

Cardiovascular Investigation of SRP-9005 (AAVrh74.MHCK7.hSGCG) in Non-Human Primates: A Gene Therapy for Limb-Girdle Muscular Dystrophy 2C/R5

Stephen Baine, Luke Lemmerman, Kaiyu He, Robert Schulingkamp, Wenjing Xu,
Mariana Guerrero, Ahmed Abokor, Louise Rodino-Klapac, Rachael Potter

Sarepta Therapeutics, Inc., Cambridge, MA, USA

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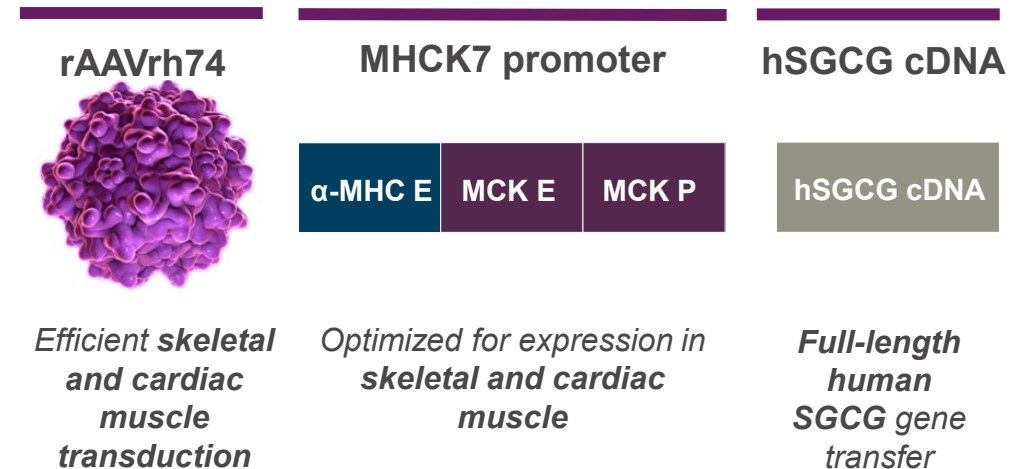
Disclosures and acknowledgments

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All authors are employees of Sarepta Therapeutics, Inc., and may own stock/options in the company
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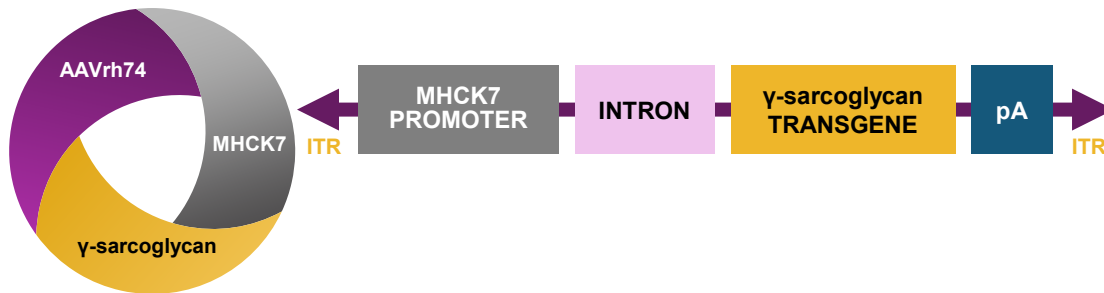
Introduction (2/2)

- SRP-9005, an investigational gene therapy, utilizes an AAVrh74 vector delivering a codon-optimized full-length human *SGCG* transgene to restore functional *SGCG* expression and reduce LGMD2C/R5 pathogenesis¹
- The safety profile of SRP-9005 in large animals following systemic delivery has not been established

