Patients can’t wait for the next breakthrough in medical research.

So neither will we.
Forward-looking statements

This presentation contains “forward-looking statements.” Any statements that are not statements of historical fact may be deemed to be forward-looking statements. Words such as “believe,” “anticipate,” “plan,” “expect,” “will,” “may,” “intend,” “prepare,” “look,” “potential,” “possible” and similar expressions are intended to identify forward-looking statements. These forward-looking statements include statements relating to our opportunities in the rare disease space; potential solutions and market opportunities with our RNA technologies, gene therapy and gene editing; our programs’ potential to treat 1.5M patients; the potential benefits of our technologies and scientific approaches, including the potential of RNA-targeted medicine to increase or decrease production of a protein involved in a disease; the potential benefits of PMO and PPMO, including PPMO’s potential to greatly increase cell penetration, lead to more efficient dosing and greater benefit for patients, deliver to unique muscle types and treat Duchenne; the potential benefits of SRP-5051, including SRP-5051’s potential to treat patients with Duchenne amenable to exon 51 skipping and lead to increased exon skipping and dystrophin over time; the predicted dystrophin trajectory of >10% expression over time with monthly dosing of SRP-5051; our belief that, for SRP-5051, serum monitoring of magnesium and oral supplementation with magnesium is a feasible approach to enable early detection and management of hypomagnesemia; the potential benefits of SRP-9001, including SRP-9001’s potential to deliver the micro-dystrophin-encoding gene to muscle tissue for the targeted production of the micro-dystrophin protein in patients with Duchenne; the potential benefits of SRP-9003, including SRP-9003’s potential to drive meaningful levels of SGBC expression over time, leading to sustained functional improvements; the potential benefits of MHCK7, AAVrh74, SR2, SR3 and β-sarcoglycan; the potential of our LGMD portfolio to generate a steady stream of gene therapy candidates in five additional subtypes representing more than 70% of all known LGMDs; the potential benefits of iCELis adherent mammalian manufacturing technology; our forecast curve for gene therapy; our sustainable model for transformative gene therapies; the potential of gene therapy’s applicability across disease; the potential of our collaborations and partnerships; the estimated number of patients suffering from Duchenne and LGMD; and expected milestones and plans, including our plan for Part B of SRP-5051-201 to be the pivotal trial in the United States and to seek accelerated approval, if the trial is successful, announcing results from Part 2 of SRP-9001-102 in Q1 2022, reporting additional functional data in 2022 for SRP-9001-103, our plan to fully enroll SRP-9001-301 by mid 2022, seeking FDA confirmation of pivotal trial study design for SRP-9003 and plans regarding the development of future PPMOs for other exons in Duchenne and other indications.

These forward-looking statements involve risks and uncertainties, many of which are beyond our control and are based on our current beliefs, expectations and assumptions regarding our business. Actual results and financial condition could materially differ from those stated or implied by these forward-looking statements as a result of such risks and uncertainties, and such risks and uncertainties could materially and adversely affect our business, results of operations and trading price. Potential known risk factors include, among others, the following: the impact of the COVID-19 pandemic on timing of our clinical trials and potential disruptions to our business and manufacturing operations; we may not be able to comply with all FDA post-approval commitments and requirements with respect to EXONDYS 51, VYONDYS 51 and AMONDYS 45 in a timely manner or at all; data for our different programs, including PMMO and gene therapy-based product candidates, may not be sufficient for obtaining regulatory approval; our product candidates, including those with strategic partners, may not result in viable treatments suitable for commercialization due to a variety of reasons, including the results of future research may not be consistent with past positive results or may fail to meet regulatory approval requirements for the safety and efficacy of product candidates; success in preclinical testing and early clinical trials, especially if based on a small patient sample, does not ensure that later clinical trials will be successful; the expected benefits and opportunities related to our agreements with our strategic partners may not be realized or may take longer to realize than expected due to a variety of reasons, including any inability of the parties to perform their commitments and obligations under the agreements, challenges and uncertainties inherent in product research and development and manufacturing limitations; if the actual number of patients living with Duchenne and LGMD is smaller than estimated, our revenue and ability to achieve profitability may be adversely affected; our dependence on our manufacturers to fulfill our needs for our clinical trials and commercial supply, including any failure on our part to accurately anticipate product demand and timely secure manufacturing capacity to meet product demand, may impair the availability of products to successfully support various programs, including research and development and the potential commercialization of our gene therapy product candidates; we may not be able to successfully scale up manufacturing of our product candidates in sufficient quality and quantity or within sufficient timelines; current reimbursement models may not accommodate the unique factors of our gene therapy product candidates; we may not be able to execute on our business plans and goals, including meeting our expected or planned regulatory milestones and timelines, clinical development plans, and bringing our product candidates to market, for various reasons including possible limitations of our financial and other resources, manufacturing limitations that may not be anticipated or resolved for in a timely manner, regulatory, court or agency decisions, such as decisions by the United States Patent and Trademark Office; and those risks identified under the heading “Risk Factors” in Sarepta’s most recent Annual Report on Form 10-K and most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) and in its other SEC filings.

