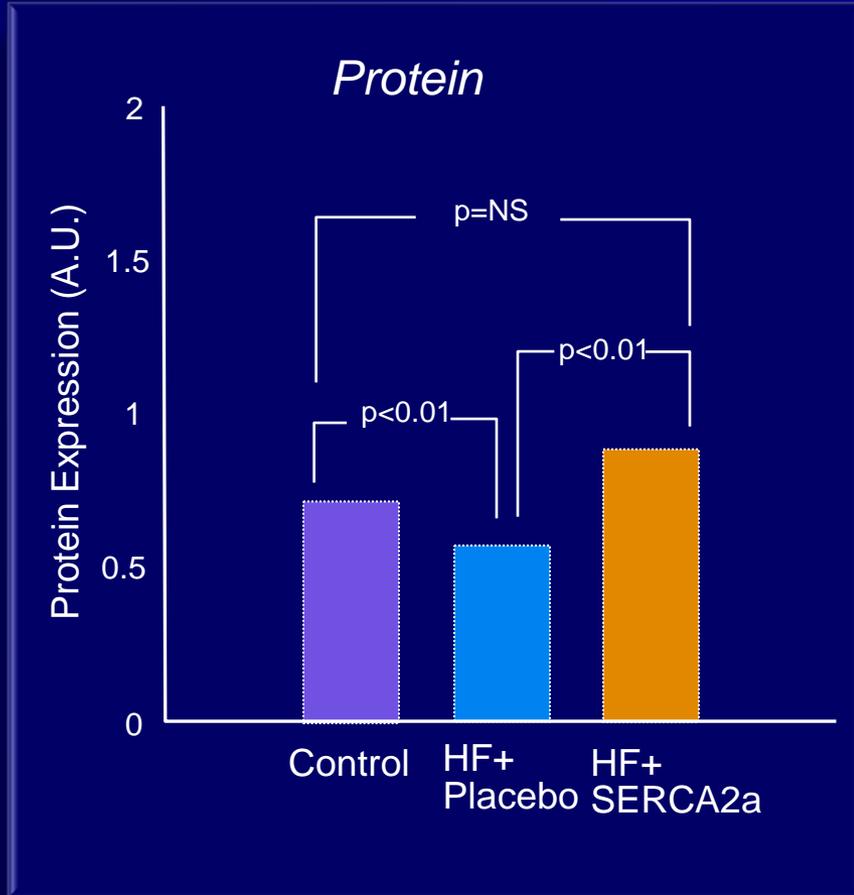
Summary of Echocardiography and Millar Catheter Measurements at 56 Days Post-MYDICAR Administration

Cardiac Function Parameters	Absolute (Relative) Median Change Day 56 to Day 112*		
	Placebo	MYDICAR	p-value
Fractional Shortening	-0.8% (-2%)	+8% (+26%)	0.05
Ejection Fraction	-5.5% (-8%)	+10.8% (+18%)	0.04
Cardiac Output	+3.4 mL/min (+60%)	+5.9 mL/min (+94%)	0.05
End Systolic Volume	+16.0 mL (+35%)	-9.9 mL (-14%)	0.02
End Diastolic Volume	+45.4 mL (+30%)	+10.7 mL (+8%)	ns
dP/dt	-41 mmHG/sec (-3%)	+466 mmHG/sec (+33%)	ns

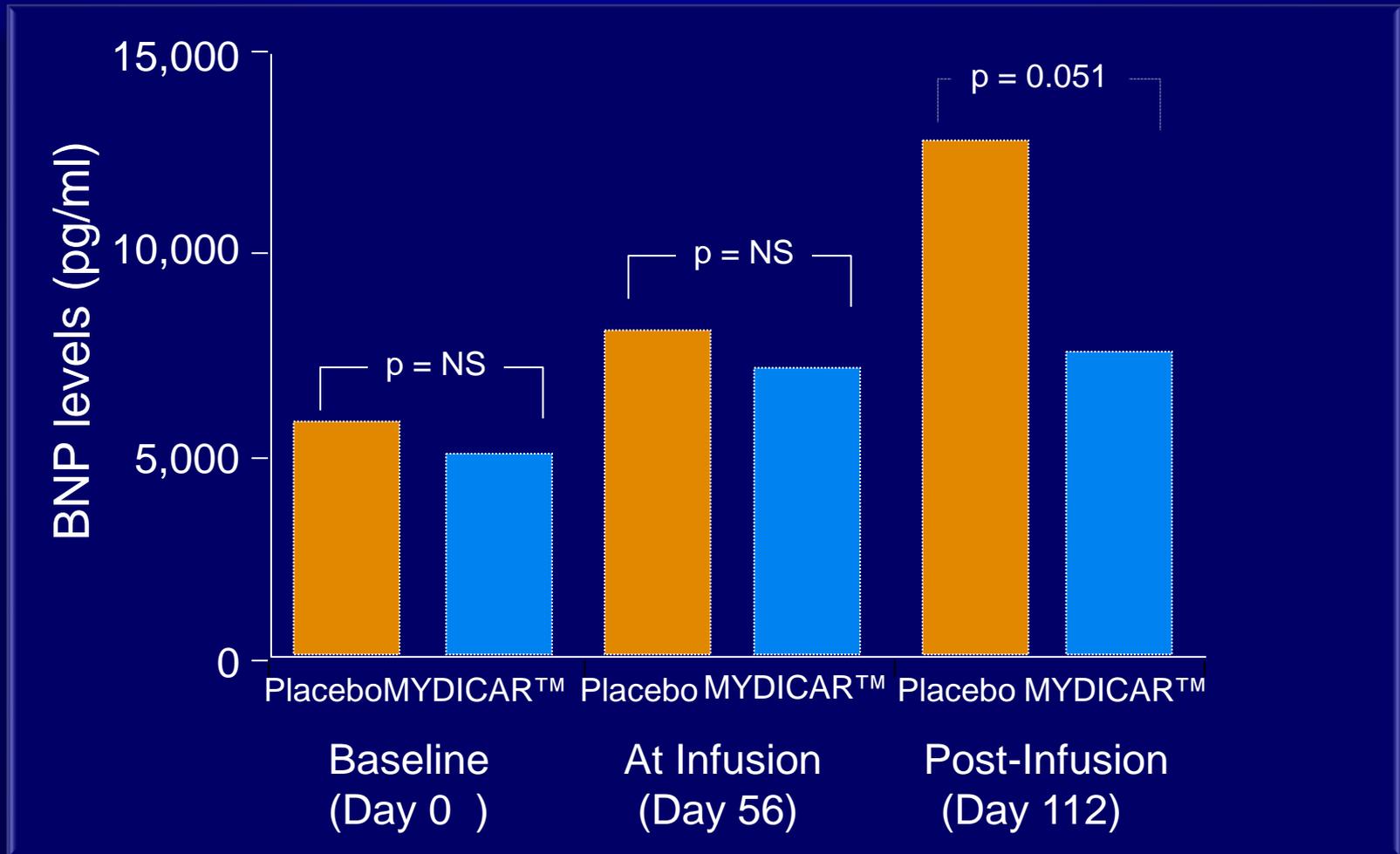
*Absolute change = (Day 112 – Day 56)

