Evaluation of the Pharmacokinetic and Pharmacodynamic Properties of SRP-5051 in Nonhuman Primates After Single and Multiple Doses

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Presented by Mohammad Shadid

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Disclosures

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- Products are investigational only

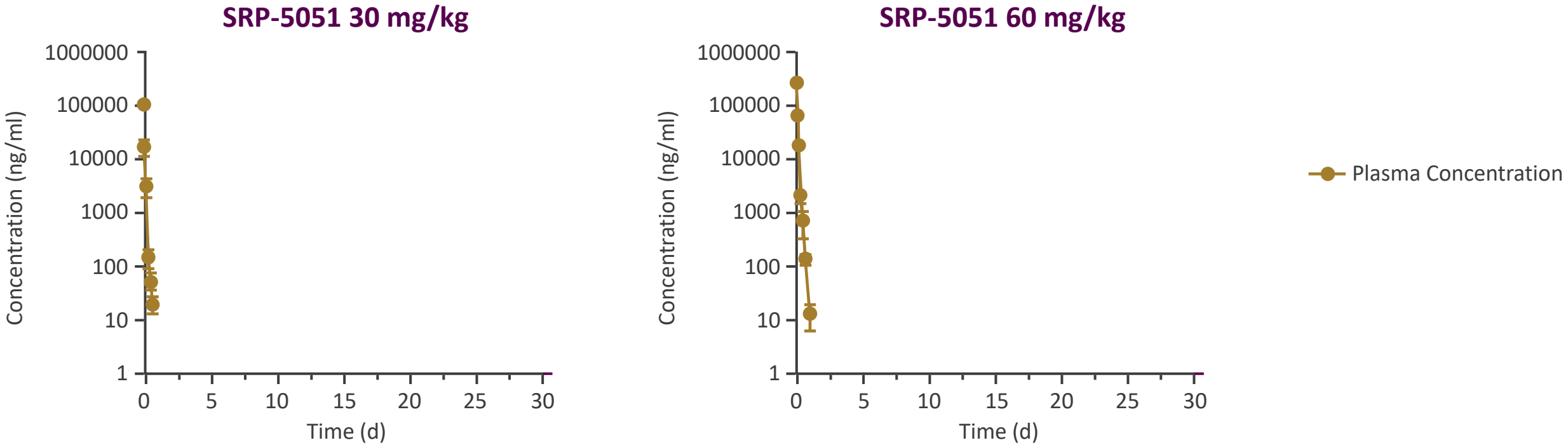
Introduction

- 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 production[7,8]
- SRP-5051 is an investigational PPMO designed to skip exon 51 of the *DMD* gene

Objective: To assess the pharmacokinetic and pharmacodynamic properties of SRP-5051, including muscle tissue uptake and duration of effect, after single and multiple doses in a nondystrophic nonhuman primate model

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.

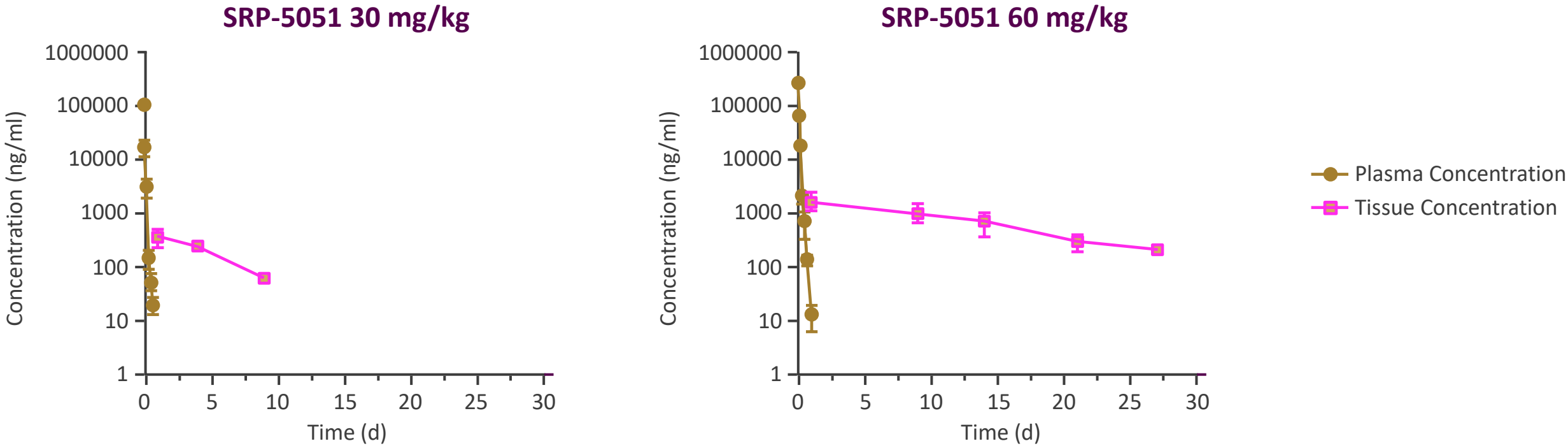
Plasma PK of SRP-5051 after Single Dose in Nondystrophic Nonhuman Primates