For a detailed description of risks and uncertainties Sarepta faces, you are encouraged to review Sarepta’s filings with the SEC. We caution investors not to place considerable reliance on the forward-looking statements contained in this presentation. The forward-looking statements in this presentation are made as of the date of this presentation only and, other than as required under applicable law, Sarepta does not undertake any obligation to publicly update its forward-looking statements.
The opportunity to save lives is **breathtaking**
7,000 Rare diseases

~80% are single gene mutations

And only approximately 5% of rare diseases currently have treatments

EVERY DAY  
Duchenne takes the life of a child

The time is now for solutions
Sarepta’s Mission

Armed with the most advanced science in genetic medicine, we are in a daily race to rescue lives otherwise stolen by rare disease.

At Sarepta, every day is another 24 hours to stand up for patients, advance technology, challenge convention and drag tomorrow into today.
A burgeoning pipeline for

*Today...and Tomorrow*
A multi-platform approach to finding solutions

RNA (PMO and PPMO)  14 PROGRAMS

GENE THERAPY  21 PROGRAMS

GENE EDITING  2 PROGRAMS

More than 40 programs in all, including our lead programs for Duchenne and limb-girdle muscular dystrophies*

Potential to treat 1.5M patients**

*Plus undisclosed targets.
**Based on published epidemiology.
More than 40 programs in development*

<table>
<thead>
<tr>
<th>RNA TECHNOLOGIES PMO</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>CLINICAL</th>
<th>COMMERCIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXONDYS 51 (eteplirsen)**</td>
<td>Duchenne</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VYONDYS 53 (golodirsen)**</td>
<td>Duchenne</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMONDYS 45 (casimersen)**</td>
<td>Duchenne</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 52</td>
<td>Duchenne</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Exon Targets***</td>
<td>Duchenne</td>
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</table>

<table>
<thead>
<tr>
<th>RNA TECHNOLOGIES PPMO</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>CLINICAL</th>
<th>COMMERCIAL</th>
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</thead>
<tbody>
<tr>
<td>SRP-5051</td>
<td>Duchenne</td>
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<td></td>
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<tr>
<td>SRP-5053</td>
<td>Duchenne</td>
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<td>SRP-5045</td>
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<td>SRP-5052</td>
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<td>SRP-5044</td>
<td>Duchenne</td>
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<td></td>
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<tr>
<td>SRP-5050</td>
<td>Duchenne</td>
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</tr>
</tbody>
</table>

*Does not include undisclosed targets.

**Candidate received accelerated approval in the U.S., confirmatory studies required.

***Other exon targets in development: 43, 44, 50, and 55.

Information is current as of 12/1/2021, updates are made on a quarterly basis.
### More than 40 programs in development*

<table>
<thead>
<tr>
<th>GENE THERAPY</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>CLINICAL</th>
<th>COMMERCIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRP-9001 micro-dystrophin**</td>
<td>Duchenne</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GALGT-2 Nationwide Children’s</td>
<td>Duchenne</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GNT 0004 Genethon</td>
<td>Duchenne</td>
<td></td>
<td></td>
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<tr>
<td>SRP-9003 (LGMD2E β-sarcoglycan)</td>
<td>LGMD</td>
<td></td>
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<td></td>
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<tr>
<td>SRP-9004 (LGMD2D α-sarcoglycan)</td>
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<tr>
<td>SRP-9005 (LGMD2C γ-sarcoglycan)</td>
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<tr>
<td>SRP-6004 (LGMD2B Dysferlin)</td>
<td>LGMD</td>
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<td>SRP-9006 (LGMD2L Anoctamin-5)</td>
<td>LGMD</td>
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<tr>
<td>Calpain 3 (LGMD2A)</td>
<td>LGMD</td>
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<td></td>
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</tr>
<tr>
<td>Neurotrophin-3 (CMT 1A) Nationwide Children’s</td>
<td>CMT</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cardiomyopathy University of Florida</td>
<td>CM</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Does not include undisclosed targets.

