Phase 2 Multiple Ascending Dose Study of SRP-5051 PPMO in Patients With DMD Amenable to Exon 51 Skipping: Part A Results

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Disclosures

- **C. Campbell** is a site investigator for Acceleron, AMO, Biogen, BioMarin, Cytokinetics, GSK, Pfizer, PTC Therapeutics, Roche, Sarepta, and Wave, and has received research support from Biogen, Genzyme, PTC Therapeutics, and Valerian for investigator-initiated grants. He has received fees for advisory functions from AMO, Biogen, Roche, and PTC Therapeutics, and is a data safety monitoring board member for Catabasis and Solid.
- **K. Mathews** has received research support as a site PI from Catabasis, Italfarmaco, Reata, Retrotope, Santhera, and Sarepta. She also has received research support from the CDC (U01 DD001248) and FARA and NIH (5 U54 NS053672, U24 NS-10718).
- **M. van de Rijn, E. Palatinsky, X. Ni, J. Tinsley, N. Sha, J. Malhotra, I. Sehinovych, and D. Stevanovic** are or have been employees of Sarepta Therapeutics, Inc, and may own stock in the company.
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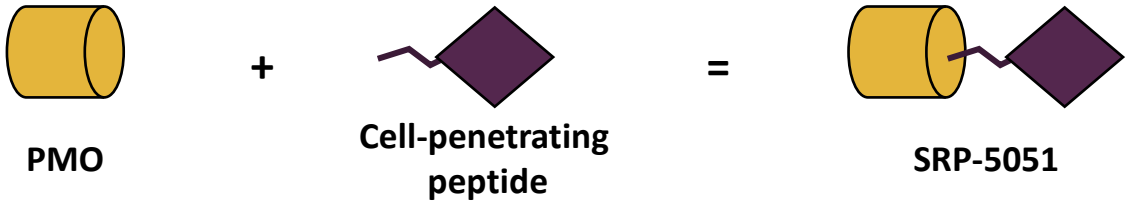
Introduction

- Peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs) are a next-generation chemistry platform: cell-penetrating peptide is conjugated to PMO backbone to increase cellular uptake, exon skipping, and dystrophin protein[1,2]
- SRP-5051 is an investigational PPMO designed to skip exon 51 of the *DMD* gene to restore the reading frame and allow production of internally truncated dystrophin



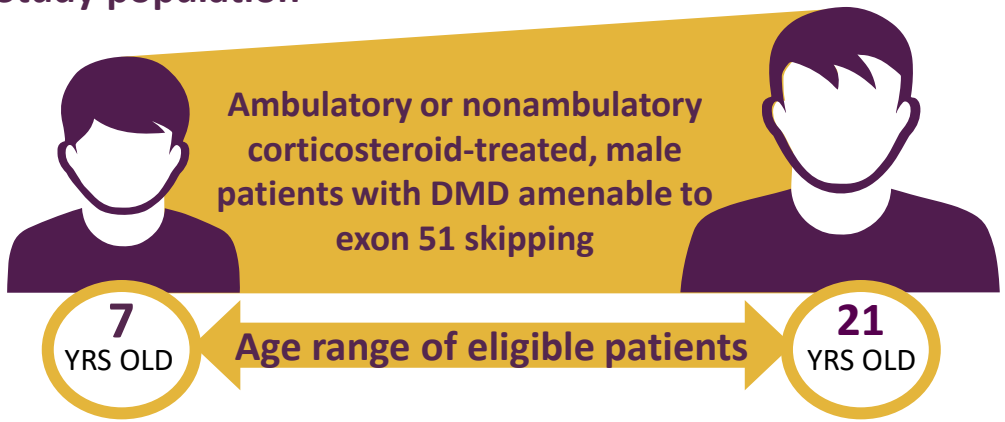
Objective: To report results from the Part A dose-finding phase of MOMENTUM (NCT04004065), an ongoing phase 2 study of SRP-5051

DMD, dystrophin

1. Gan L, et al. Poster presented at the 2019 Muscular Dystrophy Association (MDA) conference. April 13–17, 2019. Orlando, FL; 2. Echevarría L, et al. *Hum Mol Genet*. 2018;27:R163-72. .

