Safety and Exposure of SRP-1003, an αvβ6 Integrin-Targeting siRNA Therapy for Patients With Myotonic Dystrophy Type 1: Interim Findings From a Phase 1/2 Study

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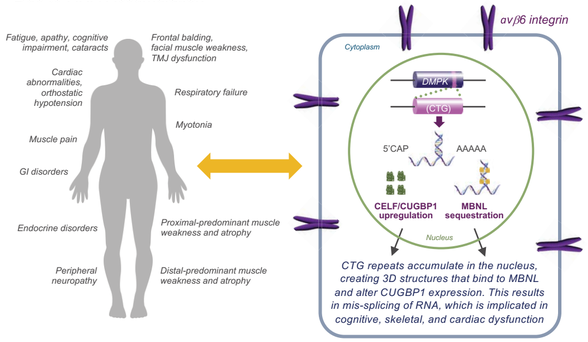
Background

- Myotonic dystrophy type 1 (DM1) is an inherited, progressive, multisystem, autosomal dominant muscular dystrophy[1,2] (**Figure 1**)
  - DM1 primarily affects skeletal and smooth muscles; however, the endocrine and central nervous systems are also commonly affected[1-3]
- DM1, caused by a pathogenic expansion allele in the dystrophia myotonica protein kinase *(DMPK)* gene, leads to RNA accumulation, which results in downstream mis-splicing of proteins[1,3] (**Figure 1**)

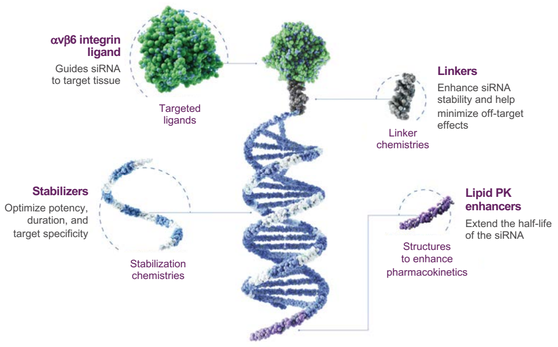
Figure 1 *DM1, a Multisystem Disorder, Is Caused by Mis-splicing of Proteins Due to RNA Accumulation*[1-6]



αvβ6, alpha-v beta-6; CELF, CUGBP elav-like family; CUGBP1, CUG-binding protein 1; DM1, myotonic dystrophy type 1; *DMPK*, dystrophia myotonica protein kinase; GI, gastrointestinal; MBNL, muscleblind-like; TMJ, temporomandibular joint.

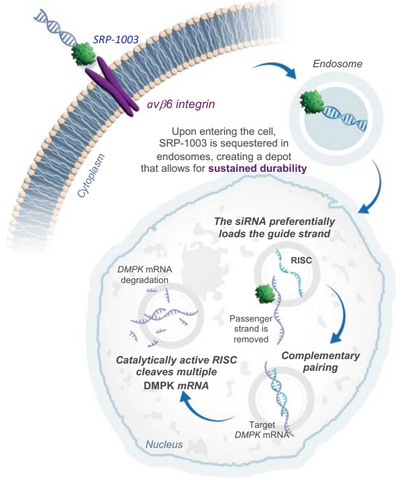
- SRP-1003 is an investigational alpha-v beta-6 (αvβ6) integrin-targeting ligand-based small interfering RNA (siRNA) therapy for DM1 that knocks down *DMPK* messenger RNA (mRNA) in the nucleus by targeting RNA for degradation[7-11] (**Figure 2** and **Figure 3**)
  - SRP-1003 enters the cells through a distinct mechanism of action via the αvβ6 integrin receptors
  - Targeting αvβ6 integrin, a transmembrane receptor with high expression and surface availability, allows for increased tissue penetration[12]

Figure 2 *SRP-1003, an αvβ6 Integrin-Targeting siRNA Therapy*[13,14]



αvβ6, alpha-v beta-6; PK, pharmacokinetic; siRNA, small interfering RNA.

Figure 3 *SRP-1003 Degrades* DMPK *mRNA in the Nucleus*[7-9]



αvβ6, alpha-v beta-6; *DMPK*, dystrophia myotonica protein kinase; mRNA, messenger RNA; RISC, RNA-induced silencing complex; siRNA, small interfering RNA.

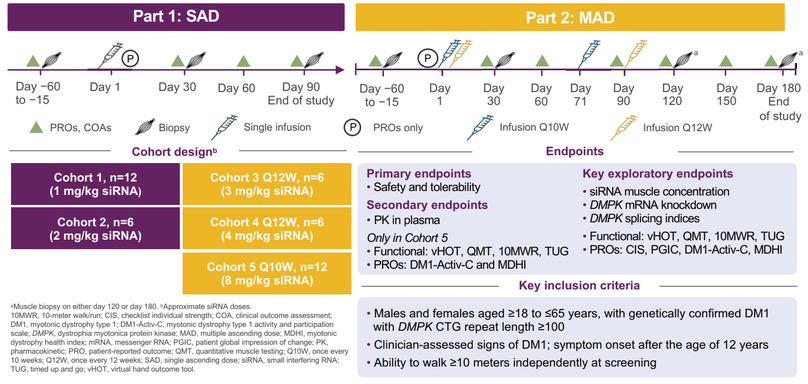
Objective

To evaluate safety and pharmacokinetic (PK) outcomes of SRP-1003 in the ongoing, phase 1/2, randomized, placebo (PBO)-controlled, 2-part trial (NCT06138743)