**Roche has the exclusive right to launch and commercialize SRP-9001 outside the United States.

LGMD - Limb-girdle muscular dystrophy  CMT – Charcot-Marie-Tooth disease  CM –Cardiomyopathy

Information is current as of 1/13/2022, updates are made on a quarterly basis.
More than 40 programs in development*

**GENE THERAPY**

<table>
<thead>
<tr>
<th>Target</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Clinical</th>
<th>Commercial</th>
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<tr>
<td>CNS-1 Lacerta</td>
<td>CNS</td>
<td></td>
<td></td>
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<td>Pompe Disease</td>
<td></td>
<td>Pompe</td>
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<tr>
<td>Niemann-Pick C</td>
<td>Niemann-Pick</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rett Syndrome 2</td>
<td>Rett</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dravet Syndrome</td>
<td>Dravet</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Angelman Syndrome</td>
<td>Angelman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emery-Dreifuss MD Type 1</td>
<td>EDMD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>MS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rett Syndrome 1</td>
<td>Rett</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duchenne</td>
<td></td>
<td>Duchenne</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GENE EDITING**

<table>
<thead>
<tr>
<th>Technology</th>
<th>University</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRISPR/CAS9</td>
<td>Duke University</td>
</tr>
<tr>
<td>Duchenne</td>
<td>Harvard University</td>
</tr>
</tbody>
</table>

*Does not include undisclosed targets.

**GTx + PPMO  CNS – Central nervous system  MD – muscular dystrophy

Information is current as of 12/1/2021, updates are made on a quarterly basis.
RNA *engine*
An elegant RNA precision genetic medicine approach

RNA transcription begins

Pre-mRNA spliced into mature mRNA

mRNA leaves the nucleus

Ribosome translates mRNA and assembles the protein

Protein is transported to perform its function

RNA-targeted medicine - Designed to increase or decrease production of a protein involved in a disease
Sarepta’s proprietary PMO technology

**Phosphorodiamidate morpholino oligomer (PMO) technology**

**Specificity:** Enhanced affinity for targeting pre-mRNA for precise binding to the selected RNA target

**Stability:** Highly resistant to degradation by enzymes

**Versatility:** Ability to rapidly design and construct drug candidates that are specific for human or pathogen RNA; and target specific tissues

**Safety:** Built upon a charge-neutral backbone, which may be reflected in tolerability

The PMO directs the splicing machinery to skip an exon when processing the pre-mRNA. As a result, the alternate mRNA allows for the production of a shortened, functional dystrophin protein.

Serving approximately 30% of the Duchenne community with 3 PMO-based therapies

**September 2016:**
Approved to treat patients with a confirmed genetic mutation that is amenable to exon 51 skipping (13% of Duchenne population)*

**December 2019:**
Approved to treat patients with a confirmed genetic mutation that is amenable to exon 53 skipping (8% of Duchenne population)*

**February 2021:**
Approved to treat patients with a confirmed genetic mutation that is amenable to exon 45 skipping (8% of Duchenne population)*

*Candidate received accelerated approval in the U.S., confirmatory studies required.
Peptide-conjugated PMO (PPMO): Next-generation technology for enhanced PMO tissue penetration leading to greater exon skipping and dystrophin production

**Enhances PMO**
- Conjugated peptide greatly increases cell penetration
- Could potentially lead to more efficient dosing and greater benefit for patients
- Non-clinical data demonstrates delivery of PPMOs to unique muscle types (e.g., heart)

**Lead PPMO candidate: SRP-5051**
- Designed to skip exon 51
- In clinical development to treat individuals with Duchenne amenable to exon 51 skipping
Lead RNA (PPMO) pipeline program:

SRP-5051 MOMENTUM multiple-ascending dose study for Duchenne (results from 30 mg/kg cohort)
SRP-5051-201 MOMENTUM Part A*: Designed to assess safety and PK of multiple doses of SRP-5051 in plasma and muscle of Duchenne patients

• Primary Outcome Measure
  – Safety

• Secondary Outcome Measures, including:
  – PK plasma concentration of SRP-5051

• Inclusion Criteria
  – Confirmed Duchenne mutation amenable to exon 51-skipping
  – Stable dose of oral corticosteroids for at least 12 weeks prior to study drug administration, or no corticosteroids for at least 12 weeks prior to study drug administration
  – Part A accepts ambulatory and non-ambulatory patients ages 7 to 21 years

*ClinicalTrials.gov identifier: NCT04004065.
SRP-5051 PPMO is investigational and has not been reviewed or approved by any regulatory authority.
### SRP-5051 30 mg/kg patient demographics at baseline