SRP-9005: Self-complementary AAV vector

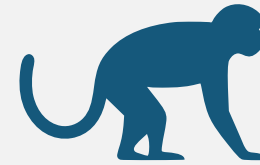


SRP-9005 (rAAVrh74.MHCK7.hSGCG) cassette



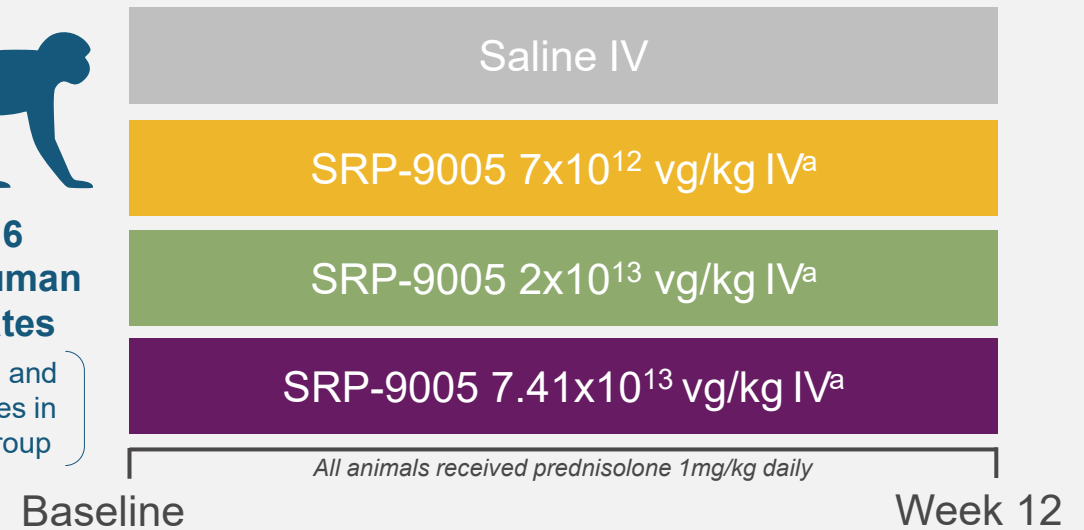
Study design, methods, and objective

- ECHO was performed at baseline, Weeks 6 and 12 to evaluate cardiac systolic and diastolic function
- ECG was performed at baseline and Week 12 to determine electrophysiological response to SRP-9005
- The effect of SRP-9005 on the cardiac injury biomarker troponin I and clinical pathology was assessed throughout the study
- The effect of SRP-9005 on heart histopathology at Week 12
- The biodistribution of SRP-9005 to muscle and organ tissues at Week 12 was determined using ddPCR
- Evaluation of SGCG expression at Week 12 was determined using Simple Western
- Cellular and humoral immunity to SRP-9005 capsid and transgene were determined by immunological assays



N=16
Non-human primates

2 males and
2 females in
each group



All procedures followed the principles of Good Laboratory Practice



Objective

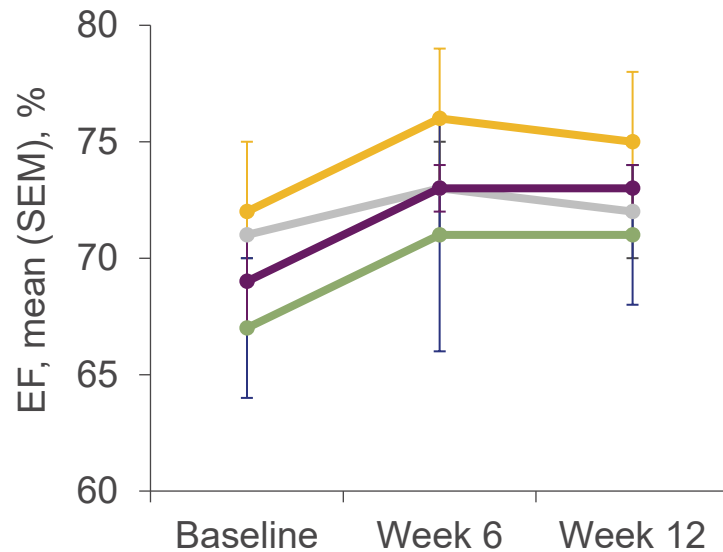
To evaluate the safety of SRP-9005 in healthy non-human primates with an emphasis on cardiac safety

RESULTS

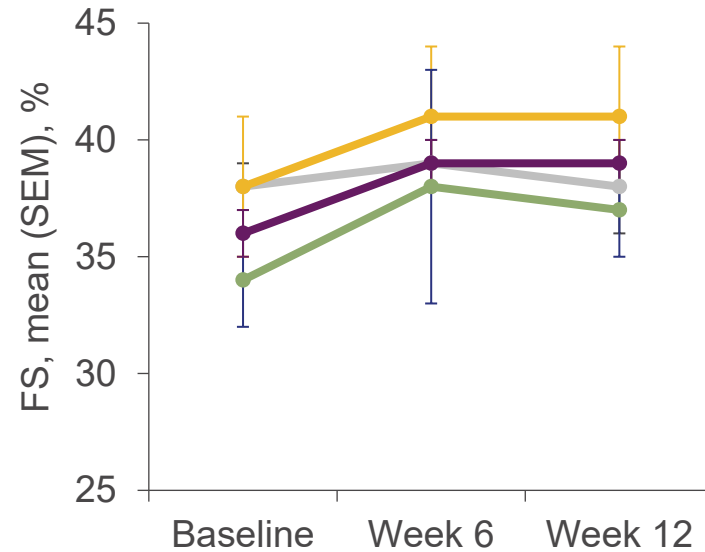
Echocardiography (1/3)

From baseline to Week 12, SRP-9005 had no effect on cardiac systolic function compared with saline-treated animals

