# SRP-5051, a Peptide-conjugated PMO, Increases Exon Skipping, Dystrophin Production, and Grip Strength in a Humanized Mouse Model of Duchenne Muscular Dystrophy

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**Presented by Leslie C.L. Wu**

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# Disclosures

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- Products are investigational only

# Introduction

- Duchenne muscular dystrophy (DMD) is a severe, X-linked neuromuscular disease caused by mutations in the dystrophin gene[1]
  - Dystrophin mutations leading to deletions flanking exon 51 account for 13% of all DMD patients[2]
- Phosphorodiamidate morpholino oligomers (PMOs) are an effective treatment approach for patients with DMD[3-6]
- PMOs are designed for targeted skipping of exons within the DMD gene; they restore the reading frame and allow for production of an internally truncated but functional dystrophin protein
- Peptide PMOs (PPMOs) are a next-generation chemistry platform in which a cell-penetrating peptide is conjugated to the PMO backbone, with the goal of increasing cellular uptake, exon skipping, and dystrophin level[7,8]
- SRP-5051 is an investigational PPMO designed to skip exon 51 of the *DMD*

**Objective: To evaluate the biological and functional efficacy of SRP-5051 in a humanized mouse model of DMD**

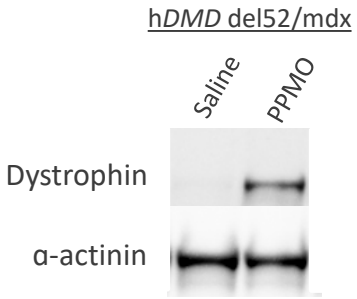
1. Birnkrant DJ, et al. *Lancet Neurol*. 2018;17:251-67. 2. Aartsma-Rus A, et al. *Hum Mutat*. 2009;30:293-9. 3. Popplewell LJ, et al. *Mol Ther.* 2009;17:554-61. 4. Exondys 51 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc.; 2020. 5. Vyondys 53 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc.; 2020. 6. Viltepso [package insert]. Paramus, NJ: NS Pharma, Inc.; 2020. 7. Gan L, et al. Poster presented at the 2019 Muscular Dystrophy Association (MDA) conference. April 13–17, 2019. Orlando, FL. 8. Echevarría L, et al. Hum Mol Genet. 2018; 27:R163-72.

# Humanized *DMD* Transgenic Mouse Allows Assessment of SRP-5051 Pharmacology in a Preclinical Disease-Relevant Model of DMD

## h*DMDdel52/mdx* mice


human *DMD* transgene with exon 52 deleted by gene editing is inserted into *mdx* mouse genome, results in **out of frame *DMD* transcript** and **lack of dystrophin protein expression**