Relative Change = 100% x (Day 112 - Day 56)/Day 56

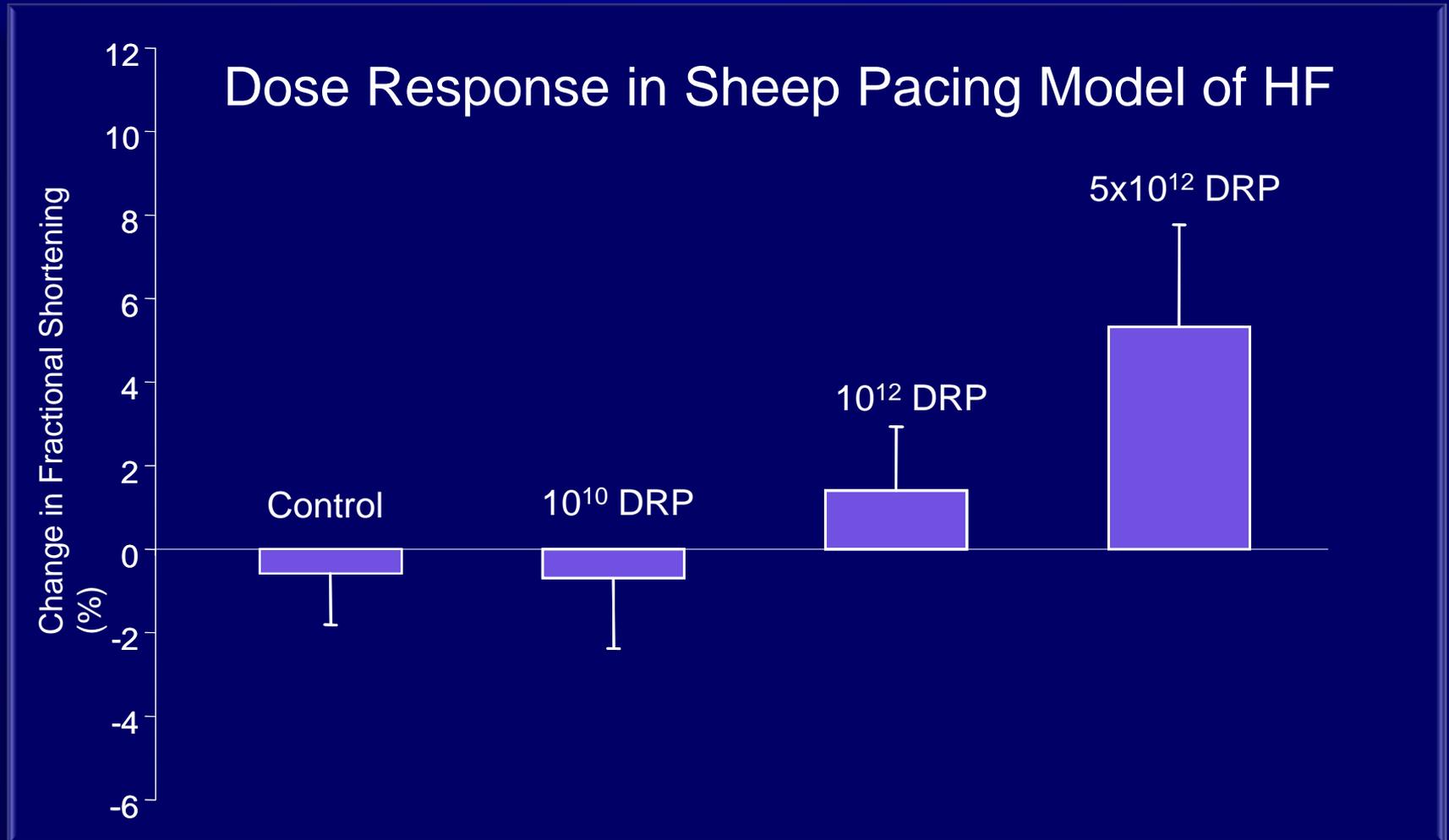
Cardiac Tissue SERCA2a Expression Increased at Day 112 vs. Placebo



BNP Levels Improved vs. Placebo in MYDICAR[®] Treated Animals



Supporting Preclinical Pharmacology Studies in Sheep



Data are presented as Least Square means \pm standard errors



Pivotal Toxicology and Biodistribution Study in Minipigs

- Up to $\approx 5 \times 10^{12}$ DRP ($4-6 \times 10^{12}$ DRP/kg) (3x high dose in CUPID)
- No signs of toxicity, clinical pathology or histopathology in Göttingen minipigs at 5, 30 and 90 days
- No abnormalities in histopathology, Echo or ECG
- Presence of vector DNA by qPCR: most abundant at the infusion site (heart) and highly perfused tissues, and decreased at distal sites with dose administered and time
 - Stable level in heart from Day 30 to 90
- Increased SERCA2a protein expression by western blot in the right and left ventricular walls 90 days following gene transfer

Phase 2 Myocardial Delivery of AAV1/SERCA2a (MYDICAR®) in Subjects with Advanced Heart Failure