Phase 2, open-label, nonrandomized, two-part dose determination and expansion study of SRP-5051 in patients with DMD (MOMENTUM): Part A

Study population



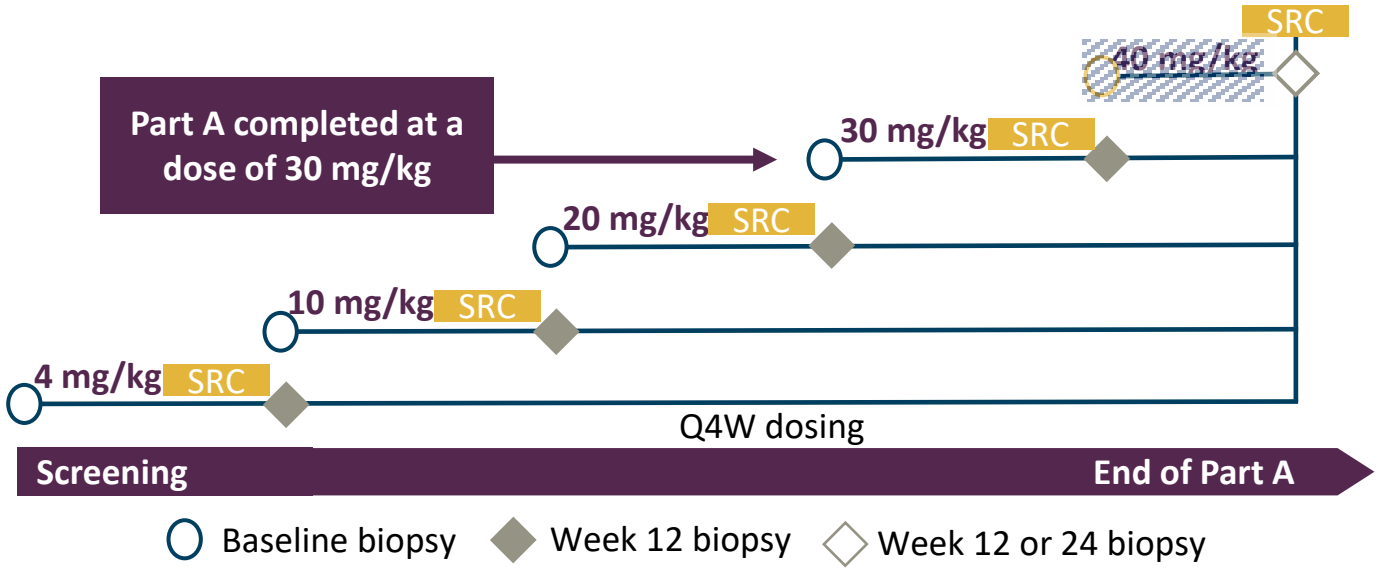
Primary endpoints:

- AEs and clinically significant laboratory abnormalities

Other endpoints:

- Change from baseline at week 12 in exon skipping level
- Change from baseline at week 12 in dystrophin production
- Pharmacokinetics

Part A (dose-finding phase):
12-week, multiple ascending dose, safety and tolerability study



AE, adverse event; DMD, Duchenne muscular dystrophy; Q4W, once every 4 weeks; SRC, Safety Review Committee.

Baseline patient characteristics

	4 mg/kg (n=3)	10 mg/kg (n=3)	20 mg/kg (n=5)	30 mg/kg (n=4)[a] (biopsy set)	30 mg/kg (n=7) (safety set)	Overall (N=18)[a]
Mean (range) age, years	11.7 (11–12)	13.3 (10–18)	9.8 (8–11)	14.0 (7–18)	13.4 (7–18)	12.1 (7–18)
Ambulatory status	1A+2N	2A+1N	4A+1N	3A+1N	4A+3N	11A+7N
Mean (range) BMI, kg/m^2	29.5 (24–36)	22.1 (17–32)	17.7 (13–27)	22.6 (17–26)	23.4 (17–29)	22.6 (13–36)
Mean (range) time since DMD diagnosis, months	47.0 (42–51)	104.9 (80–118)	67.9 (19–121)	134.2 (81–190)	123.9 (59–190)	92.4 (19–190)
Mean (range) no. of infusions before biopsy	3.3 (3–4)	4.0 (4–4)	4.3 (4–5)[b]	3.5 (3–5)	N/A	3.8 (3–5)[c]

~60% of patients were ambulatory at baseline and **all patients received at least three doses before biopsy**

[a]The four patients in the biopsy set are also counted as part of the safety set (n=7) and are not counted again for the overall total; [b](n=4); [c](n=14).
A, ambulatory; BMI, body mass index; DMD, Duchenne muscular dystrophy; N, nonambulatory; N/A, not applicable.