<table>
<thead>
<tr>
<th>SRP-5051 30 mg/kg/month X4</th>
<th>AGE (YEARS)</th>
<th>WEIGHT (KG)</th>
<th>Doses at the time of biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>18</td>
<td>57.9</td>
<td>5</td>
</tr>
<tr>
<td>Patient 2</td>
<td>7</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Patient 3</td>
<td>15</td>
<td>51</td>
<td>3</td>
</tr>
<tr>
<td>Patient 4</td>
<td>16</td>
<td>52.5</td>
<td>3</td>
</tr>
</tbody>
</table>
SRP-5051 30 mg/kg arm at 12 weeks drove 18x increase in exon skipping vs. eteplirsen at 24 weeks¹

>4x increase in exon skipping in the 30mg/kg arm vs. 20 mg/kg at 12 weeks

1. Comparative data produced with the same analytical methods using biopsies obtained from Part A of Study 5051-201 MOMENTUM and Study 4658-202 PROMOVI.

2. NA = Not Applicable, data not collected at these time points

*Target dose was 12 weeks. Patient 1 had 5 doses, 19 weeks from baseline to biopsy.
SRP-5051 30 mg/kg arm at 12 weeks drove 8x increase of dystrophin vs. eteplirsen at 24 weeks<sup>1</sup>

~2x increase in dystrophin in the 30 mg/kg arm vs. 20 mg/kg at 12 weeks

---

**Table: Dystrophin (%)**

<table>
<thead>
<tr>
<th></th>
<th>Dystrophin (%)</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eteplirsen (week 24)</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>SRP-5051 20 mg/kg (week 12)</td>
<td>3.06</td>
<td></td>
</tr>
<tr>
<td>SRP-5051 30 mg/kg (week 12)</td>
<td>6.55</td>
<td></td>
</tr>
</tbody>
</table>

---

<sup>1</sup> Comparative data produced with the same analytical methods using biopsies obtained from Part A of Study 5051-201 MOMENTUM and Study 4658-202 PROMOVI.

<sup>2</sup> NA = Not Applicable, data not collected at these time points

*Target dose was 12 weeks. Patient 1 had 5 doses. 19 weeks from baseline to biopsy.*
Strong evidence that exon skipping and dystrophin increase over time, as seen in PROMOVI with eteplirsen

* A quantitative ddPCR assay was used to measure % exon skipping, providing precise and accurate measurements.

** As measured by western blot, adjusted for muscle content.
Predicted dystrophin trajectory of >10% expression is achievable over time with monthly dosing of SRP-5051

- Model assumes that trajectory of PPMO will be similar to the increase of dystrophin that we observed in PROMOVI longitudinal study
- Predictions are based on dystrophin turnover model using PROMOVI and SRP-5051 data at 30 mg/kg and predicting dystrophin production over time

Reference: Dystrophin estimated half life in the turnover model

136 days based on PROMOVI data
103 days in quad 2OMePS in mdx mice. Verhaart et al Molecular Therapy-Nucleic Acids 2014 3:e418.

- Dystrophin levels from 30 mg/kg 5051-201 data
- Red numbers are predicted values
Predicted dystrophin trajectory of >10% expression is achievable over time with monthly dosing of SRP-5051

- Dystrophin levels from 30 mg/kg SRP-5051-201 data
- Red numbers are predicted values

<table>
<thead>
<tr>
<th>Number of Doses at Time of Biopsy</th>
<th>Western Blot</th>
<th>Exon Skipping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>5</td>
<td>12.1%</td>
</tr>
</tbody>
</table>

Reference: Dystrophin estimated half life in the turnover model

136 days based on PROMOVI data

60 days in skeletal muscle PPMO in mdx mice. Wu et al Am J Pathol 2012 181:392-400

103 days in quad 2OMePS in mdx mice. Verhaart et al Molecular Therapy-Nucleic Acids 2014 3:e418
## Safety experience

### Adverse Event Summary

<table>
<thead>
<tr>
<th>Subjects with at least one</th>
<th>4 mg/kg (N=3)</th>
<th>10 mg/kg (N=3)</th>
<th>20 mg/kg (N=5)</th>
<th>30 mg/kg (N=7)</th>
<th>Overall (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent AE (TEAE)</td>
<td>2 (66.7%)</td>
<td>3 (100.0%)</td>
<td>5 (100.0%)</td>
<td>7 (100.0%)</td>
<td>17 (94.4%)</td>
</tr>
<tr>
<td>TEAE related to study drug</td>
<td>0</td>
<td>3 (100.0%)</td>
<td>2 (40.0%)</td>
<td>7 (100.0%)</td>
<td>12 (66.7%)</td>
</tr>
<tr>
<td>Grade ≥3 TEAE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (28.6%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>1 (33.3%)</td>
<td>0</td>
<td>0</td>
<td>2 (28.6%)</td>
<td>3 (16.7%)</td>
</tr>
<tr>
<td>Serious TEAE related to study drug</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (28.6%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>TEAE leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Severe and serious TEAEs in the 30 mg/kg cohort are summarized in the next slide.
### Serious TEAEs at 30 mg/kg