## Treatment with SRP-5051

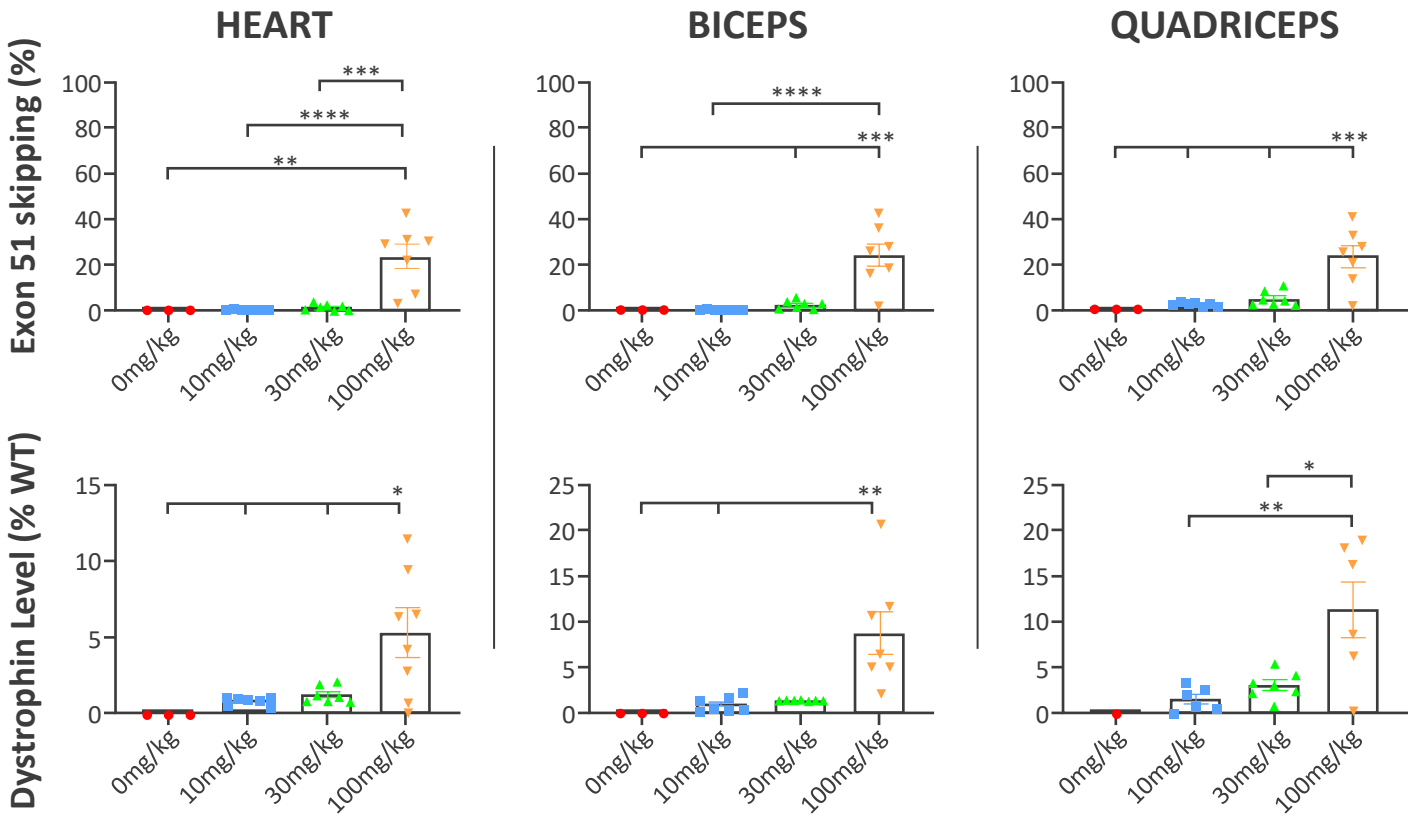

SRP-5051 induced exon 51 skipping, which results in **restoration of *DMD* reading frame**, and expression of **truncated, but functional dystrophin protein**

**Experimental design summary:**

- Single injection dose response and time course: exon skipping and dystrophin were measured
- Repeated doses time course: exon skipping, dystrophin and grip strength were measured

# Single-dose SRP-5051 Increased Exon Skipping and Dystrophin Protein in h*DMD*del52/mdx Mice

**Dose response (single dose):** 6-8 w/o male h*DMD*del52/mdx mice were injected with SRP-5051 IV at indicated doses and analyzed 7 post dose



