Presented virtually at the Muscular Dystrophy Association Clinical & Scientific Conference, March 13–16, 2022, Nashville, TN

Evaluation of Skin Biopsy as a Method to Assess Pharmacokinetic and Pharmacodynamic Properties of SRP-5051 in Preclinical Species

Marie Claire Mukashyaka, Mohammad Shadid, Leslie C.L. Wu, Mark Wysk, Jenna Wood, Jianbo Zhang, Miralem Prijic, Kamela Bellovoda, Bryan Mastis, Sam Foley, Annika Malmberg, Shawn Harriman, John R. Hadcock

Sarepta Therapeutics, Inc., Cambridge, MA, USA

Please scan QR code to download poster

Objective

To determine if the pharmacokinetic/pharmacodynamic (PK/PD) response of SRP-5051 can be assessed with skin biopsy in nonhuman primate (NHP) and human Duchene muscular dystrophy (hDMD) gene del52/*mdx* mouse models

Key Takeaway

Skin biopsy may serve as a less invasive method to allow for longitudinal PK/PD biomarker assessments after treatment with SRP-5051, with potential application to other exon-skipping or gene therapies in future clinical studies

CONCLUSIONS

- Exposure and PD response of SRP-5051 are detectable in skin of 2 preclinical species (NHPs and del52/*mdx* mice) after single or repeat dosing
- Drug exposure is comparable or higher in skin samples compared with other tissues, while PD (exon skipping and dystrophin) is comparable or lower in skin compared with other tissues
  - Total (exon 51 skipped+unskipped) transcripts in skin are lower than other tissues; these results suggest skin may have lower muscle content and levels of dystrophin mRNA available for SRP-5051 engagement
- This analysis shows that skin can be used to assess exposure, target engagement, and PD response of SRP-5051; however, there is no clear correlation of PK and/or PD response between skin and target tissues

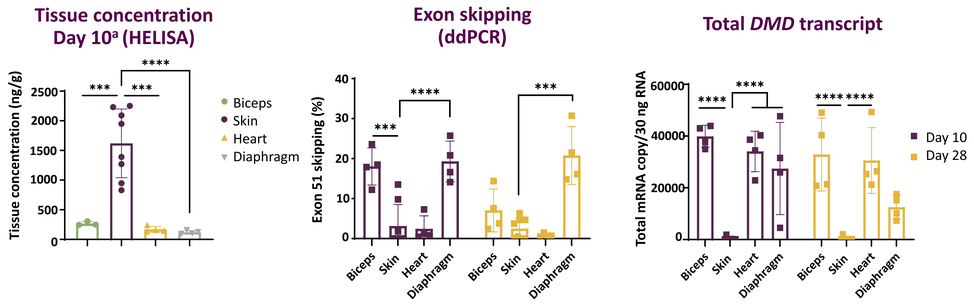
BACKGROUND

- SRP-5051 is an investigational peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO) designed to target exon 51 skipping with the goal of increasing tissue uptake, exon skipping, and dystrophin production[1]
- PK/PD properties of exon-skipping therapies designed to restore the *DMD* reading frame are traditionally evaluated by invasive muscle biopsies that limit longitudinal study of individual patients

RESULTS

PK/PD properties of SRP-5051 in NHP tissues

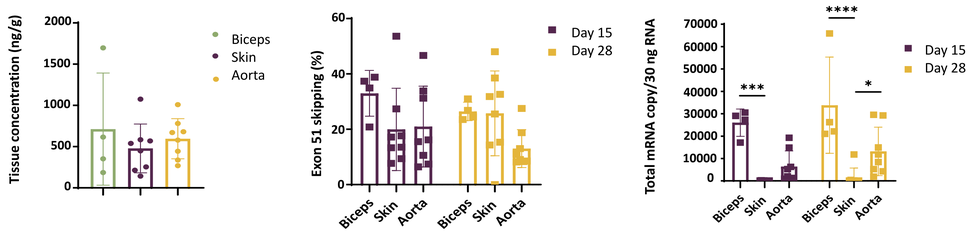
Single 30-mg/kg dose



- SRP-5051 concentration was higher in skin compared with other muscle tissues at Day 10
- Exon skipping was lower in skin than in other muscle tissues at Days 10 and 28
- Total *DMD* transcript copies were lower in skin compared with other muscle tissues at Days 10 and 28