<table>
<thead>
<tr>
<th>Patient</th>
<th>Preferred Term</th>
<th>Severity*</th>
<th>Causality</th>
<th>Onset Day</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Hypomagnesemia</td>
<td>Grade 4</td>
<td>Related</td>
<td>3</td>
<td>Resolved</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>Grade 3</td>
<td>Related</td>
<td>1</td>
<td>Resolved</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Hypomagnesemia</td>
<td>Grade 4</td>
<td>Related</td>
<td>7</td>
<td>Resolved</td>
</tr>
</tbody>
</table>

*Severity is based on CTCAE laboratory value.

An earlier version of this slide listed hypokalemia as a grade 4 event with onset at day 5. None of the SAEs were life-threatening, and both patients remained asymptomatic.

Onset day: interval (days) from last dose.
Safety summary

• Hypomagnesemia is a newly identified risk in the SRP-5051 program
  – Most cases were mild and asymptomatic with some serious cases occurring prior to the implementation of serum monitoring and magnesium repletion
  – Analysis of clinical and non-clinical studies (serum and urine) indicated that hypomagnesemia is both manageable and monitorable
    • Cases rapidly improved with magnesium supplementation
    • Serum monitoring of magnesium and oral supplementation with magnesium is a feasible approach to enable early detection and management going forward
  – Markers of kidney function (glomerular filtration rate) have generally been normal and have not shown any consistent relationship to the hypomagnesemia
Clinical summary

- 30 mg/kg arm at 12 weeks dosing drove 18x increase in exon skipping vs. eteplirsen at 24 weeks dosing
  - >4x increase in exon skipping in the 30 mg/kg arm vs. 20 mg/kg at 12 weeks

- 30 mg/kg arm at 12 weeks dosing drove 8x increase in dystrophin vs. eteplirsen at 24 weeks dosing
  - ~2x increase in dystrophin in the 30 mg/kg arm vs. 20 mg/kg at 12 weeks

- Strong evidence that exon skipping and dystrophin will increase with longer term dosing
  - Predicted dystrophin trajectory of >10% expression is achievable over time with monthly dosing of SRP-5051

- Patient receiving the most doses of SRP-5051 had the highest dystrophin expression

- Benefit/risk supports continued clinical development
Next steps

• Part A of 5051-201 (MOMENTUM) is now complete

• Part B of MOMENTUM is intended to be the pivotal trial in the U.S.
  – Plan to enroll between 20-40 patients between ages 7 to 21 amenable to exon 51 skipping who are naïve to SRP-5051
  – Those previously dosed in Study 5051-201, Part A or Study 5051-102 who meet the entrance criteria will be eligible to participate
  – Both ambulatory and non-ambulatory patients are eligible for participation
  – Plan to seek accelerated approval if trial is successful

• Have engaged international regulatory agencies on the overall clinical package and future registration strategy

• Learnings from the clinical studies of SRP-5051 will help inform the development of future PPMOs for other exons in Duchenne and other indications
Gene therapy *engine*
Sarepta’s gene therapy engine is built on 3 pillars

INDUSTRY-LEADING PIPELINE

MANUFACTURING CAPACITY AND EXPERTISE

EXPERTISE & TOOLS TO ADVANCE THE SCIENCE AND EFFECTIVENESS OF GENE THERAPY
Sarepta’s gene therapy pipeline

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>CLINICAL</th>
<th>COMMERCIAL</th>
</tr>
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<tbody>
<tr>
<td>SRP-9001 micro-dystrophin*</td>
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<td>GALGT2  Nationwide Children’s</td>
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<td>SRP-9003 (LGMD2E β-sarcoglycan)</td>
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<td>SRP-9004 (LGMD2D α-sarcoglycan)</td>
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<td>SRP-9005 (LGMD2C γ-sarcoglycan)</td>
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<td>Niemann-Pick Type C StrideBio</td>
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<td>Rett Syndrome 1 University of Massachusetts</td>
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<tr>
<td>Duchenne Institute of Myology</td>
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</tbody>
</table>

*Roche has the exclusive right to launch and commercialize SRP-9001 outside the United States.

All pipeline compounds are in various stages of development.

