Safety and Exposure of SRP-1001, an αvβ6 Integrin-Targeting siRNA Therapy for Patients With FSHD1: Interim Findings From a Phase 1/2 Study

Richard Roxburgh,[1] Angela Rosenbohm,[2] Philip H.C. Kremer,[3,4] Cecile Phan,[5] Jiyeon Denninger,[6] Alvin Estilo,[6] Wenhua Hu,[6] Ihor Sehinovych,[6] Lilly East,[6] Rachael Potter,[6] Suzanne Hodgkinson[7]

[1]Auckland City Hospital, Auckland, New Zealand; [2]University of Ulm, Ulm, Germany; [3]Center for Human Drug Research (CHDR), Leiden, Netherlands; [4]Leiden University Medical Center (LUMC), Leiden, Netherlands; [5]University of Alberta, Edmonton, AB, Canada; [6]Sarepta Therapeutics, Inc., Cambridge, MA, USA; [7]University of New South Wales, Sydney, NSW, Australia

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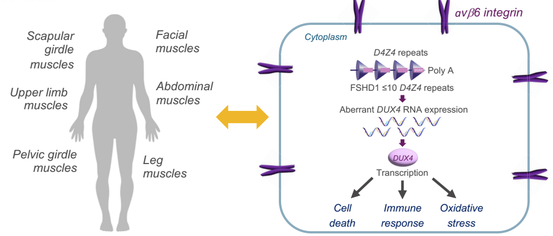
Background

- Facioscapulohumeral muscular dystrophy type 1 (FSHD1) is a rare genetic disease that causes weakness in the skeletal muscles[1] (**Figure 1**)
  - FSHD1 is caused by contraction of the *D4Z4* repeat, leading to activation of the double homeobox 4 (*DUX4*) gene, which is typically silenced early in life[2]
  - FSHD1 progressively spreads from the face into other areas, including the scapular girdle, upper limb, pelvic girdle, and abdominal and leg muscles[1,2]

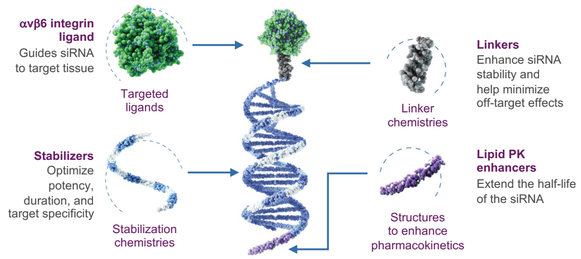
Figure 1 *FSHD1, Impacting Skeletal Muscles, Is Caused by Aberrant Activation of the* DUX4 *Gene*[1-3]



αvβ6, alpha-v beta-6; *DUX4*, double homeobox 4; FSHD1, facioscapulohumeral muscular dystrophy type 1.

- SRP-1001 is designed to knock down *DUX4* expression in FSHD1[4] (**Figure 2**)
  - SRP-1001 is an investigational alpha-v beta-6 (αvβ6) integrin-targeting ligand-based small interfering RNA (siRNA) therapy
  - Targeting αvβ6 integrin, a transmembrane receptor with high expression and surface availability, allows for increased muscle penetration[5]

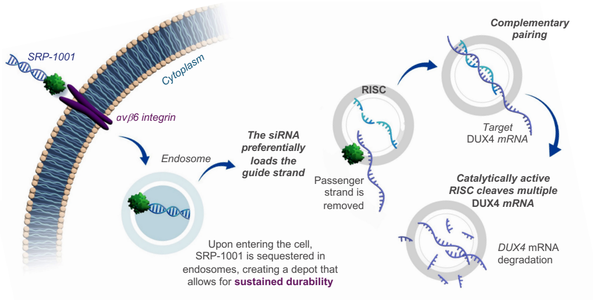
Figure 2 *SRP-1001, an αvβ6 Integrin-Targeting siRNA Therapy*[6,7]



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

- SRP-1001 enters the cells via the αvβ6 integrin receptors and allows the targeted degradation of *DUX4* messenger RNA[8-11] (**Figure 3**)

Figure 3 *SRP-1001 Specifically Degrades* DUX4 *mRNA*[8-11]



αvβ6, alpha-v beta-6; *DUX4*, double homeobox 4; mRNA, messenger RNA; RISC, RNA-induced silencing complex; siRNA, small interfering RNA.