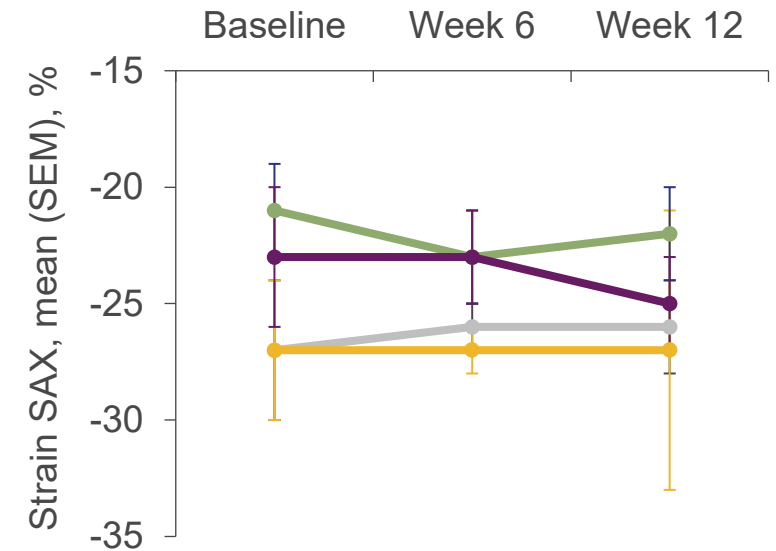
Ejection fraction



Fractional shortening



Strain short-axis



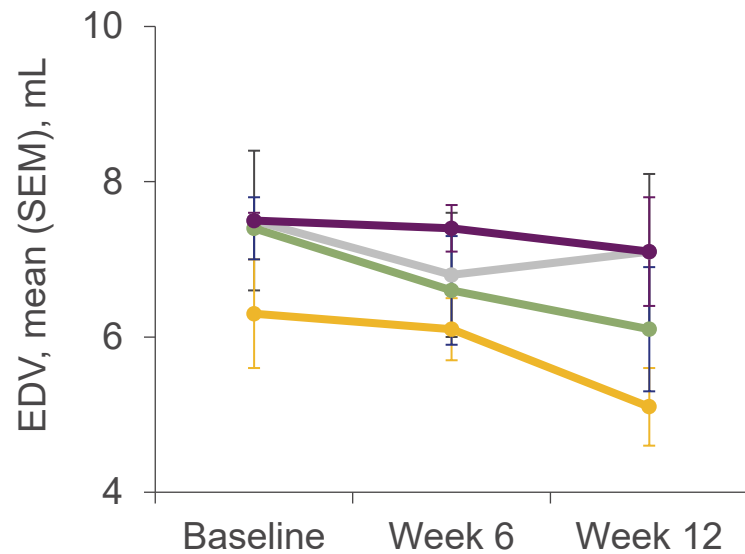
—●— Saline (n=4) —●— SRP-9005 7×10^{12} (n=4) —●— SRP-9005 2×10^{13} (n=4) —●— SRP-9005 7.41×10^{13} (n=4)

RESULTS

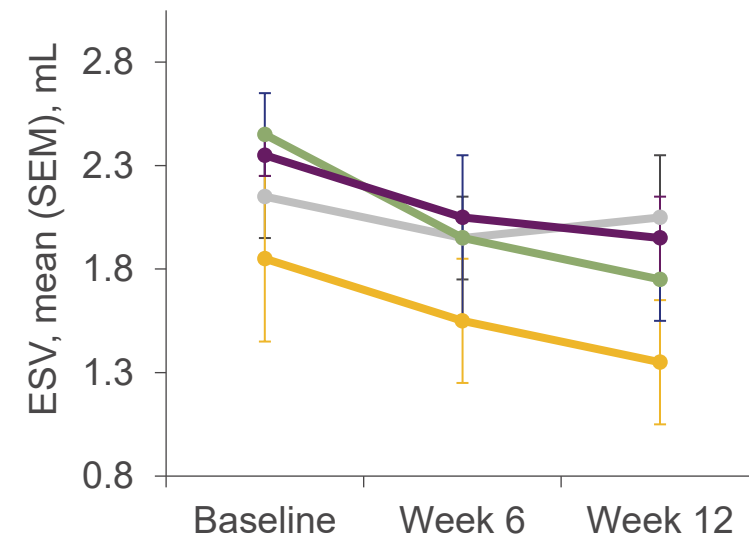
Echocardiography (2/3)

From baseline to Week 12, SRP-9005 treatment did not lead to systolic/diastolic volume changes compared with saline-treated animals

End diastolic volume



End systolic volume



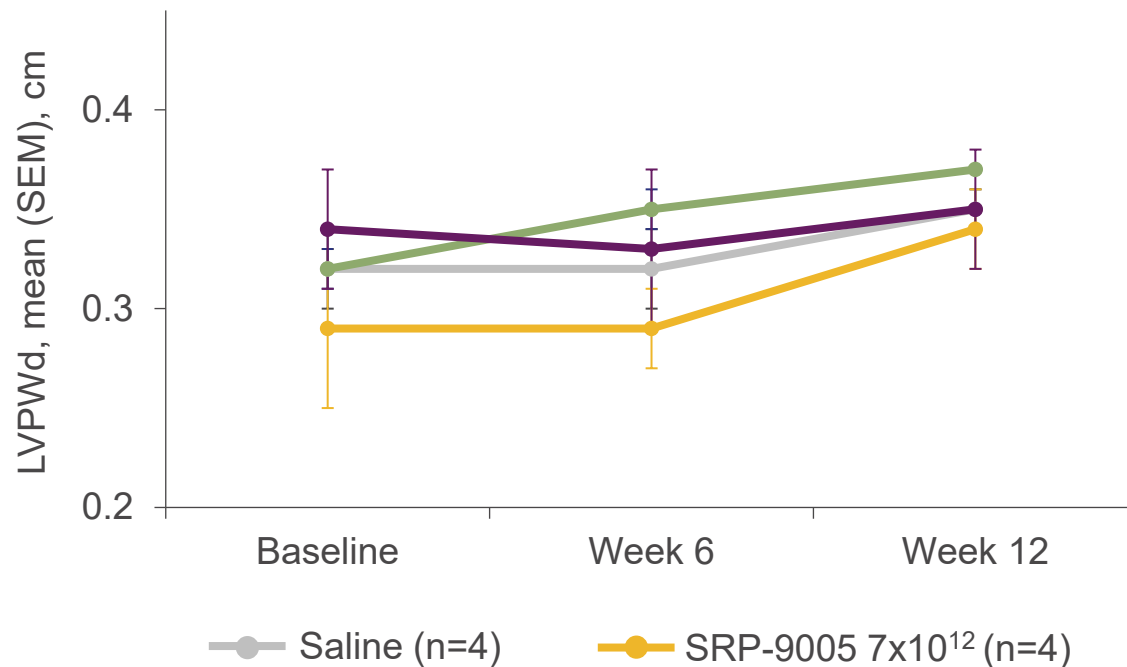
—●— Saline (n=4) —●— SRP-9005 7x10¹² (n=4) —●— SRP-9005 2x10¹³ (n=4) —●— SRP-9005 7.41x10¹³ (n=4)