Information is current as of 12/1/2021, updates are made on a quarterly basis.
Critical components of any gene therapy

Lead gene therapy pipeline program:

*Micro-dystrophin SRP-9001 for Duchenne*
Duchenne muscular dystrophy (Duchenne) disease overview

Duchenne is a rare, fatal neuromuscular genetic disease

INHERITANCE
Duchenne is inherited in an X-linked recessive pattern.¹

SYMPTOMS
Muscle weakness becomes increasingly noticeable by age 3 to 5, and most patients use a wheelchair by the time they are 11. During adolescence, cardiac and respiratory muscle deterioration lead to serious, life-threatening complications.²,³

POPULATION
Duchenne affects approximately 1 in 3,500-5,000 males born worldwide.³,⁴

TREATMENT
Exon-skipping drugs are available for patients with certain dystrophin mutations, broadly applicable gene therapy in development.⁵

Genetic Root of Disease
One or more mutations in the gene that codes for dystrophin⁶

Missing Protein
Dystrophin⁶

Cellular Alteration
Instability of skeletal and cardiac muscle cell membranes⁶

Tissue Deterioration
Muscle deterioration and replacement with fatty and fibrotic tissue¹,⁷

Function Loss
Typically loss of ambulation in early teens and progressive pulmonary and cardiac complications leading to mortality in late 20s²

Sarepta’s differentiated gene therapy construct

Lead pipeline program, SRP-9001, in clinical development for Duchenne muscular dystrophy 1,2,3

**VECTOR**

**AAVrh74**
- Provides systemic delivery to muscle cells, including the heart and skeletal muscle
- Low level of pre-existing immunity

**PROMOTER**

**MHCK7**
- Optimized for desired skeletal and cardiac muscle expression levels
- 120% expression in cardiac muscle vs skeletal muscle1

**TRANSGENE**

**MICRO-DYSTROPHIN**
- Designed to generate a functional micro-dystrophin
- Includes SR2 and SR3 - essential for muscle force2

---


Micro-dystrophin is investigational and has not been FDA reviewed or approved.
SRP-9001 in clinical development for Duchenne

**SRP-9001 is an investigational gene therapy intended to deliver the micro-dystrophin-encoding gene to muscle tissue for the targeted production of the micro-dystrophin protein.**

**Trial 1 (SRP-9001-101)**
NCT03375164
Nationwide Children’s Hospital

**STUDY 101**
4 patients
Open-label

- 4-7 years of age
- Goals included safety, proof-of-concept
- One-year results published in JAMA Neurology
- Positive 3-year functional data announced in September 2021

**Trial 2 (SRP-9001-102)**
NCT03769116

**STUDY 102**
41 patients
Placebo-controlled

- 4-7 years of age
- Goals included safety, function
- Part 1 clinical results presented in January 2021; Part 2 underway
- Next Milestone:
  - Announce results for Part 2 in 1Q22

**Trial 3 (SRP-9001-103)**

**STUDY 103**
38 patients
Open-label

- Ages ≥4; expanded cohorts to include older ambulant and non-ambulant individuals, and younger participants
- Goals include expression and safety
- Safety and expression results for first 11 of 20 ambulatory boys in Cohort 1 reported in May 2021
- Positive 6-month functional data (NSAA score) from cohort 1 in first 11 patients reported in October 2021
- Next Milestone:
  - Additional functional data in 2022

**Trial 1 (SRP-9001-104)**
NCT04626674

**STUDY 104**

**CLINICAL SUPPLY**

**COMMERCIAL REPRESENTATIVE MATERIAL**

Study design: SRP-9001-101*

- **Design**: Single center, open-label clinical trial
- **Objectives**: Evaluating the safety, tolerability and proof-of-concept of a single dose of clinical process SRP-9001
- **Participants**: 4 ambulatory boys with Duchenne, 4-7 years of age
- **Dose**: Weight-based dosing, $1.33 \times 10^{14}$ (linear standard qPCR method)
- **Inclusion criteria**:
  - Confirmed DMD mutation between exons 18-58, inclusive
  - Negative for AAVrh74 antibodies
- **Primary endpoint**:
  - Safety
- **Secondary endpoints**:
  - Change in micro-dystrophin expression pre- vs post-treatment
  - Decrease in creatine kinase (CK)
  - North Star Ambulatory Assessment (NSAA)
  - Timed function tests
- **Results to date**:
  - 12-week expression data and 3-year functional results

*ClinicalTrials.gov identifier: NCT03375164.
Clinical results* (N=4)¹,²

What was the safety and tolerability experience with SRP-9001? | Is the transgene DNA inside muscle cells? | Is the desired protein made? | Is the protein at the cell membrane? How much is there? | Is muscle function improved?
---|---|---|---|---