clinicaltrials.gov Identifier NCT00454818

Protocol: J Card Fail. 2008;14:355-367

Phase I: J of Cardiac Fail 2009;15(3):171-181

Phase 2: Circulation. 2011 Jul 19;124(3):304-313

Eligibility

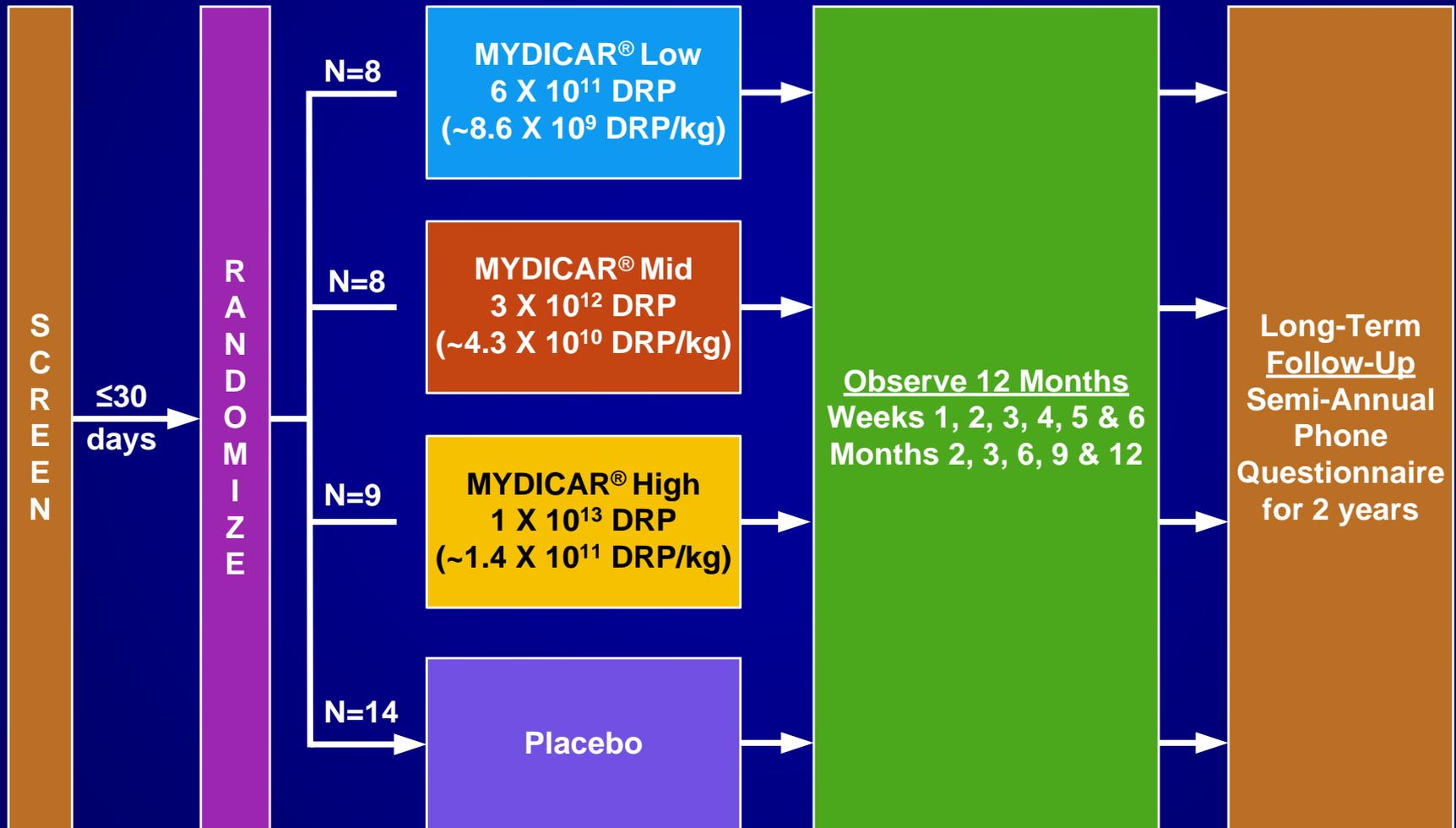
Main Inclusion Criteria

- Age 18-75 years old
- NYHA Class III/IV
- Ischemic or non-ischemic cardiomyopathy
- Maximal oxygen consumption (VO_2 max) of ≤ 20 mL/kg/min
- Left ventricular ejection fraction $\leq 35\%$
- ICD implanted
- If indicated, biventricular pacemaker implanted for >6 months
- Stable, optimized HF regimen for 30 days, except for diuretics

Main Exclusion Criteria

- Anti-AAV1 neutralizing antibody titer (NAb) $\geq 1:2$
- Clinically significant MI within 6 months
- Likely need for HF-related surgery within next 6 months
- Expected survival <1 years
 - Based on investigator's clinical judgment of HF and co-morbid conditions

Study Outline: Randomized, Double-Blind, Placebo Controlled (n=39)



Baseline Patient Characteristics

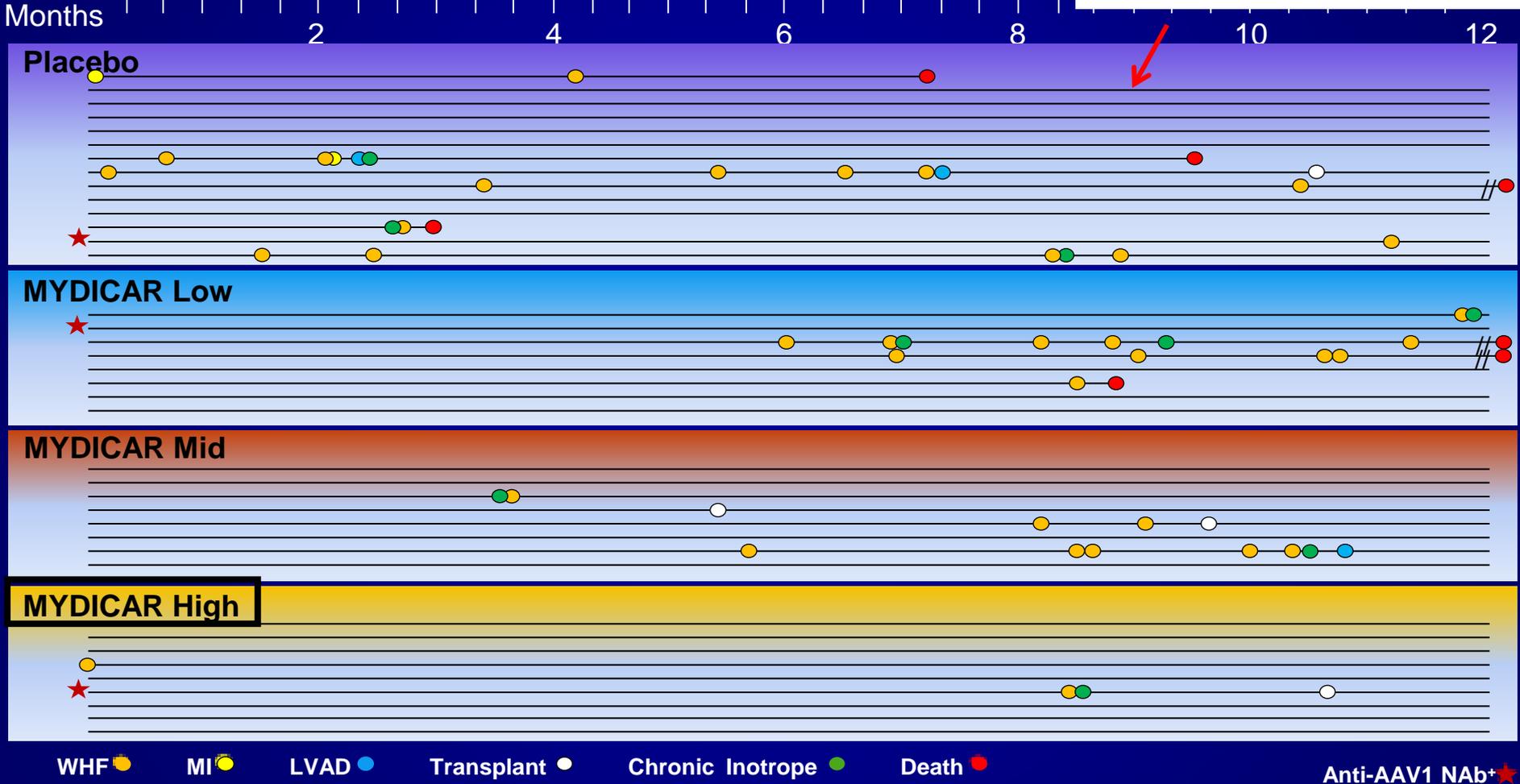
Characteristic	All Subjects N=39
Age, years, mean (SD)	60.5 (11.5)
Sex, n	34 Male
Race, n	34 White
HF Etiology, n (%)	
Ischemic cardiomyopathy	19 (48.7)
Idiopathic cardiomyopathy	14 (35.9)
Hypertensive cardiomyopathy	4 (10.3)
Other	3 (7.7)