*** *P* <0.001; ****P* <0.0001 (tissue concentration: 1-way analysis of variance [ANOVA] followed by Tukey's multiple comparisons test; exon skipping and total *DMD* transcript: 2-way ANOVA followed by Tukey's multiple comparison test). [a]Tissue concentrations were not analyzed by HELISA on Day 28 and are therefore not included in this analysis. ddPCR=droplet digital polymerase chain reaction; *DMD*=Duchenne muscular dystrophy gene; HELISA=hybridization-ligation enzyme-linked immunosorbent assay; NHP=nonhuman primate; PK/PD=pharmacokinetic/pharmacodynamic.

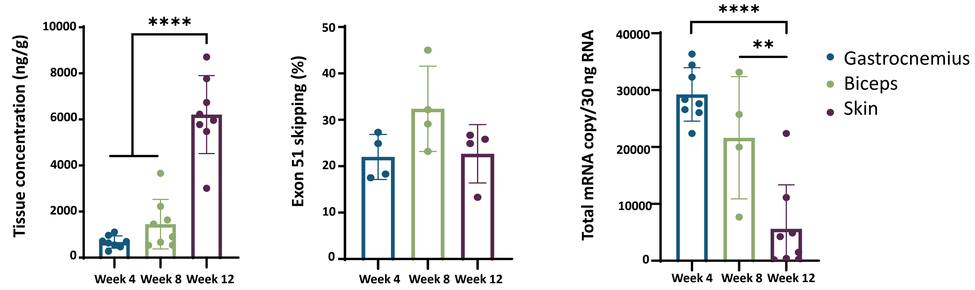
Single 60-mg/kg dose



- SRP-5051 tissue concentration and exon skipping levels were similar in skin, biceps, and aorta in NHP after one 60-mg/kg dose
- Total *DMD* transcript copies were lower in skin compared with biceps but at comparable levels to aorta

*P <0.05; ***P <0.001; ****P <0.0001 vs skin (2-way analysis of variance followed by Tukey's multiple comparisons test). [a]Most tissue concentrations were below the limit of quantification by LC/MS-MS on Day 28 and are therefore not included in this analysis. ddPCR=droplet digital polymerase chain reaction; *DMD*=Duchenne muscular dystrophy gene; LC/MS-MS=liquid chromatography with tandem mass spectrometry; NHP=nonhuman primate.

Repeat dosing Q4W 60 mg/kg (Week 12)