Methods

Patients received a single ascending dose (part 1) or multiple ascending doses (part 2) of SRP-1003 or PBO (**Figure 4**)

Figure 4 *Study Design*



[a]Muscle biopsy on either day 120 or day 180. [b]Approximate siRNA doses.
10MWR, 10-meter walk/run; CIS, checklist individual strength; COA, clinical outcome assessment; DM1, myotonic dystrophy type 1; DM1-Activ-C, myotonic dystrophy type 1 activity and participation scale; *DMPK*, dystrophia myotonica protein kinase; MAD, multiple ascending dose; MDHI, myotonic dystrophy health index; mRNA, messenger RNA; PGIC, patient global impression of change; PK, pharmacokinetic; PRO, patient-reported outcome; QMT, quantitative muscle testing; Q10W, once every 10 weeks; Q12W, once every 12 weeks; SAD, single ascending dose; siRNA, small interfering RNA; TUG, timed up and go; vHOT, virtual hand outcome tool.

Results

Participants

- Mean (SD) age at baseline was 39.1 (10.32) years, and 38.9% of participants were female (**Table 1**)

Table 1 *Baseline Characteristics*

	Part 1 SAD		Part 2 MAD		Overall	
Parameter	C1 n=10	C2 n=6	C3 n=5	C4 n=4	Pooled PBO n=11	Total N=36
Age, mean (SD), years	39.2 (11.84)	36.0 (9.06)	47.0 (12.04)	41.8 (7.09)	36.3 (9.16)	39.1 (10.32)
Female, n (%)	6 (60.0)	1 (16.7)	1 (20.0)	1 (25.0)	5 (45.5)	14 (38.9)
Weight, mean (SD), kg	74.97 (19.11)	63.92 (12.98)	78.34 (6.20)	72.45 (21.85)	75.31 (15.83)	73.42 (15.99)
BMI, mean (SD), kg/m²	25.84 (3.86)	20.77 (3.13)	25.88 (4.27)	25.23 (5.81)	25.68 (4.66)	24.88 (4.47)

BMI, body mass index; C, cohort; MAD, multiple ascending dose; PBO, placebo; SAD, single ascending dose; SD, standard deviation.

Safety

- Overall, 28 (77.8%) patients experienced any treatment-emergent adverse events (TEAEs) (**Table 2**)
  - Most TEAEs were mild to moderate in severity and did not appear to be dose dependent; the most common TEAEs (≥10% of participants) were headache and upper respiratory tract infection (13.9%, each)
- No TEAEs and no related serious TEAEs occurred in ≥20% of participants
- Three serious TEAEs (fatal arrhythmia, limb abscess, and emotional distress) were reported in 2 (5.6%) participants and were deemed unrelated to study drug
- No related TEAEs led to death, study drug withdrawal, or study discontinuation

Pharmacokinetics

- A dose-dependent increase in plasma area under the curve up to 3 mg/kg was observed, representing the highest SRP-1003 dose cohort with data to date (**Figure 5**)
- SRP-1003 had a half-life of about 5 hours and showed consistent dose-dependent increase in plasma exposure, supportive of overall PK linearity

Muscle delivery

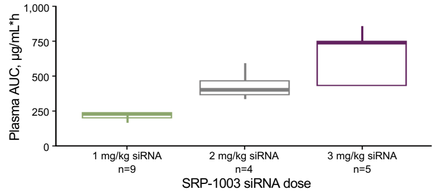
- SRP-1003 in the lowest dose cohort (1 mg/kg siRNA) mediates robust siRNA delivery into the muscle (12 nM, n=7 [1 participant was excluded due to study conduct])

Table 2 *Summary of TEAEs*

	Part 1 SAD (active + PBO)		Part 2 MAD (active + PBO)		Overall
TEAEs, n (%)	C1 n=14	C2 n=9	C3 n=7	C4 n=6	Total N=36
Any TEAEs	12 (85.7)	6 (66.7)	7 (100)	3 (50.0)	28 (77.8)
Serious TEAEs	2 (14.3)	0	0	0	2 (5.6)
Related TEAEs[a]	2 (14.3)	0	3 (42.9)	0	5 (13.9)

[a]An adverse event is considered treatment-related if the relationship to the study drug is "related" or missing. Participants are counted only once at the maximum relationship.
C, cohort; MAD, multiple ascending dose; PBO, placebo; SAD, single ascending dose; TEAE, treatment-emergent adverse event.

Figure 5 *Plasma Exposure by Dose Level*[a]



[a]One participant in cohort 1 was excluded due to study conduct.
AUC, area under the curve; siRNA, small interfering RNA.

Conclusions

- SRP-1003 showed an acceptable safety and tolerability profile with no dose-dependent increase in TEAEs and no dose-limiting safety signal
- SRP-1003 plasma exposure increased proportionally and achieved high-level muscle delivery with the αvβ6 integrin-targeting approach
- These interim data support continued investigation of SRP-1003

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