RESULTS

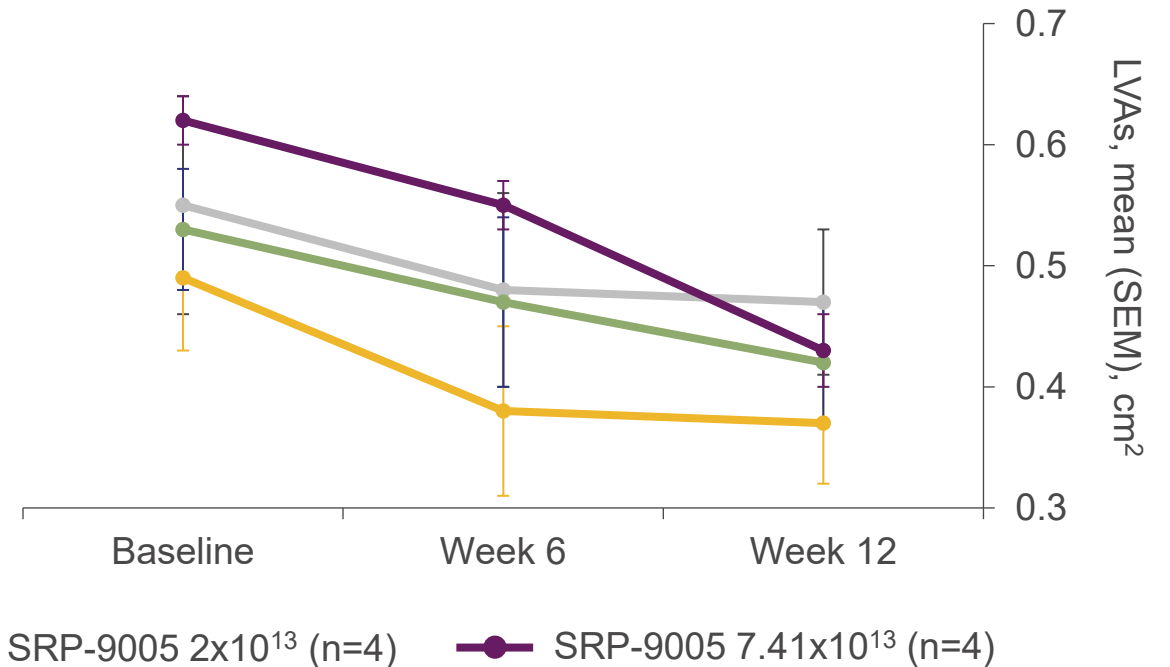
Echocardiography (3/3)

From baseline to Week 12, SRP-9005 treatment did not lead to abnormalities in left ventricular dimensions compared with the saline-treated animals

Left ventricular posterior wall thickness in diastole



Left ventricular area in systole

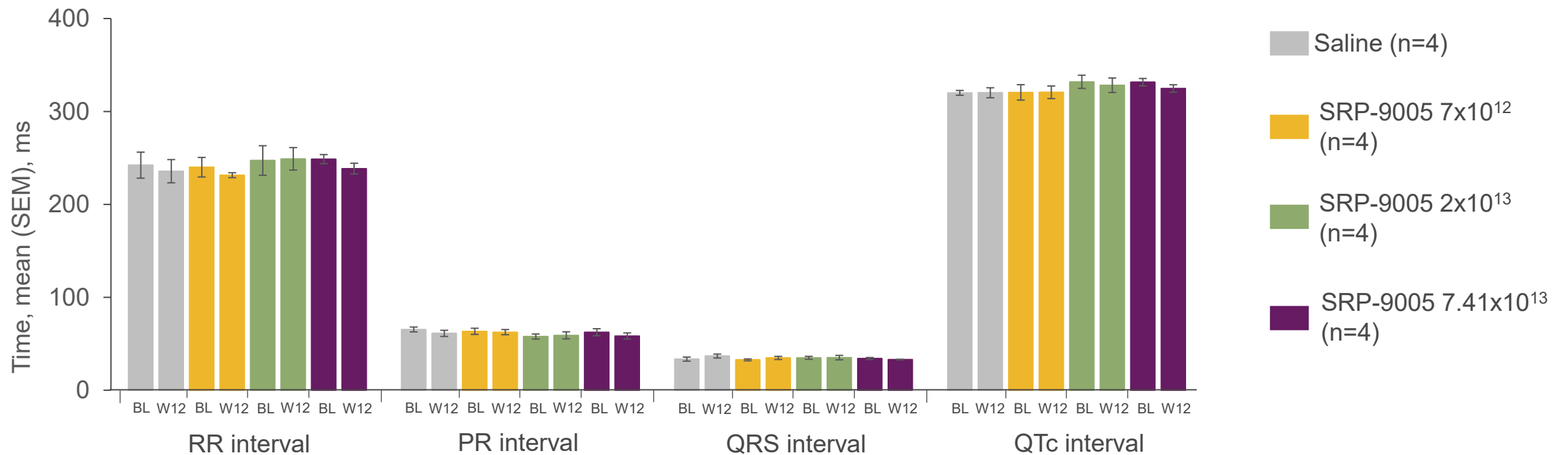


RESULTS

Electrocardiography

From baseline to Week 12, SRP-9005 had no effect on RR, PR, QRS and QTc intervals compared with the saline-treated animals