MYDICAR® Reduced Incidence of Serious Cardiovascular Clinical Events

- Prospectively Defined Clinical Events Adjudicated by Blinded Clinical Endpoints Committee:
 - Cardiovascular Death
 - Left Ventricular Assist Device Implantation
 - Cardiac Transplant
 - Worsening Heart Failure (WHF, >90% resulted in hospitalizations)
 - Myocardial Infarction
 - Need for Chronic IV Inotrope Use

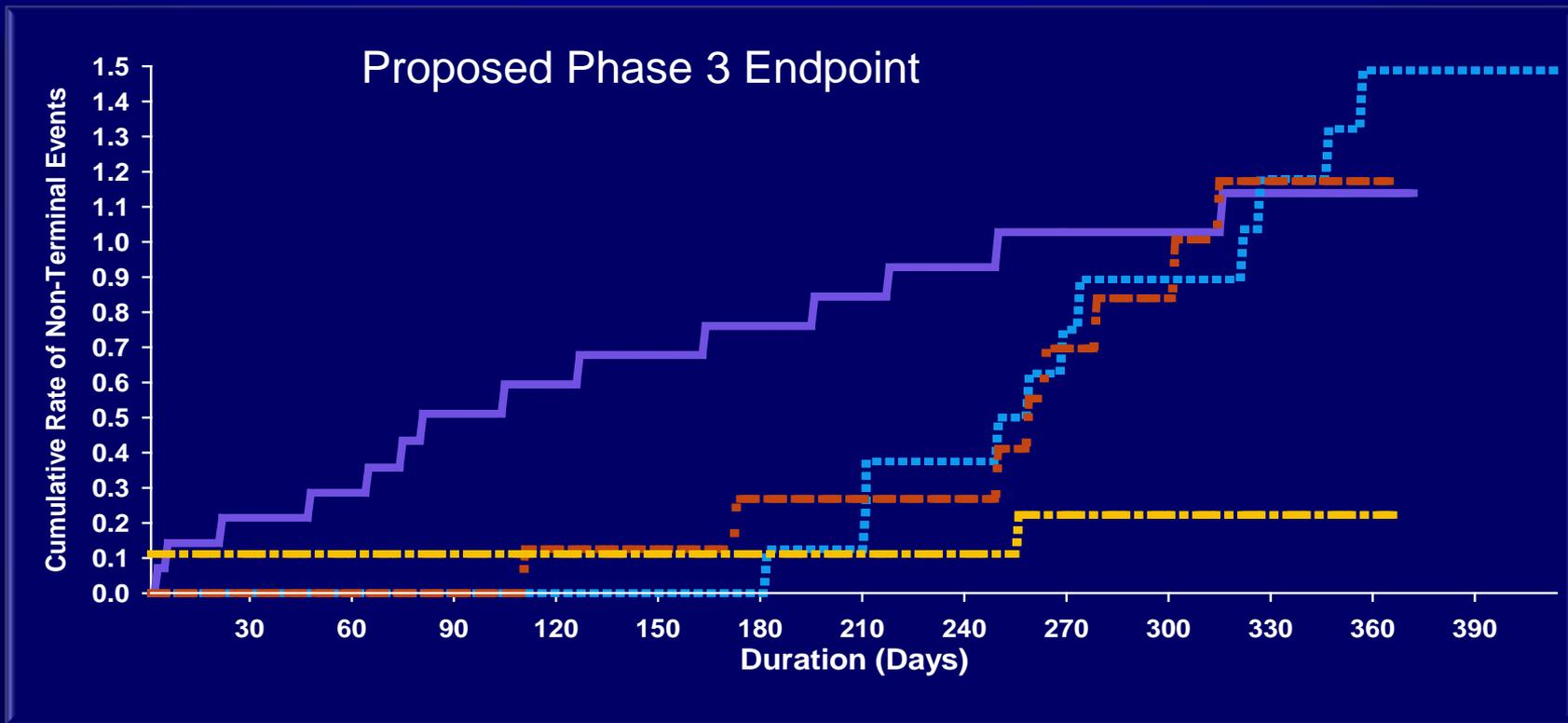
MYDICAR® High Dose Reduced Adjudicated Heart Failure Clinical Events Through Month 12

Each line is a patient;
bubbles are clinical events coded at bottom



Time-to-Recurrent HF-related Hospitalizations

Adjusted for Competing Risk of Terminal Event (CV Death, Transplant, LVAD)