**Safety**
- Generally well tolerated⁴
- No patients experienced a serious adverse event (SAE) or an adverse event (AE) that led to discontinuation
- Treatment-related TEAEs were mild or moderate and all resolved
- There were no serious abnormalities observed in haematological and chemistry panels
- 3 patients had elevated γ-glutamyl transpeptidase in the first 3 months post-treatment, which resolved with steroid treatment
- The most common treatment-related AE was vomiting (9 of 18)

**Vector Genome Copies/Nucleus**
- Mean of >10⁵ vector copies/µg DNA detected
- 3.3 vector copies/nucleus

**Western Blot**
- Mean micro-dystrophin protein expression vs normal by western blot (SRPT/NCH Western Blot Quantification Method)
- 74.3%/95.8%

**Immunofluorescence**
- Mean dystrophin-positive fibers observed with 96% intensity
- 81.2%

**Functional Outcomes**
- Subjects exhibited mean of 5.5-POINT IMPROVEMENT on NSAA from baseline to year 1
- Subjects exhibited mean of 7.5-POINT IMPROVEMENT on NSAA from baseline to year 3

Micro-dystrophin gene transfer therapy is investigational and has not been reviewed or approved by any regulatory authority.

*ClinicalTrials.gov Identifier: NCT03375164.
SRP-9001-101 mean NSAA - observed vs predicted values

SRP-9001 patients improved 8.6 points on NSAA compared to matched natural history group at Year 3

- A Bayesian prediction model was developed using data from 292 unique patients from the natural history data sources (Leuven, Telethon and CINRG).
- The individual patient trajectory of NSAA is modeled to generate predicted controls that adjusts for age and baseline NSAA.
- An MMRM model was then fit to compare the mean NSAA of treated patients in SRP-9001-101 against the mean value of predicted controls based on natural history across time points with a highly significant p value (<0.0001).
**Study design: SRP-9001-102* (Parts 1 and 2)**

- **Design:** Ongoing, multi-center, randomized, double-blind, placebo-controlled clinical trial; remains blinded.

- **Objectives:** Evaluating the safety, efficacy and tolerability of a single dose of clinical process SRP-9001 compared to placebo.

- **Participants:** 41 ambulatory boys with DMD, 4-7 years of age.

- **Dose:** Weight-based dosing, 1.33x10^{14}** (linear standard qPCR method).

- **Inclusion criteria:**
  - Confirmed DMD mutation between exons 18-58, inclusive.
  - Negative for AAVrh74 antibodies.

- **Primary endpoints:**
  - Micro-dystrophin protein expression, from Baseline to Week 12, as measured by western blot.
  - Change in NSAA total score from Baseline to Week 48.

- **Results to date:** Part 1 and biomarker data for first 11 patients in Part 2 placebo-crossover disclosed in January 2021.

**Randomization was stratified by age group at baseline (4–5 vs. 6–7 years)**

- **Part 1:** 48 weeks
  - Biopsy at baseline (both groups)

- **Part 2:** 48 weeks
  - Biopsy at 12 weeks (both groups)

- **Part 3:** up to 168 weeks
  - Biopsy at 12 weeks (both groups)

**All patients received the target dose as determined by the supercoiled standard qPCR method specified in the protocol at the time. Subsequent retrospective analysis using the new linear standard qPCR method indicated that 60% of the patients received a dose lower than the target dose based on the new method. All patients going forward will receive the target dose as determined by the new method. Target dose 2E14 vg/kg was estimated by supercoiled standard qPCR and is equivalent to 1.33E14 vg/kg using the linear standard qPCR method.**
## Baseline demography

*Intent-to-treat population*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statistics</th>
<th>Placebo (N=21)</th>
<th>SRP-9001 (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD) Min, Max</td>
<td>6.24 (1.13) 4.34, 7.98</td>
<td>6.29 (1.19) 4.47, 7.85</td>
</tr>
<tr>
<td>Age, 4-5 years</td>
<td>n (%)</td>
<td>8 (38.1)</td>
<td>8 (40.0)</td>
</tr>
<tr>
<td>Years since diagnosis of DMD</td>
<td>Mean (SD) Min, Max</td>
<td>2.69 (1.30) 0.66, 5.39</td>
<td>2.54 (1.34) 0.36, 5.10</td>
</tr>
<tr>
<td>Years since corticosteroid treatment started</td>
<td>Mean (SD) Min, Max</td>
<td>1.26 (1.22) 0.23, 5.07</td>
<td>0.99 (1.07) 0.22, 3.80</td>
</tr>
<tr>
<td>Dosing Weight (kg)</td>
<td>Mean (SD) Min, Max</td>
<td>21.60 (3.49) 15.0, 30.0</td>
<td>23.28 (4.37) 18.0, 34.5</td>
</tr>
</tbody>
</table>
# Baseline functional assessments