Primary endpoint: AEs and clinically significant laboratory abnormalities

AE summary as of January 27, 2021

Patients with TEAEs, n (%)	4 mg/kg (n=3)	10 mg/kg (n=3)	20 mg/kg (n=5)	30 mg/kg (safety set) (n=7)	Overall (N=18)
TEAE	2 (66.7)	3 (100.0)	5 (100.0)	7 (100.0)	17 (94.4)
TEAE related to study drug	0	3 (100.0)	2 (40.0)	7 (100.0)	12 (66.7)
Grade ≥3 TEAE	0	0	0	2 (28.6)	2 (11.1)
Serious TEAE	1 (33.3)	0	0	2 (28.6)	3 (16.7)
Serious TEAE related to study drug	0	0	0	2 (28.6)	2 (11.1)
TEAE leading to death	0	0	0	0	0
Total number of TEAEs by severity					
Grade 1	14	12	19	19	64
Grade 2	13	4	2	8	27
Grade 3 or higher	0	0	0	3	3

- The **majority of TEAEs were mild to moderate** in severity
- **Markers of kidney function** (estimated glomerular filtration rate, serum BUN, Cr, cystatin C) **have generally been normal**
- There have been **no TEAEs leading to permanent study drug discontinuation or death**

AE, adverse event; BUN, blood urea nitrogen; Cr, creatinine; TEAE, treatment-emergent adverse event.

Treatment-related TEAEs

Treatment-related TEAEs in >10% of patients as of January 27, 2021

Patients with ≥1 treatment-related TEAE, n (%)	4 mg/kg (n=3)	10 mg/kg (n=3)	20 mg/kg (n=5)	30 mg/kg (safety set) (n=7)	Overall (N=18)
Hypomagnesemia	0	2 (66.7)	2 (40.0)	6 (85.7)	10 (55.6)
Headache	0	2 (66.7)	0	0	2 (11.1)
Nausea	0	1 (33.3)	0	1 (14.3)	2 (11.1)

- The **most common treatment-related TEAE was hypomagnesemia**
  - In most cases, hypomagnesemia was mild to moderate; **all patients were asymptomatic,** and **all recovered after dose pause and magnesium supplementation**
  - Hypomagnesemia related to study drug was **severe in 2 of the 6 patients in the 30 mg/kg cohort** who experienced hypomagnesemia
- **All other treatment-related TEAEs** listed were **mild or moderate in severity**

TEAE=treatment-emergent adverse event.

Serious treatment-related TEAEs

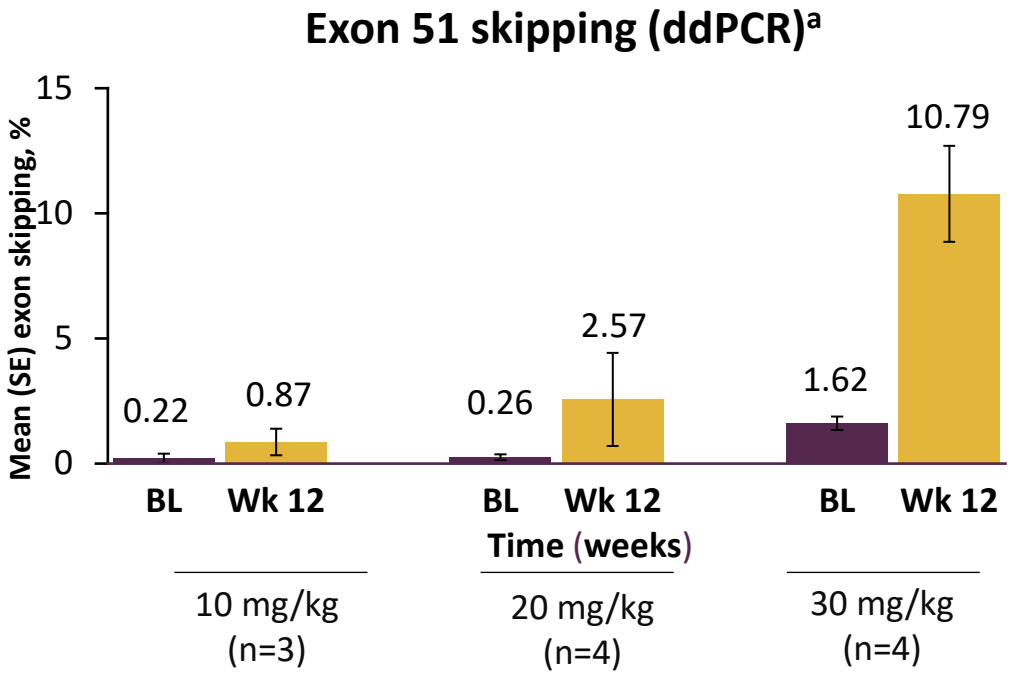
Serious TEAEs with severity grade ≥3 as of January 27, 2021