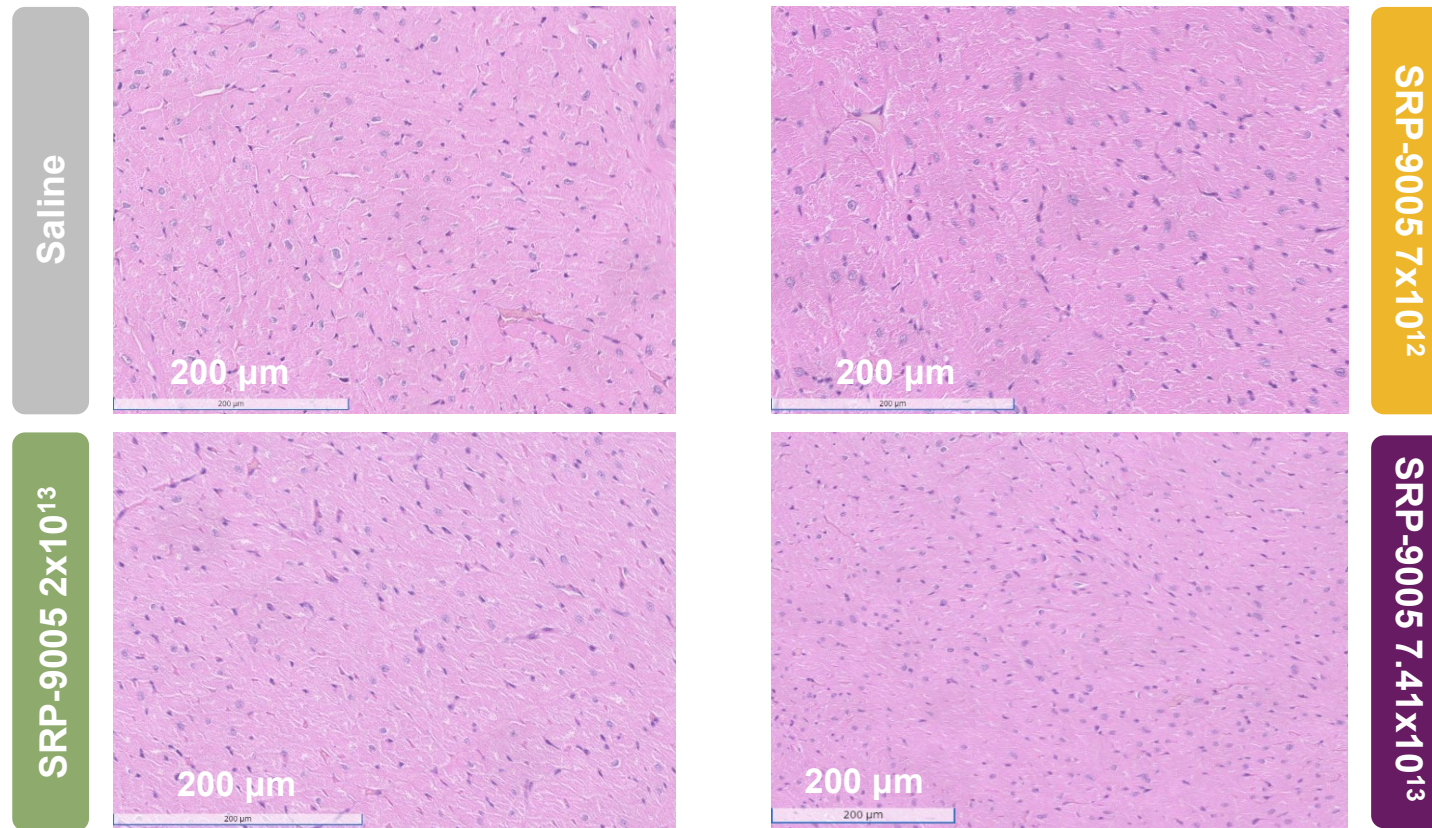
ECG values at Baseline and Week 12



RESULTS

Cardiac histopathology

Histopathology analysis in the heart revealed no evidence of cardiac remodeling or degeneration with SRP-9005 at all doses tested



RESULTS

Anatomic and clinical pathology in non-human primates

Anatomic pathology

- No SRP-9005–related effects on heart histopathology, organs weight, gross pathology including liver were observed

Summary of heart histopathology findings at Week 12

Heart, n (%)	Saline	SRP-9005 7x10 ¹²	SRP-9005 2x10 ¹³	SRP-9005 7.41x10 ¹³
No visible lesions	0	0	1	1
Mixed inflammatory cells infiltration	0	0	1	0
Mononuclear cells infiltration	4	4	2	3
Degeneration/regeneration	1	1	0	1

N=4 for each group.