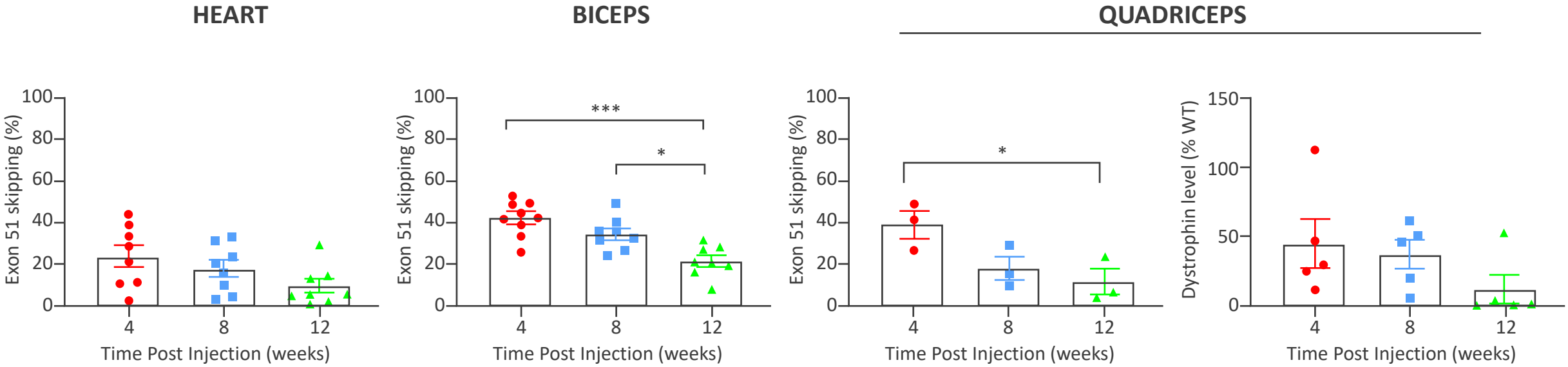

**Biological Activity at the 100 mg/kg Dose**

| | Exon skipping | Dystrophin protein |
|---|---|---|
| Heart | 24% | 5% |
| Skeletal muscles | 22% | 10% |

Each bar represents mean ± SE. One-way ANOVA was used to compare means among dose groups. Exon skipping results showed significant difference among the groups ($P$<0.0001), whereas dystrophin level showed significant differences among groups in heart ($P$=0.0042), biceps ($P$=0.0007) and quadriceps ($P$=0.0047). Dunnett multiple comparison test was used to compare the 2 groups of interest; *, **, ***, **** denotes $P$< 0.05, 0.005, 0.0005 or 0.0001, respectively.

# Exon Skipping was Sustained 4 Weeks After Single Dose SRP-5051 and Remained Detectable to 12 Weeks in h*DMD*del52/mdx Mice

**Time course (single dose):** 6-8 w/o male h*DMD*del52/mdx mice were injected with SRP-5051 at 100 mg/kg IV; exon skipping and dystrophin were measured 4, 8, and 12 weeks post-dose




- Dystrophin was undetectable in the vehicle-treated samples
- Exon skipping and dystrophin protein level were maintained for ≥8 weeks after a single dose

Each bar represents mean ± SD. One-way ANOVA was used to compare group means across 3 time points (biceps, *P*=0.0002; exon skipping for quadriceps, *P*=0.0443). Dunnett multiple comparison test was used to compare the 2 timepoints of interest; *, *** denotes *P*<0.05 or 0.0005, respectively.