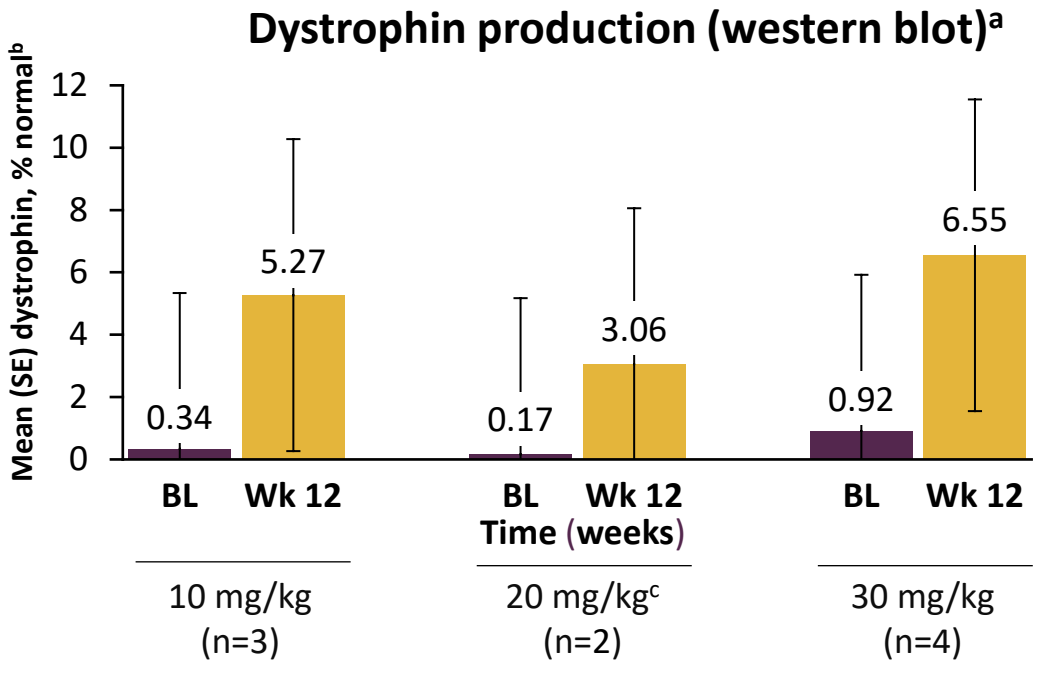
Patient	Preferred term	Severity[a]	Outcome
Patient 8 (30 mg/kg)	Hypomagnesemia	Grade 4	Resolved
	Hypokalemia	Grade 3	Resolved
Patient 10 (30 mg/kg)	Hypomagnesemia	Grade 4	Resolved

- **Two serious cases** of hypomagnesemia **occurred prior to the implementation of magnesium monitoring and supplementation**
- **None** of the **serious treatment-related TEAEs were life-threatening**, and **both patients remained asymptomatic**

[a]Severity is based on Common Terminology Criteria for Adverse Events laboratory value. TEAE=treatment-emergent adverse event.