Error bars represent SE. Animals received a single 1-hour IV infusion of SRP-5051 at dose levels of 30 and 60 mg/kg. Blood samples were collected on Day 1: pre-dose and 1, 2, 4, 8, 12, 16, and 24 hours post-infusion. Muscle samples were collected on days 2, 5 (only for the 30 mg/kg group), 10, 15, 22 and 28 by biopsy.

SRP-5051 has a short plasma half-life (~2 hours)

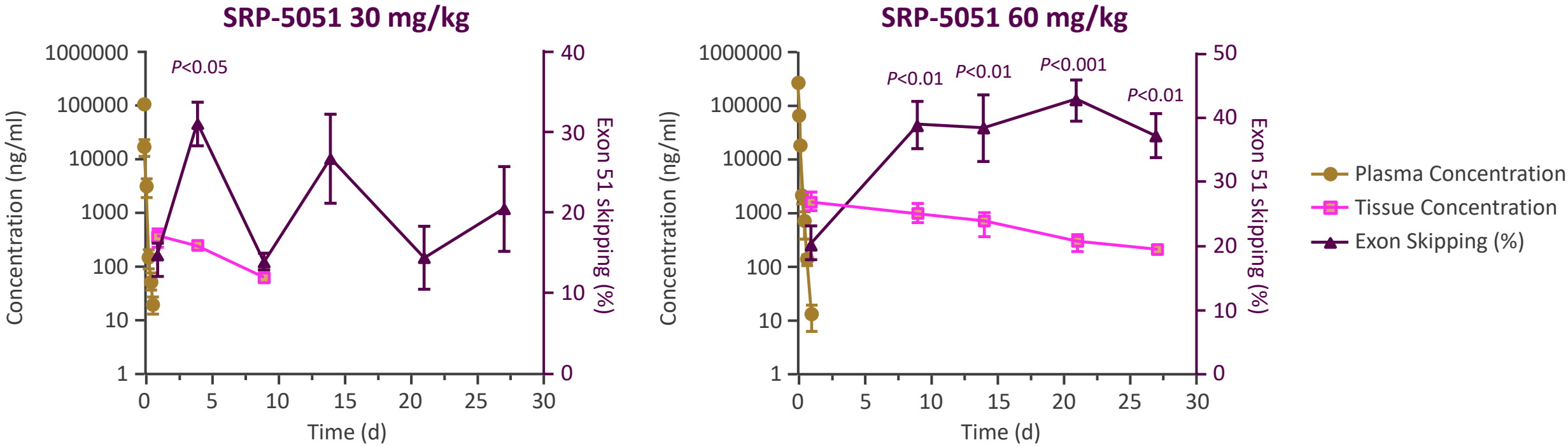
Tissue PK of SRP-5051 after Single Dose in Nondystrophic Nonhuman Primates



Error bars represent SE. Animals received a single 1-hour IV infusion of SRP-5051 at dose levels of 30 and 60 mg/kg. Blood samples were collected on Day 1: pre-dose and 1, 2, 4, 8, 12, 16, and 24 hours post-infusion. Muscle samples were collected on days 2, 5 (only for the 30 mg/kg group), 10, 15, 22 and 28 by biopsy. After day 10, tissue concentration for the 30 mg/kg dose was below the limit of quantification.