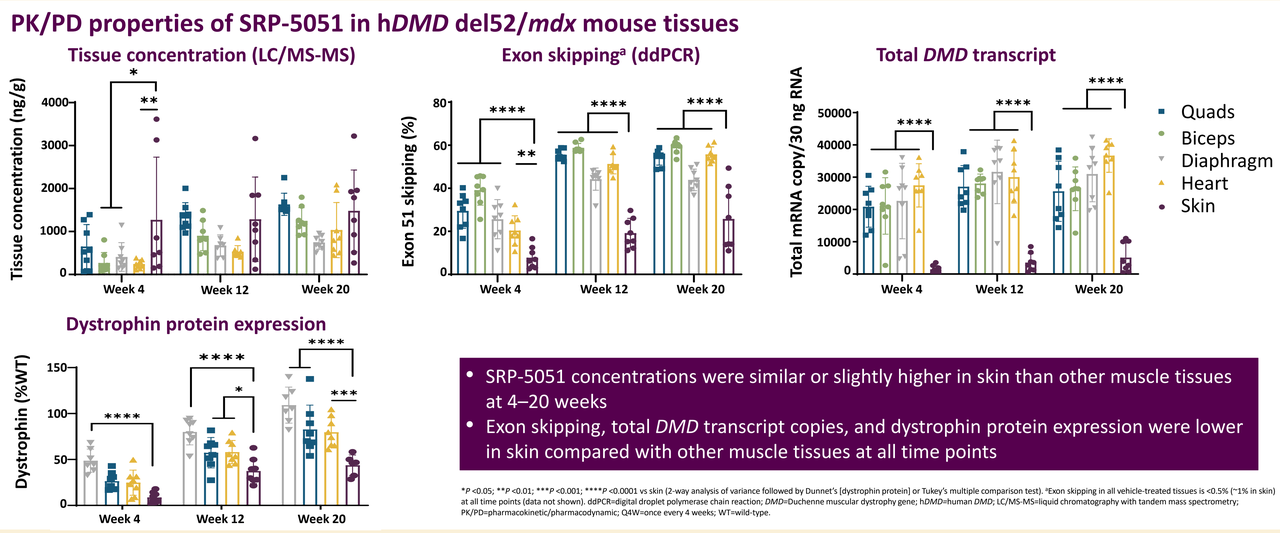


- SRP-5051 concentration was higher in skin compared with other muscle tissues
- Exon skipping was similar between skin, biceps, and gastrocnemius
- Total *DMD* transcript copies were lower in skin compared with biceps and gastrocnemius

**P <0.01; ****P <0.0001 vs skin (1-way analysis of variance followed by Tukey's multiple comparisons test). ddPCR=digital droplet polymerase chain reaction; *DMD*=Duchene muscular dystrophy gene; LC/MS-MS=liquid chromatography with tandem mass spectrometry; Q4W=every 4 weeks.

PK/PD properties of SRP-5051 in h*DMD* del52/*mdx* mouse tissues

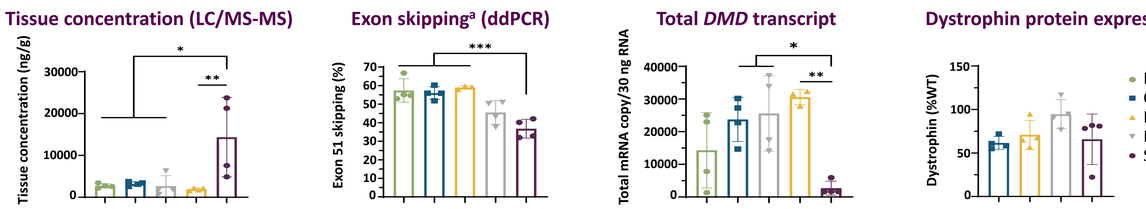
Repeat dosing Q4W 100 mg/kg



- SRP-5051 concentrations were similar or slightly higher in skin than other muscle tissues at 4–20 weeks
- Exon skipping, total *DMD* transcript copies, and dystrophin protein expression were lower in skin compared with other muscle tissues at all time points

*P <0.05; **P <0.01; ***P <0.001; ****P <0.0001 vs skin (2-way analysis of variance followed by Dunnet's [dystrophin protein] or Tukey's multiple comparison test). [a]Exon skipping in all vehicle-treated tissues is <0.5% (~1% in skin) at all time points (data not shown). ddPCR=digital droplet polymerase chain reaction; *DMD*=Duchenne muscular dystrophy gene; h*DMD*=human *DMD*; LC/MS-MS=liquid chromatography with tandem mass spectrometry; PK/PD=pharmacokinetic/pharmacodynamic; Q4W=once every 4 weeks; WT=wild-type.

Repeat dosing Q4W 200 mg/kg (Week 12)



- SRP-5051 concentration was higher in skin than in muscle tissues
- Exon skipping and total *DMD* transcript copies were lower in skin compared with other muscle tissues
- Dystrophin protein expression was comparable between skin and other muscle tissues, relative to individual muscle beds

*P <0.05; **P <0.01; ***P <0.001 vs skin (1-way analysis of variance followed by Tukey's multiple comparisons test). ddPCR=digital droplet polymerase chain reaction; *DMD*, Duchenne muscular dystrophy gene; LC/MS-MS=liquid chromatography with tandem mass spectrometry; Q4W=once every 4 weeks; WT=wild-type.

REFERENCE

1. Echevarría L, et al. *Hum Mol Genet.* 2018;27:R163-72.

ACKNOWLEDGMENTS & DISCLOSURES

This study was sponsored by Sarepta Therapeutics, Inc. Editorial support was provided by Paraskevi Briassouli, PhD, of Eloquent Scientific Solutions, and funded by Sarepta Therapeutics, Inc. All authors are employees or former employees of Sarepta Therapeutics, Inc. and may own stock in the company. Products are investigational only. Previously presented at the 17th Annual Meeting of the Oligonucleotide Therapeutics Society: Virtual Conference, September 26–29, 2021.