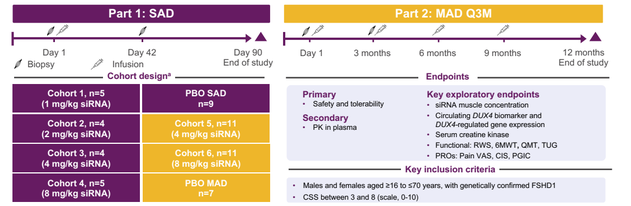
Objective

- To present the interim data on safety and exposure of SRP-1001 from the ongoing, first-in-human, phase 1/2, randomized, placebo (PBO)-controlled, dose-escalation trial (NCT06131983)

Methods

- Patients received a single ascending dose (part 1) or multiple ascending doses (part 2) of SRP-1001 or PBO (**Figure 4**)

Figure 4 *Study Design*



[a]Approximate siRNA doses.
6MWT, 6-minute walk test; CIS, checklist individual strength; CSS, clinical severity score; *DUX4*, double homeobox 4; FSHD1, facioscapulohumeral muscular dystrophy type 1; MAD, multiple ascending dose; PBO, placebo; PGIC, patient global impression of change; PK, pharmacokinetic; PRO, patient-reported outcome; QMT, quantitative muscle testing; Q3M, once every 3 months; RWS, reachable workspace score; SAD, single ascending dose; siRNA, small interfering RNA; TUG, timed up and go; VAS, visual analog scale.

Results

Participants

- At baseline, the mean (standard deviation) age was 44.9 (12.75) years and 21.4% of participants were female (**Table 1**)

Table 1 *Baseline Characteristics*

	Part 1 SAD				Part 2 MAD		Overall		
Parameter	C1 n=5	C2 n=4	C3 n=4	C4 n=5	C5 n=11	C6 n=11	Pooled PBO n=16	Treated n=40	Total N=56
Age, mean (SD), years	36.2 (14.15)	49.0 (6.00)	42.8 (9.29)	34.4 (11.44)	50.2 (9.13)	51.0 (13.35)	42.8 (13.75)	45.8 (12.41)	44.9 (12.75)
Female, n (%)	0	2 (50.0)	1 (25.0)	0	2 (18.2)	2 (18.2)	5 (31.3)	7 (17.5)	12 (21.4)
Weight, mean (SD), kg	84.32 (12.64)	84.75 (26.00)	78.06 (7.17)	81.66 (15.08)	83.05 (13.00)	82.65 (15.77)	80.63 (14.21)	82.60 (14.35)	82.03 (14.21)
BMI, mean (SD), kg/m^2	25.66 (4.87)	27.88 (7.57)	26.20 (2.04)	24.46 (3.81)	26.10 (3.55)	26.85 (3.18)	25.07 (4.04)	26.23 (3.91)	25.90 (3.95)
CSS, mean (SD)	4.4 (1.95)	6.5 (1.29)	5.8 (2.06)	6.6 (1.14)	6.1 (1.14)	5.2 (1.33)	5.0 (1.67)	5.7 (1.51)	5.5 (1.57)

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

Safety

- Overall, 43 (76.8%) patients experienced any treatment-emergent adverse events (TEAEs) (**Table 2**)
- Most TEAEs were mild to moderate in severity; the most common TEAEs (≥10% of participants) were headache (16.1%) and upper respiratory tract infection (14.3%)
  - No TEAEs occurred in ≥20% of participants
- One serious TEAE (chest discomfort) was reported and deemed not related to study drug; this was also the only severe TEAE reported in the study
- No related TEAEs or serious TEAEs led to death, study drug withdrawal, or study discontinuation