Despite a short plasma half-life, SRP-5051 was observed in muscles for days after dosing

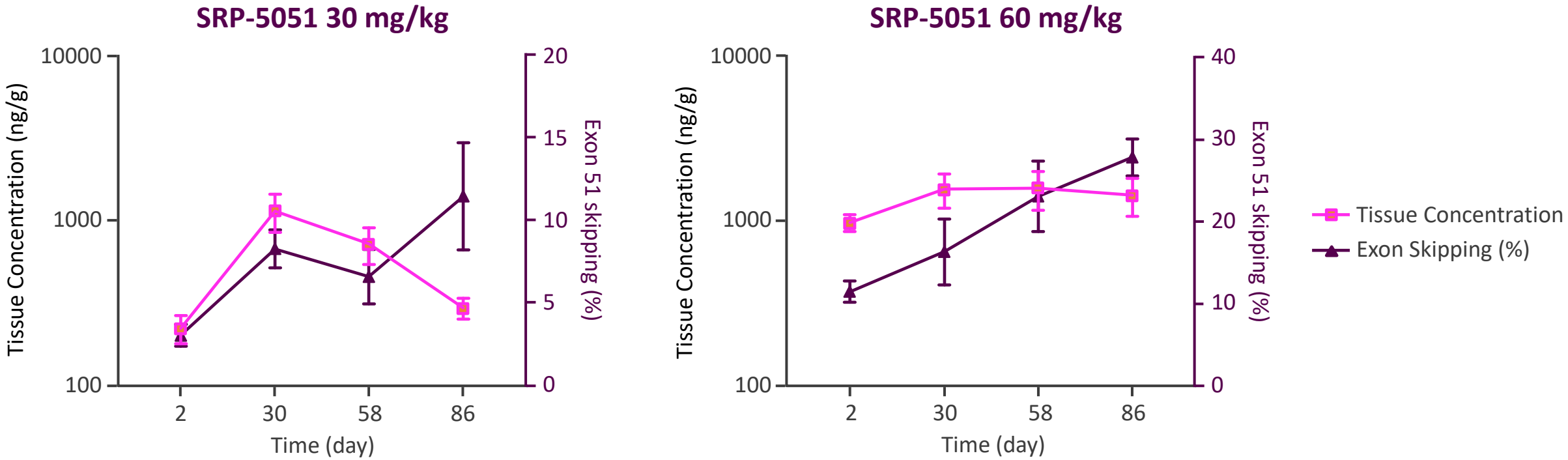
PK/PD of SRP-5051 after Single Dose in Nondystrophic Nonhuman Primates



Error bars represent SE. Animals received a single 1-hour IV infusion of SRP-5051 at dose levels of 30 and 60 mg/kg. Blood samples were collected on Day 1: pre-dose and 1, 2, 4, 8, 12, 16, and 24 hours post-infusion. Muscle samples were collected on days 2, 5 (only for the 30 mg/kg group), 10, 15, 22 and 28 by biopsy. After day 10, tissue concentration for the 30 mg/kg dose was below the limit of quantification. 2-way ANOVA followed by Sidak's multiple comparison test used to compare exon skipping at different sampling times to earliest time point.

Single dose of SRP-5051 results in muscle tissue accumulation and exon 51 skipping that last for at least 28 days

PK/PD of SRP-5051 after Q4W Repeat Dosing for 12 weeks in Nondystrophic Nonhuman Primates



Error bars represent SE. Animals received 1-hour IV infusion of vehicle, 30 mg/kg or 60 mg/kg SRP-5051 once every 4 weeks. Muscle biopsy tissue was collected on the second day after each infusion.

- **Tissue exposure and exon 51 skipping was dose-dependent**
- **Cumulative exon-skipping was observed at the end of the study**
- **No safety signals were detected after 12 weeks of dosing**

Conclusions

- The PK/PD of SRP-5051, a peptide-conjugated PMO, was evaluated in non-dystrophic nonhuman primates
- After a single injection of SRP-5051, a dose dependent and sustained exposure in muscle tissue was observed for days
  - Despite the short plasma half-life, quantifiable tissue exposure persisted for 10 days and 28 days for the 30 and 60 mg/kg dose groups; respectively
  - This clearly demonstrates the role of SRP-5051 tissue exposure to drive the PD effect
- The sustained exon skipping observed after a single dose of SRP-5051 supports the Q4W dosing regimen currently being studied in the clinic
  - A single dose of SRP-5051 resulted in sustained exon 51 skipping that was maintained for at least 28 days
- Repeat Q4W dosing of SRP-5051 for 12 weeks, demonstrate cumulative exon-skipping effect that increased after each infusion
- SRP-5051 appeared to be well tolerated after 12 weeks of dosing
- These studies further support the Q4W clinical investigation of SRP-5051
  - A phase 2 multiple-ascending-dose study is currently ongoing (NCT04004065)

Q4W=once every 4 weeks.

Questions?

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