Clinical pathology

- SRP-9005 had no effects on
 - Hematology
 - Coagulation
 - Serum chemistry
 - Urinalysis
 - Cardiac biomarker troponin I levels



All variations observed in anatomic (heart) and clinical pathology were within normal range of non-human primate fluctuations

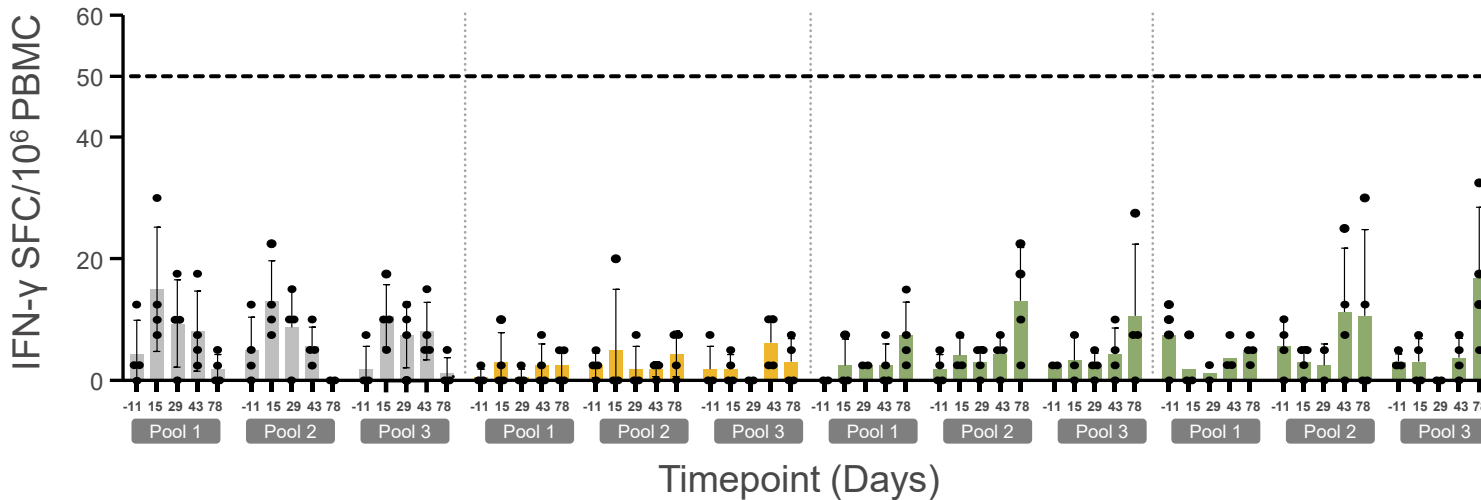
RESULTS

Immune response

From baseline to Week 12 (Day 78),
SRP-9005 did not elicit a
cellular immune response to the AAVrh74 capsid

A humoral response was seen by
Week 12 (Day 85)
across all dose groups

Anti-AAVrh74 ELISpot



--- Threshold of positivity for the ELISpot assay at ≥50 SFC per million cells

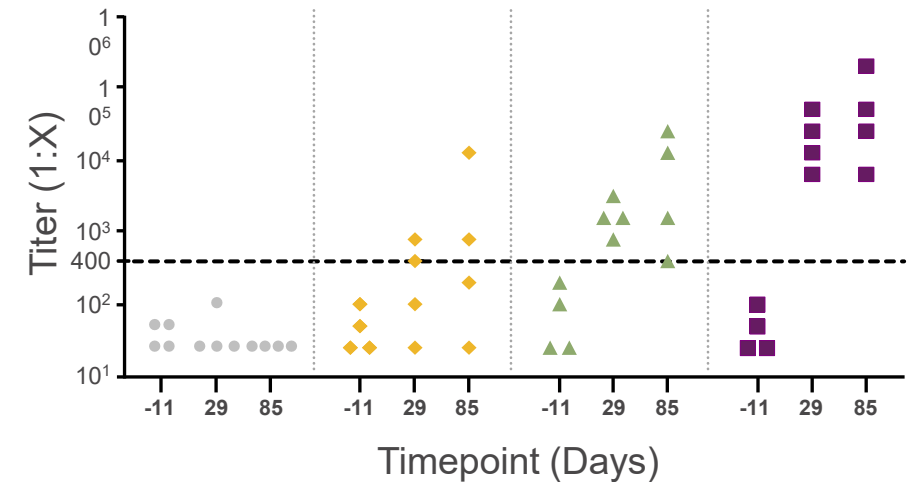
Saline (n=4)

SRP-9005 7×10^{12} (n=4)

SRP-9005 2×10^{13} (n=4)

SRP-9005 7.41×10^{13} (n=4)