Biometrics 2000;56(2):554-62;
Circulation 2009; 119(7): 969-977

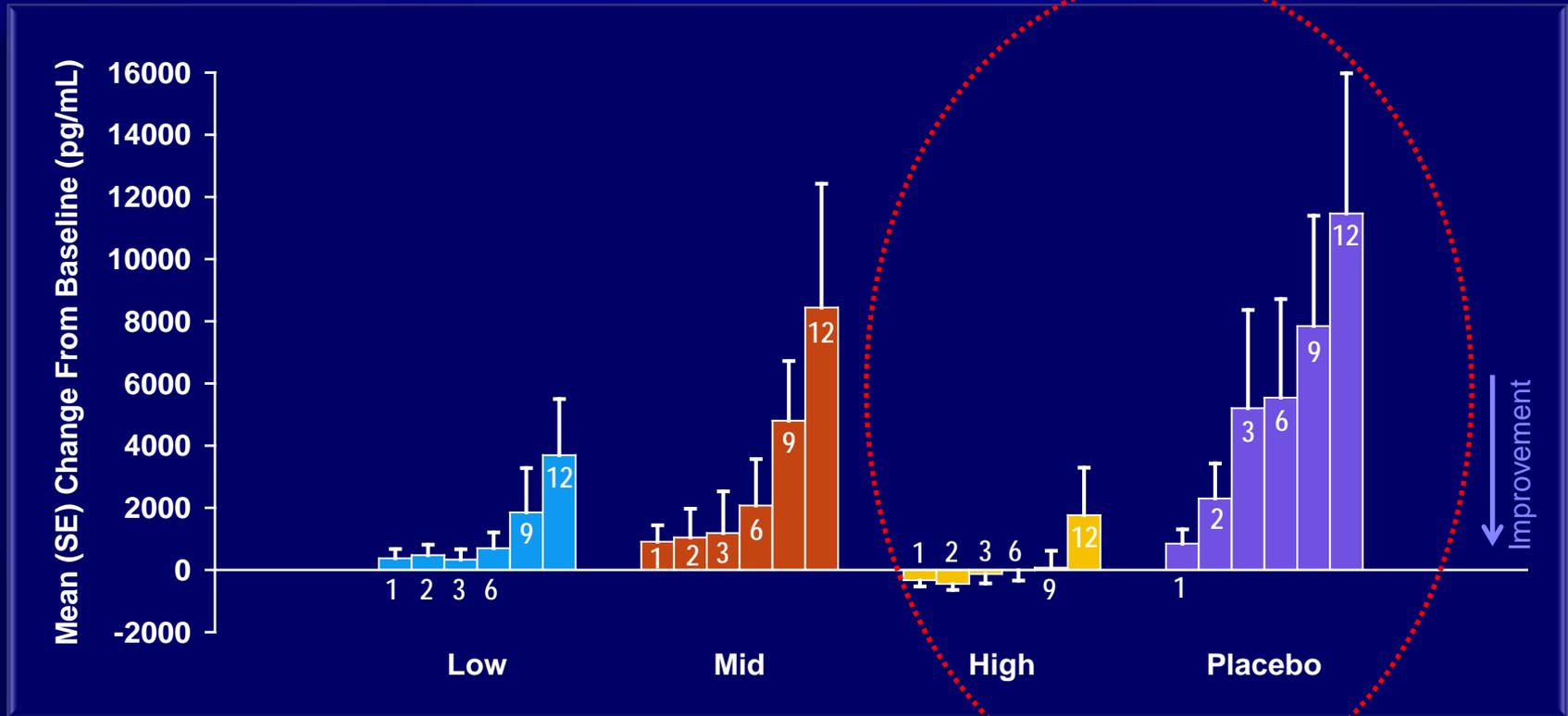
CUPID Met the Study Primary End-Point*

- Primary endpoint at 6 months included safety and positive concurrent trends without clinically significant worsening in:
 - Heart failure symptoms, exercise tolerance, serum biomarkers, cardiac function and duration of HF-related hospitalizations
- Study false positive rate is <3%