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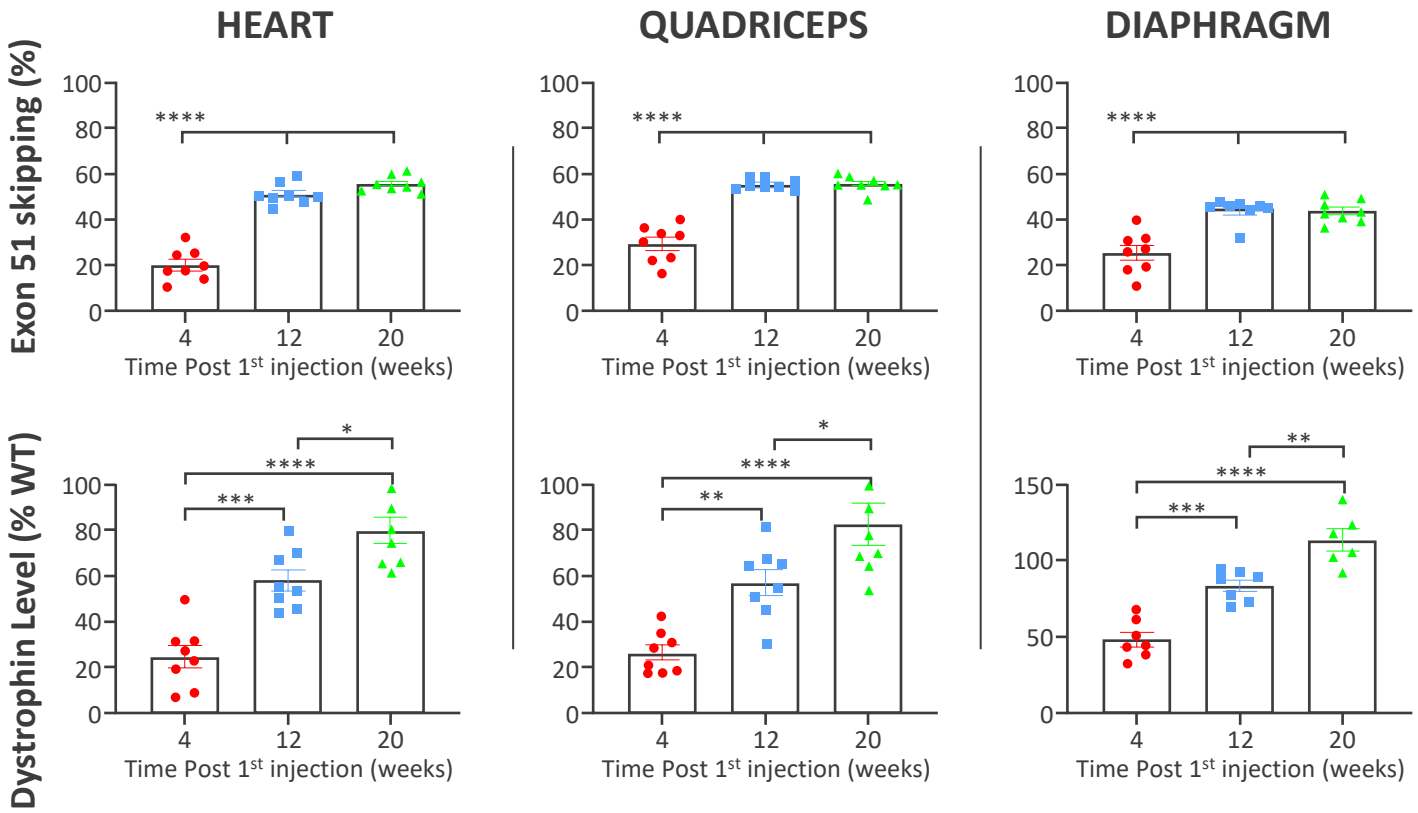
# Every 4 Weeks Repeated SRP-5051 Dosing Resulted in Increased Exon Skipping and Accumulation of Dystrophin in h*DMD*del52/mdx Mice

**Time course (repeated doses):** 6-8 w/o male h*DMD*del52/mdx mice were injected with SRP-5051 100 mg/kg IV every 4 weeks and analyzed 4 weeks after 1 dose, 3 doses, or 5 doses




- Exon skipping reached a steady-state after 3 doses (12 weeks)
- Dystrophin protein level continued to increase up to 5 doses (20 weeks)

Each bar represents mean ± SEM. One-way ANOVA was used to compare group means ($P<0.0001$ for exon skipping and dystrophin level in all structures examined). Dunnett multiple comparison test was used to compare the 2 groups of interest; *, **, ***, **** denotes $P< 0.05$, 0.005, 0.0005 or 0.0001, respectively.