Exon skipping and dystrophin production

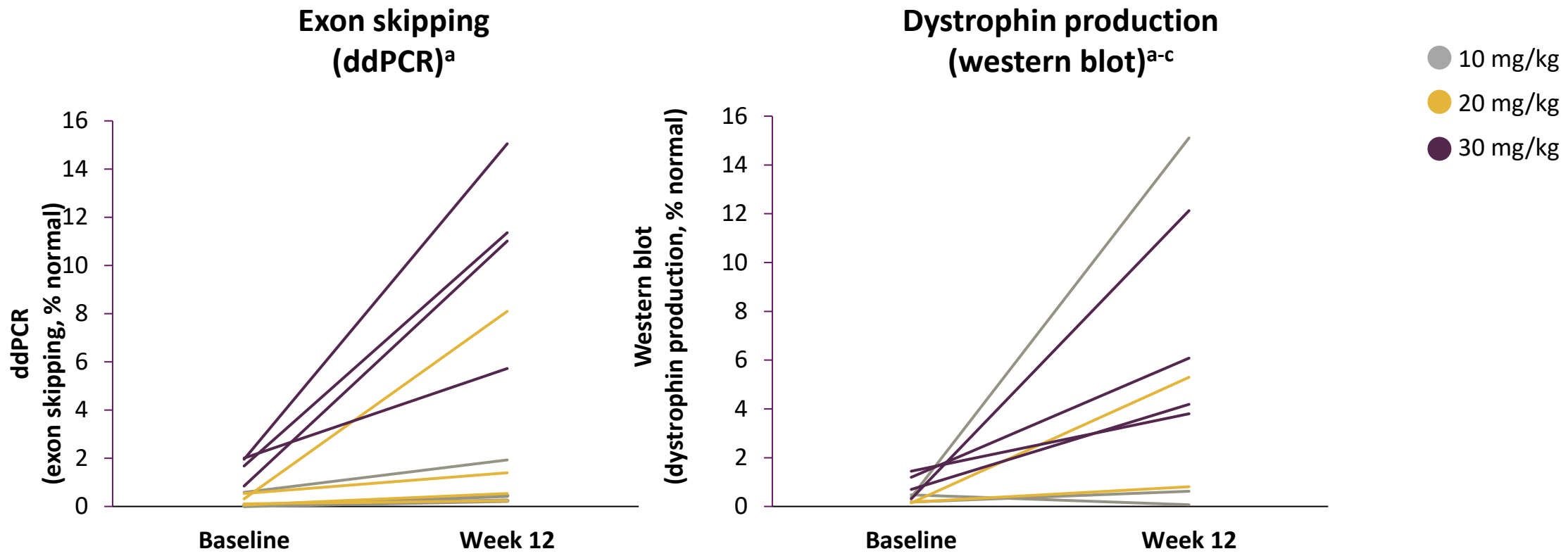




Higher levels of exon skipping and dystrophin production were seen **with the 30 mg/kg dose cohort** compared with other dosing cohorts at week 12 biopsy

[a]Target biopsy was at week 12; Patients from the 4 mg/kg cohort were omitted due to missing western blot data; 10 mg/kg cohort: four doses (n=3 patients; biopsy taken mean [range] 6 [4–9] days after last dose); 20 mg/kg cohort: four doses (n=3) or five doses (n=1) (biopsy taken 9 [1–21] days after last dose); 30 mg/kg cohort: three doses (n=3) or five doses (n=1) (biopsy taken 28 [27–31] days after last dose); [b]Adjusted for muscle content; [c]Biopsy is missing for two patients in the 20 mg/kg cohort due to insufficient tissue or low muscle content in sample. BL, baseline; ddPCR, droplet digital PCR; SE, standard error; Wk, week.