Table 2 *Summary of TEAEs*

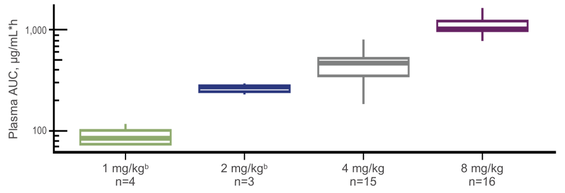
	Part 1 SAD (active + PBO)				Part 2 MAD[a] (active + PBO)		Overall
TEAEs, n (%)	C1 n=7	C2 n=7	C3 n=6	C4 n=7	C5 n=14	C6 n=15	Total N=56
Any TEAEs	7 (100)	4 (57.1)	5 (83.3)	5 (71.4)	10 (71.4)	12 (80.0)	43 (76.8)
Serious TEAEs	0	1 (14.3)	0	0	0	0	1 (1.8)
Related TEAEs[b]	2 (28.6)	0	1 (16.7)	0	6 (42.9)	1 (6.7)	10 (17.9)

[a]As of February 18, 2026. [b]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.

Pharmacokinetics

- SRP-1001 showed consistent dose-dependent increase in plasma with no evidence of saturation (**Figure 5**)
  - Dose-dependent increase in plasma area under the plasma curve up to 8 mg/kg, representing the highest siRNA dose evaluated to date for FSHD1
- At 42 days, a 4 mg/kg dose of SRP-1001 achieved 28.4 nM muscle concentration without dose-limiting toxicities that would limit further dose escalation

Figure 5 *SRP-1001 Plasma Exposure by siRNA Dose Level*[a]



[a]Plasma PK includes data at day 1 following a single dose across SAD and MAD cohorts. [b]One participant in each of cohorts 1 (1 mg/kg) and 2 (2 mg/kg) with all BLOQ samples was excluded from the analysis.
AUC, area under the plasma concentration-time curve between time 0 and 8 hours; BLOQ, below levels of quantification; MAD, multiple ascending dose; PK, pharmacokinetics; SAD, single ascending dose; siRNA, small interfering RNA.

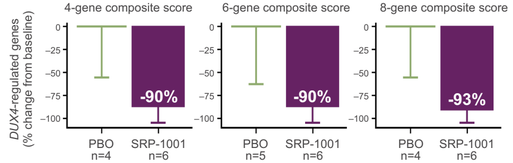
Serum creatine kinase

- At day 42, SRP-1001 (pooled siRNA single doses of 4 mg/kg and 8 mg/kg; n=31) achieved a 33% reduction in levels of creatine kinase vs placebo (n=16)

Suppression of *DUX4*-regulated genes

- A single dose of SRP-1001 suppressed *DUX4*-regulated genes (**Figure 6**)

Figure 6 DUX4*-Regulated Gene Suppression by SRP-1001*



BLOQ, below levels of quantification; *DUX4*, double homeobox 4; MRI, magnetic resonance imaging; PBO, placebo; qPCR, quantitative polymerase chain reaction; siRNA, small interfering RNA.

- SRP-1001 treatment cohorts pooled from siRNA dose cohort 1 (1 mg/kg), cohort 2 (2 mg/kg), and cohort 3 (4 mg/kg)
- qPCR composite scores were calculated as the sum across contributing target genes and normalized to baseline and PBO

Patients excluded from analysis

- One participant in cohort 1 (1 mg/kg) with all BLOQ plasma and muscle samples was excluded from the analysis
- One participant in cohort 2 (2 mg/kg) with all BLOQ plasma and muscle samples was excluded from the analysis
- Additional participants were excluded if BLOQ for *DUX4* genes
  - Muscle *DUX4*-regulated genes were characterized in MRI-guided biopsy samples collected from lower-body muscles

Conclusions

- These results suggest that the αvβ6 integrin-targeting ligand mediates robust siRNA delivery
- A single dose of SRP-1001 achieved a high level of siRNA muscle delivery and effective reduction of *DUX4* expression
- SRP-1001 showed an acceptable safety and tolerability profile with no dose-limiting safety signal

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Disclosures: RR, **AR**, **PHCK**, **CP**, and **SH** have nothing to disclose. **JD**, **AE**, **WH**, **IS**, **LE**, and **RP** are employees of Sarepta Therapeutics, Inc., and may own stock/options in the company.

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