Anti-AAVrh74 ELISA titer



--- Titer cutoff for positive samples based on AAVrh74 titer cutoff

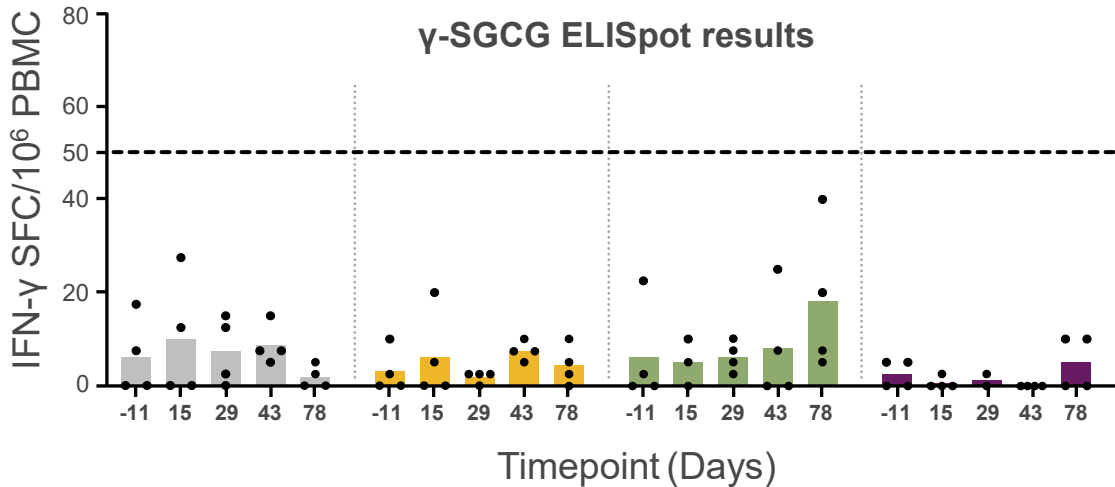
RESULTS

Immune response

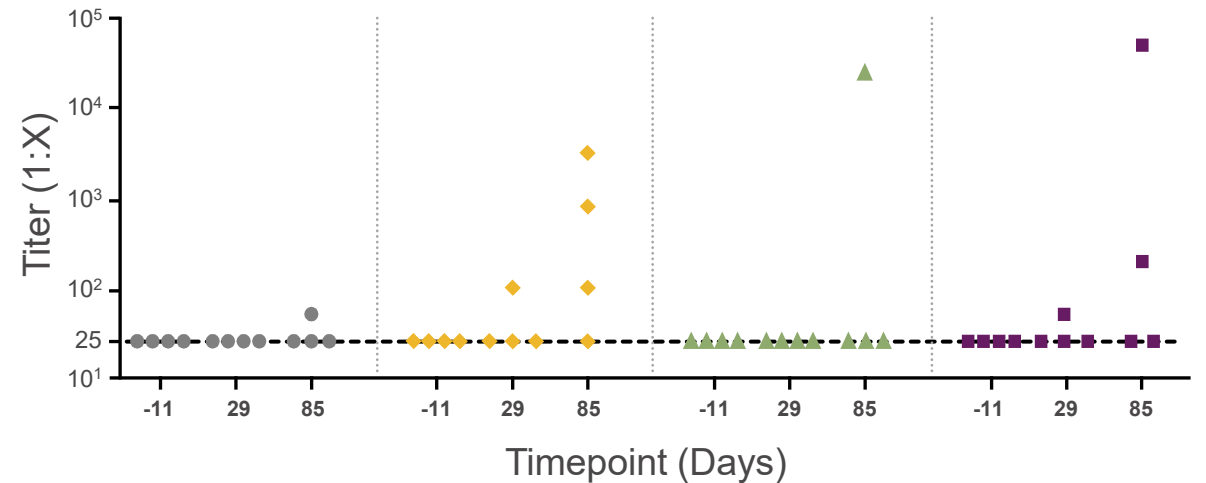
From baseline to Week 12 (Day 78), SRP-9005 did not elicit a cellular immune response to the human SGCG transgene

A humoral response was seen by Week 12 (Day 85) across all dose groups

Anti-hSGCG ELISpot



Anti-hSGCG ELISA titer



Saline (n=4)

SRP-9005 7×10^{12} (n=4)

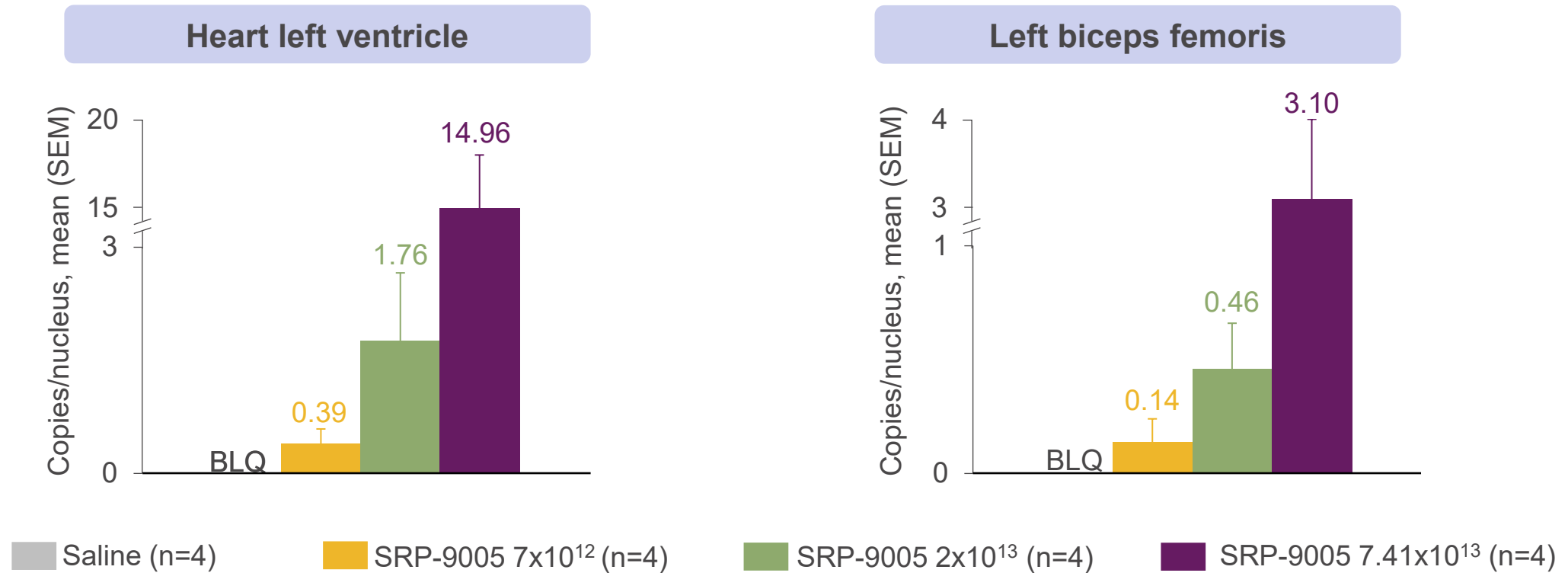
SRP-9005 2×10^{13} (n=4)