* Circulation. 2011 Jul 19;124(3):304-313

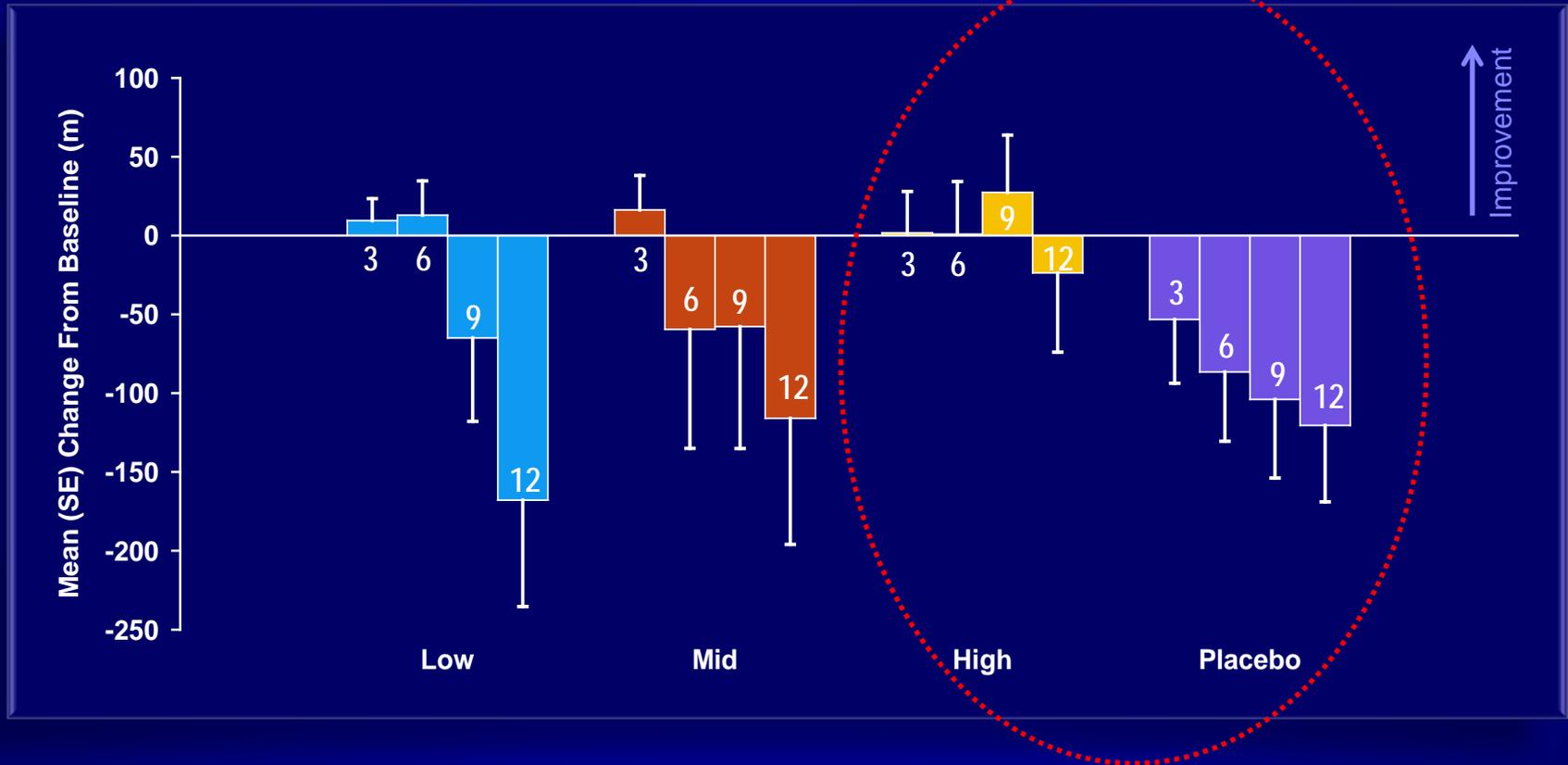
NT-ProBNP

Serum Biomarker



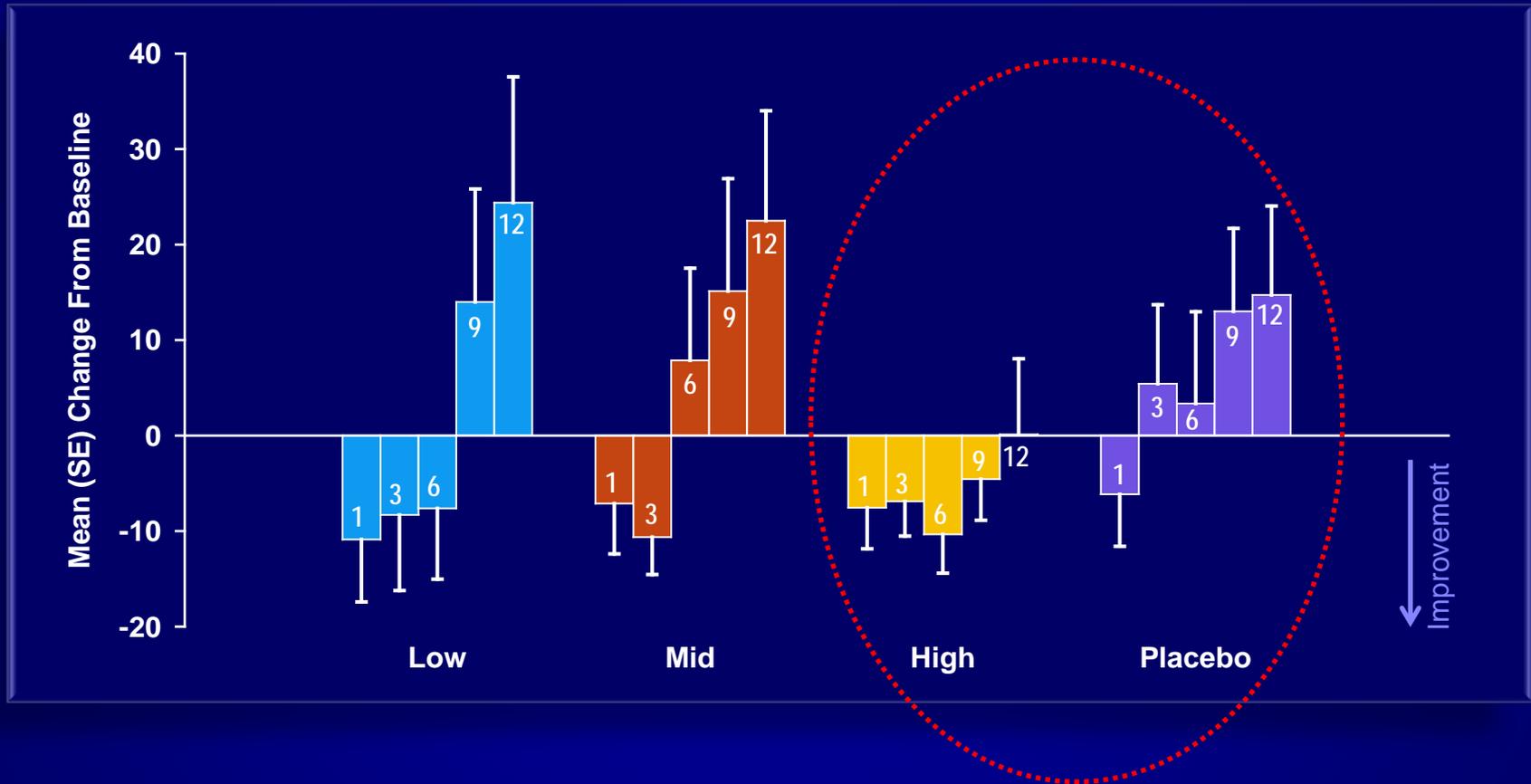
6 Minute Walk Test

Exercise Capacity



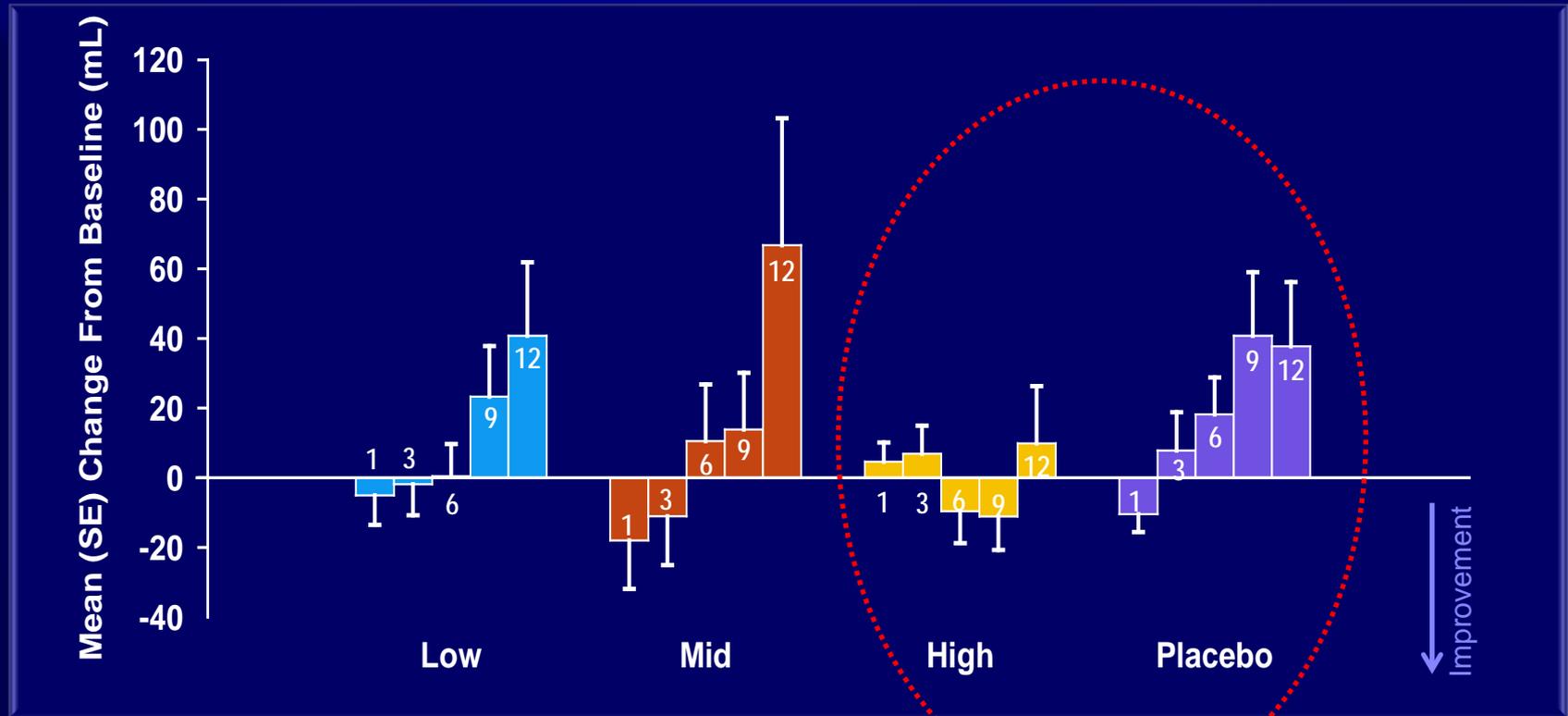
Quality of Life

Minnesota Living with Heart Failure Questionnaire

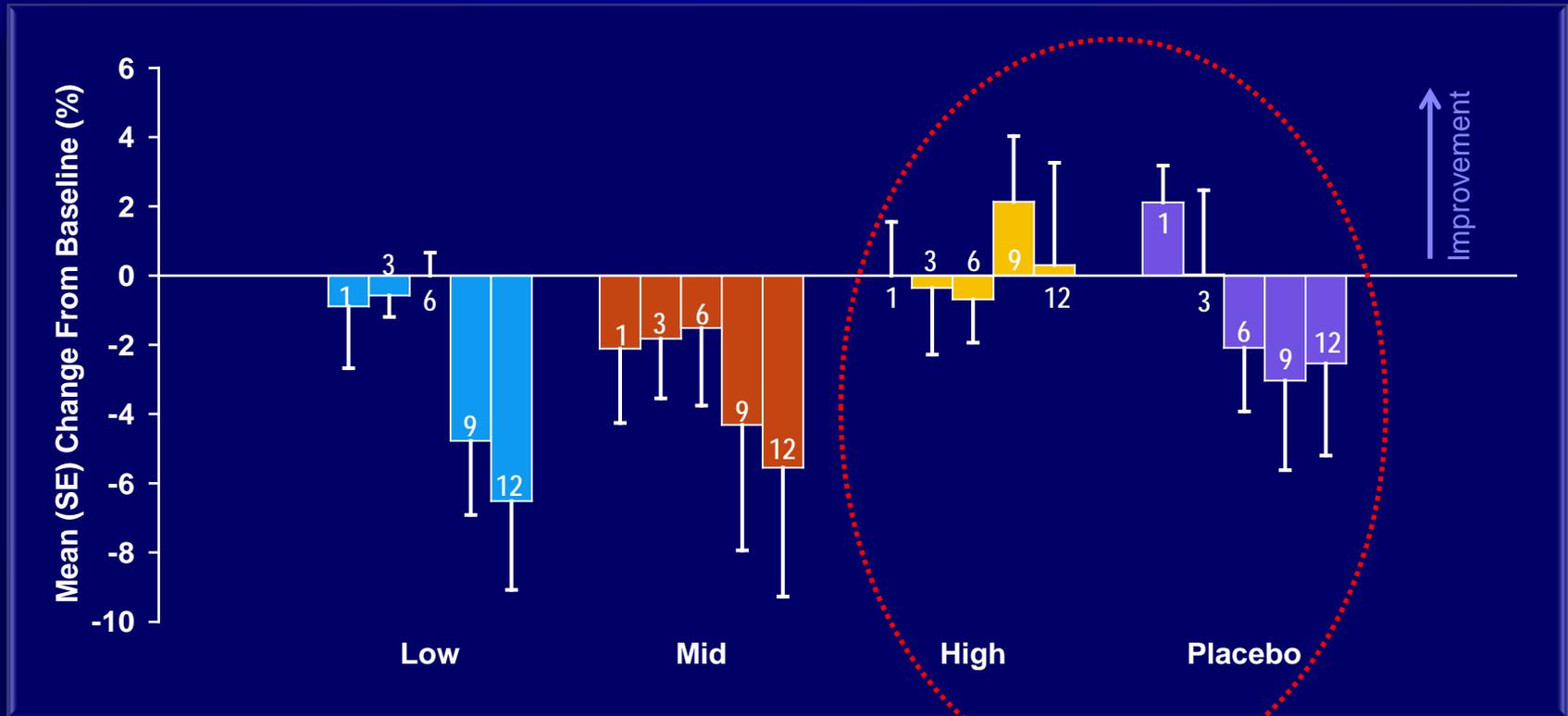


Left Ventricular End Systolic Volume

Tissue Remodeling



Left Ventricular Ejection Fraction Contractility



MYDICAR® Demonstrated an Excellent Safety Profile

As of 9/1/11 (Including Long-term Follow-up)

- 9 Deaths in Phase 2 trial (No clinical holds)
 - 4 in Placebo
 - 4 in Low Dose
 - 1 in Mid Dose
 - 1 in High Dose

Through 12 months on study:

- No findings for changes over time between groups for:
 - Cardiac enzymes
 - Serum Chemistries and Hematology
 - Vitals
 - Heart Rate
- No new findings compared to baseline for interrogation of ICD's (implantable cardioverter defibrillator) or ECG

ELISPOT Assay

- Four overlapping AAV1 peptide pools tested in wells of 3×10^5 PBMCs
- Detection of human interferon gamma
- Algorithm:
 - Positive: ≥ 30 spots adjusted for medium control and baseline
 - Equivocal: 10 to < 30 spots AND peptide/medium ≥ 3
 - Negative: (10 to < 30 spots and peptide/medium < 3) OR < 10 spots
- Performed at Cellular Technology Limited (CTL), Shaker Heights, Ohio

ELISPOT Assay Results

All Asymptomatic and Not Clinically Significant

- No symptomatic CTL response against AAV1 capsid proteins via ELISPOT were detected in any subject
- Asymptomatic positive ELISPOT results in four subjects
 - In all cases results returned to baseline
 - 3 out of 4 cases occurred concurrent with a viral infection (2) or pancreatitis flare-up (1)