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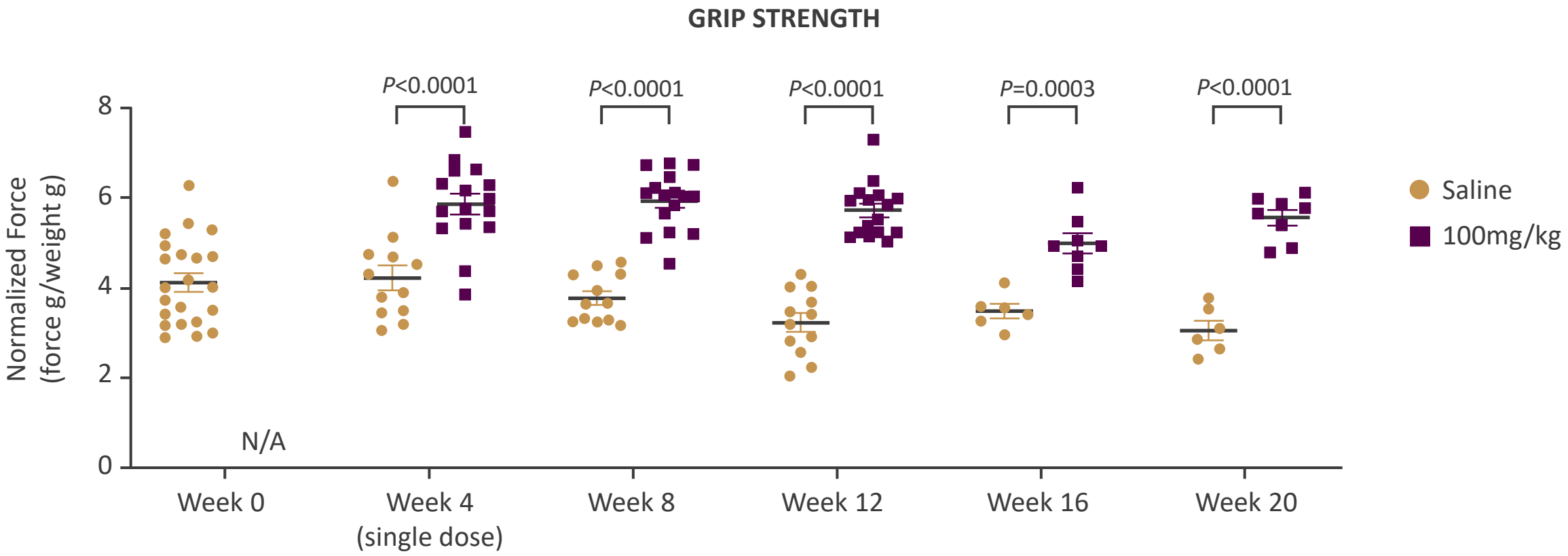
# Single and Repeated SRP-5051 Dosing Every 4 Weeks Restored Grip Strength in h*DMD*del52/mdx Mice to Wild Type Levels

**Time course (repeated doses):** h*DMD*del52/mdx mice were injected with SRP-5051 100 mg/kg IV every 4 weeks and analyzed every 4 weeks




Unpaired T-test was used to compare the grip strength between the 2 groups at each timepoint.

# Conclusions

- This is the first-time examination of the pharmacology of SRP-5051, a peptide conjugated PMO, in a disease-relevant, humanized mouse model of DMD
- A single dose of SRP-5051 resulted in sustained exon 51 skipping and human dystrophin levels in muscle and heart, which was associated with improved grip strength, a surrogate measure of muscle function
  - Significant exon 51 skipping and human dystrophin were detected in skeletal muscle and heart 7 days post injection of ascending doses and for at least 8 weeks after a single 100 mg/kg dose
- Once every 4-week SRP-5051 dosing for 20 weeks resulted in improved pharmacodynamic effect compared with vehicle-treated animals
  - Improvement in grip strength was sustained throughout the 20-week study
- These studies further support the clinical investigation of SRP-5051
  - A phase 2 multiple-ascending-dose study is currently ongoing (NCT04004065)

# Questions?

**Please direct any questions you may have to the Sarepta Medical Information team at medinfo@sarepta.com**