SRP-9005 7.41×10^{13} (n=4)

RESULTS

Vector biodistribution at Week 12

In all SRP-9005 treatment groups, quantifiable vector genome copies were observed in the heart and skeletal muscles

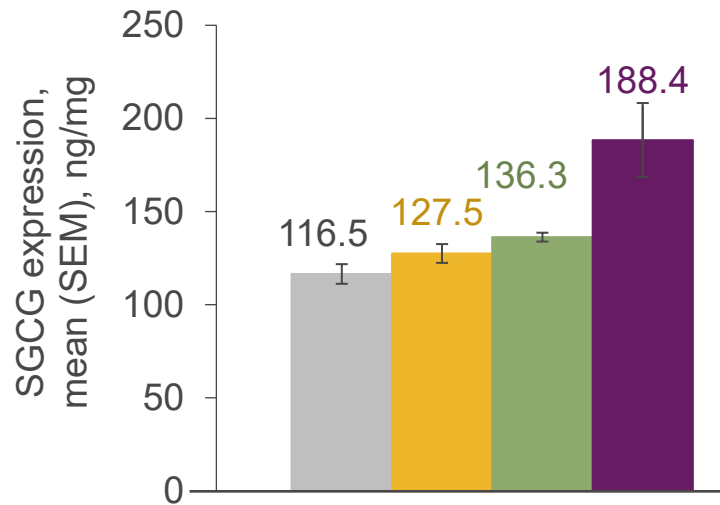


RESULTS

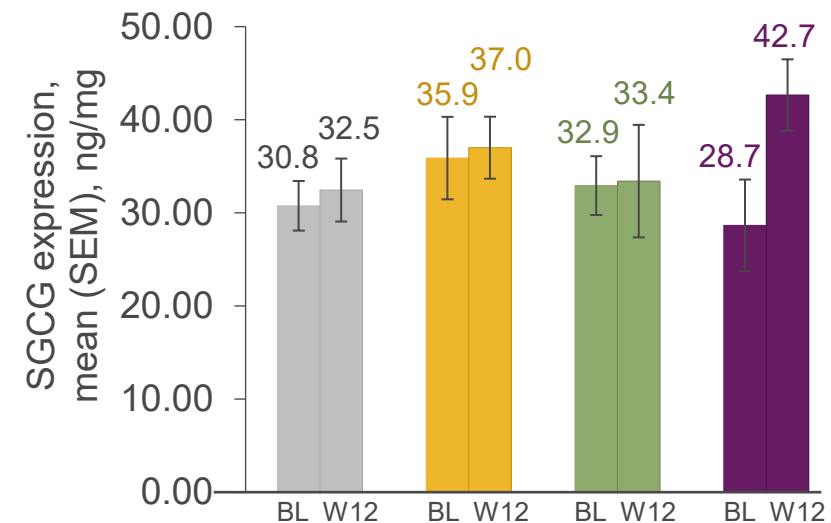
SGCG expression at Week 12

A dose-dependent increase in SRP-9005 SGCG expression was observed in the heart and skeletal muscles^a

Cardiac apex



Right biceps femoris



Saline (n=4)

SRP-9005 7x10¹² (n=4)

SRP-9005 2x10¹³ (n=4)

SRP-9005 7.41x10¹³ (n=4)

BL=baseline; SEM=standard error of the mean; SGCG=γ-sarcoglycan; W12=Week 12.
^aThe automated western blot system quantified overexpression of SGCG due to endogenous levels present.

Key takeaways

- SRP-9005 was well tolerated at all tested doses in non-human primates, showing no adverse effects or cardiotoxicity at doses up to 7.41×10^{13} vg/kg
- There were no SRP-9005–related effects on cardiovascular anatomic or clinical pathology parameters including cardiac biomarker troponin I
- SRP-9005 induced hSGCG expression in heart and muscle supporting further investigation in clinical trials for LGMD2C/R5
- **SRP-9005 will be evaluated in humans in the first-in-human COMPASS study¹**



Thank You