ELISPOT: # Positive / # Tested

4 Positive Out of 236 Serial Tests Performed

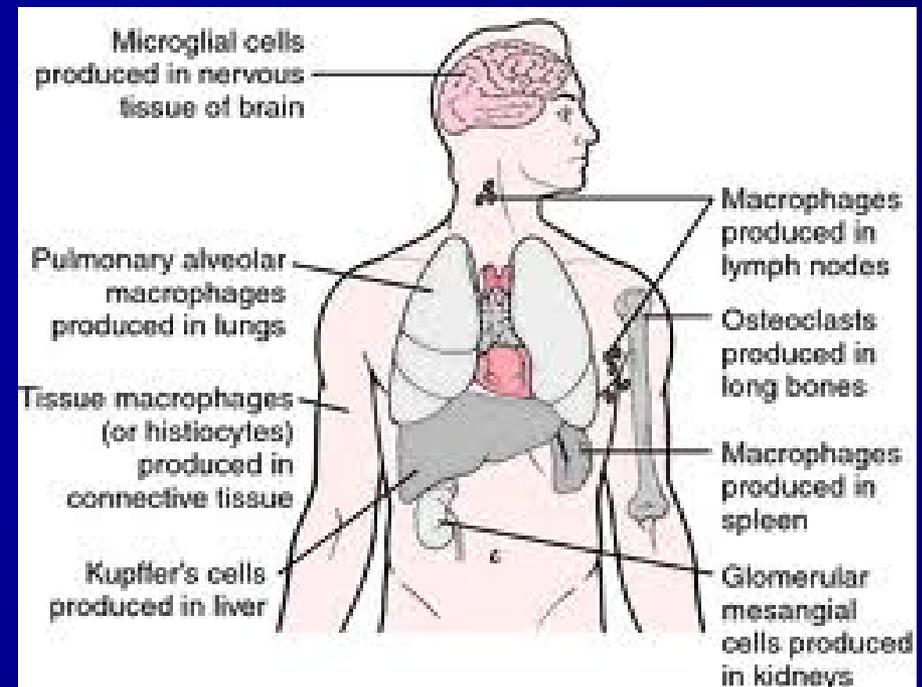


Treatment Group:	N	Week 2	Week 4	Month 2	Month 3	Month 9
1.4 x 10 ¹¹ DRP <i>MYDICAR V. Low</i>	3	0/3	0/3	0/3	0/3	0/2
6 x 10 ¹¹ DRP <i>MYDICAR Low</i>	11	0/9	0/11	0/11	0/11	0/9
3 x 10 ¹² DRP <i>MYDICAR Mid</i>	11	1/10	2/11	0/11	0/11	0/9
1 x 10 ¹³ DRP <i>MYDICAR High</i>	12	0/12	0/10	0/11	0/12	2/12
Placebo	14	0/14	0/13	0/14	0/12	0/9

Lack of a T Cell Response – Why???

- Mode of Administration:
Antegrade epicardial coronary artery infusion into coronary arteries via percutaneous catheter
 - No tissue trauma or damage from injections
- Rate of Infusion: 10 minute slow infusion
- Coronary venous drainage:
 - Via coronary sinus to lungs
 - Lungs are a major organ for Mononuclear Phagocyte System (Reticuloendothelial System) and exposed to airborne pathogens

Human Mononuclear Phagocyte System



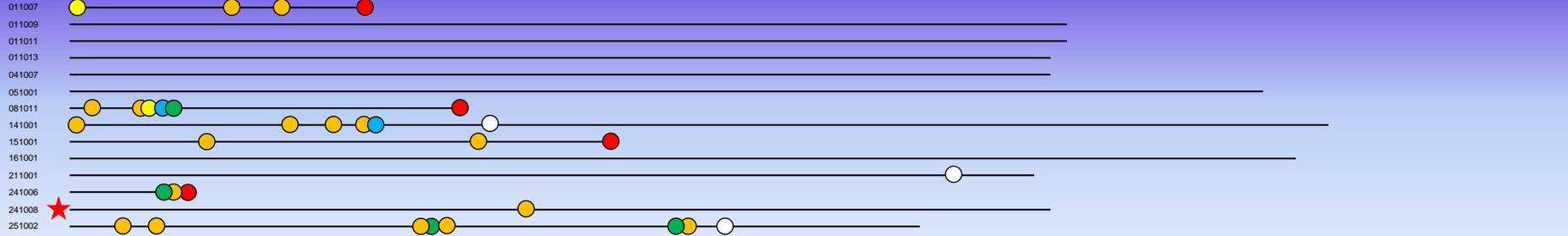
Summary

- In this phase 2 study of patients with advanced HF, MYDICAR® was found to be safe and associated with benefit in the following:
 - Clinical outcomes
 - Symptoms
 - Functional status
 - NT-proBNP
 - Cardiac structure
- These encouraging results support further studies to determine the value of genetically targeted enzyme replacement of SERCA2a in advanced heart failure.

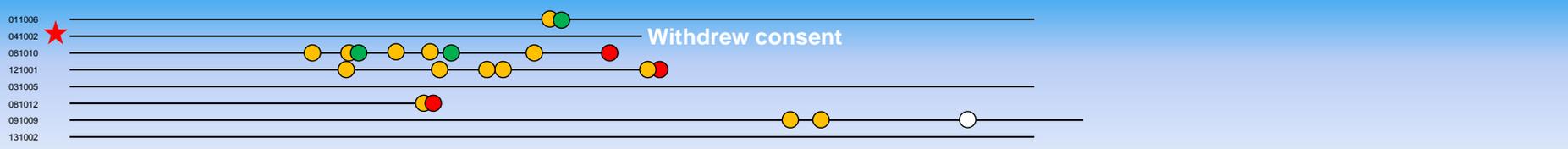
Clinical Events – Phase 2 (as of 6-Sep-2011)

Months 1 6 12 18 24 30 36

Placebo



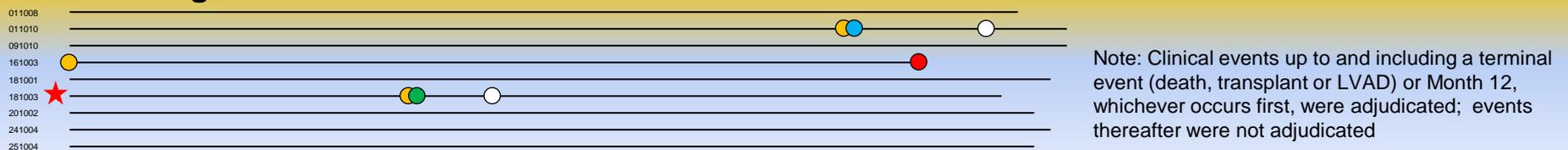
MYDICAR Low



MYDICAR Mid



MYDICAR High



Note: Clinical events up to and including a terminal event (death, transplant or LVAD) or Month 12, whichever occurs first, were adjudicated; events thereafter were not adjudicated