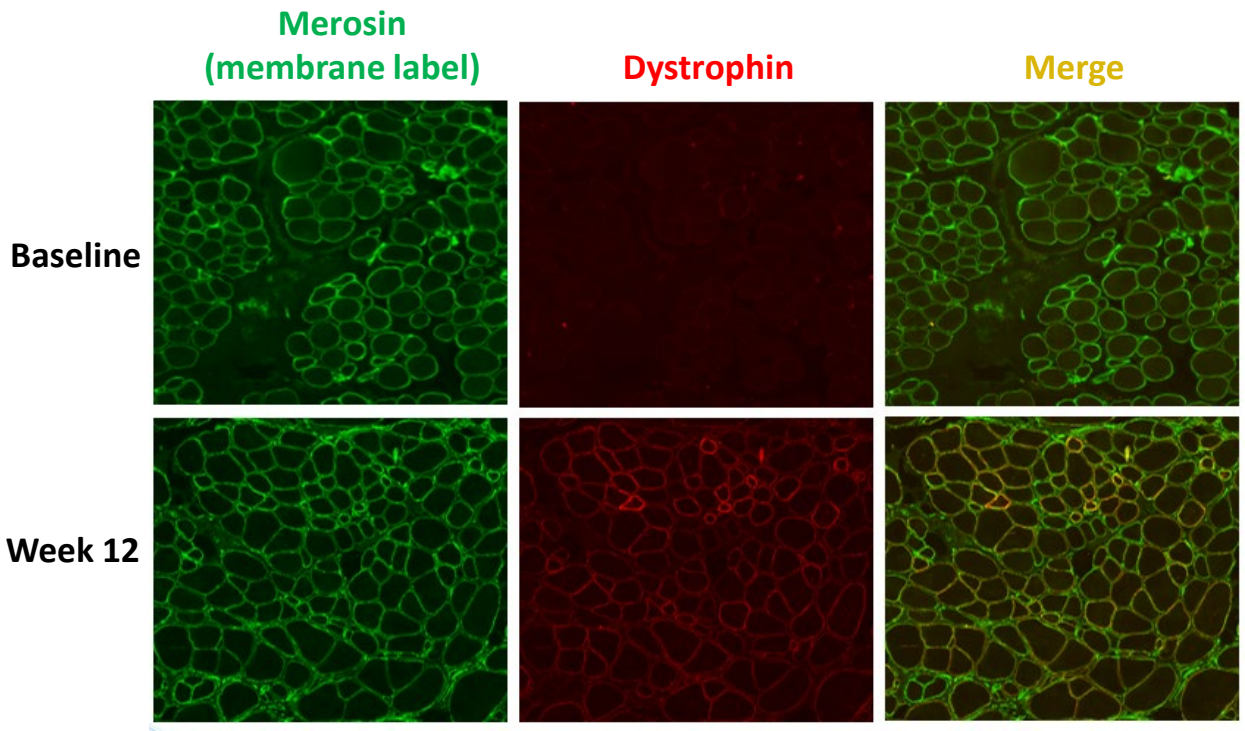
Exon skipping and dystrophin production following treatment with SRP-5051



In the 20 and 30 mg/kg cohorts, all patients experienced **an increase in exon skipping and dystrophin production**

[a]Target biopsy was at week 12; patients from the 4 mg/kg cohort were omitted due to missing western blot data; 10 mg/kg cohort: four doses (n=3 patients; biopsy taken mean [range] 6 [4–9] days after last dose); 20 mg/kg cohort: four doses (n=3) or five doses (n=1) (biopsy taken 9 [1–21] days after last dose); 30 mg/kg cohort: three doses (n=3) or five doses (n=1) (biopsy taken 28 [27–31] days after last dose); [b]Adjusted for muscle content; [c]Biopsy is missing for two patients in the 20 mg/kg cohort due to insufficient tissue or low muscle content in sample. ddPCR, droplet digital PCR.

Dystrophin localization at the sarcolemma, percent dystrophin-positive fibers, and fluorescence intensity



30 mg/kg biopsy set (n=4)	Mean (SE) % positive fibers	Mean (SE) % fluorescence intensity
Week 12 biopsy	64.53 (9.21)	30.36 (3.30)

Mean baseline values were 17.18% and 15.68% for dystrophin-positive fibers and intensity, respectively

In the 30 mg/kg cohort, immunofluorescence at week 12 biopsy showed an **increase in PDPF and mean intensity** from baseline

PDPF, percent dystrophin-positive fibers; SE, standard error.

Conclusions

- SRP-5051 is an investigational PPMO designed to skip exon 51 of the *DMD* gene with a Q4W dosing schedule
- The majority of TEAEs were mild or moderate in severity
- After the emergence of a new safety signal of hypomagnesemia, analysis of all available data indicates that hypomagnesemia can be monitored and is manageable
- All patients in the 20 and 30 mg/kg dosing cohorts experienced an increase in exon skipping and dystrophin production
- Immunofluorescence analysis performed on biopsies from the 30 mg/kg dosing cohort demonstrated correct localization of dystrophin protein at the sarcolemma
- All participants from Part A are invited to enroll in Part B of MOMENTUM, which is currently enrolling additional participants

Key Takeaway
MOMENTUM Part A results support further clinical investigation of SRP-5051

DMD, dystrophin; MOMENTUM, Study for Dose Determination of SRP-5051, Then Dose Expansion in Patients With Duchenne Muscular Dystrophy Amenable to Exon 51-Skipping Treatment; PPMO, peptide-conjugated phosphorodiamidate morpholino oligomer; Q4W, once every 4 weeks; TEAE, treatment-emergent adverse event.

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List of participating sites

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