*Intent-to-treat: the placebo group is better in all parameters relative to the SRP-9001 group*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statistics</th>
<th>Placebo (N=21)</th>
<th>SRP-9001 (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAA</td>
<td>Mean (SD)</td>
<td>22.6 (3.30)</td>
<td>19.8 (3.3)</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>15, 29</td>
<td>13, 26</td>
</tr>
<tr>
<td>100 meter (seconds)</td>
<td>Mean (SD)</td>
<td>53.86 (8.30)</td>
<td>61.04 (12.71)</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>40.6, 69.1</td>
<td>42.3, 99.3</td>
</tr>
<tr>
<td>Ascend 4 Steps (seconds)</td>
<td>Mean (SD)</td>
<td>3.10 (0.98)</td>
<td>3.69 (1.46)</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>1.9, 5.8</td>
<td>2.1, 6.5</td>
</tr>
<tr>
<td>Time to Rise (seconds)</td>
<td>Mean (SD)</td>
<td>3.56 (0.65)</td>
<td>5.10 (2.17)</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>2.7, 4.8</td>
<td>3.2, 10.4</td>
</tr>
<tr>
<td>10 meter (seconds)</td>
<td>Mean (SD)</td>
<td>4.83 (0.72)</td>
<td>5.35 (1.14)</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>4.0, 7.2</td>
<td>4.1, 8.9</td>
</tr>
</tbody>
</table>

Note that an imbalance in NSAA and timed tests exist between the two groups with the treated group worse than placebo. Baseline NSAA was not a stratification factor for randomization.
Micro-dystrophin protein expression and vector genome copies per nucleus achieved endpoints in Part 1 of Study 102 (n=20, Week 12)

### Micro-dystrophin Expression (Western Blot)

<table>
<thead>
<tr>
<th></th>
<th>Percentage of Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) n=20</td>
<td>28.1% (40.1%)</td>
</tr>
</tbody>
</table>

### Micro-dystrophin Expression (IF)

<table>
<thead>
<tr>
<th></th>
<th>Intensity (% Normal)</th>
<th>Percentage of Dystrophin-positive Fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) n=20</td>
<td>63.7% (46.4%)</td>
<td>32.9% (28.1%)</td>
</tr>
</tbody>
</table>

### Vector Genome Copy Number

<table>
<thead>
<tr>
<th></th>
<th>Copies per Nucleus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) n=20</td>
<td>1.6 (1.5)</td>
</tr>
</tbody>
</table>

Part 1 functional results: NSAA primary endpoint

NSAA change from baseline of +1.7 in SRP-9001 treated group vs. +0.9 in placebo group, which is not statistically different (p=0.37)

BL, baseline; LS, least squares; NSAA, NorthStar Ambulatory Assessment; SE, standard error.

A pre-specified analysis of the 4- to 5-year-old group showed statistically significant improvement in NSAA vs. placebo group at week 48.

**NSAA change from baseline of +4.3 in SRP-9001 treated 4- to 5-year-olds vs. 1.9 in placebo (p=0.0172)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Treatment</th>
<th>Baseline</th>
<th>LSM change at 48 weeks (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAA</td>
<td>SRP-9001</td>
<td>20.1</td>
<td>4.3 (0.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>PBO</td>
<td>20.4</td>
<td>1.9 (0.6)</td>
<td>0.0126</td>
</tr>
<tr>
<td></td>
<td>SRP-9001 vs. PBO</td>
<td>2.5 (0.9)</td>
<td>0.0172</td>
<td></td>
</tr>
</tbody>
</table>

**Age 4–5 years**

Age was a stratification factor at randomization.

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**Baseline NSAA: SRP-9001 patients vs. placebo patients**

(6 to 7 years of age: 19.6 vs. 24, p=0.0046)

In 6 to 7-year-olds, functional measures were not well-matched between groups at baseline; this may have cofounded the analysis.

In the study, SRP-9001 showed a statistically significant improvement in NSAA compared to placebo (p=0.0046). The least-squares mean change at 48 weeks for SRP-9001 was 0.2 (0.7), while it was 0.5 (0.7) for placebo. The difference between SRP-9001 and placebo at 48 weeks was 0.5384.

**Table:**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Treatment</th>
<th>Baseline</th>
<th>Mean age (SD)</th>
<th>LSM change at 48 weeks (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAA</td>
<td>SRP-9001</td>
<td>19.6</td>
<td>7.2 (0.6)</td>
<td>−0.2 (0.7)</td>
<td>0.7807</td>
</tr>
<tr>
<td></td>
<td>PBO</td>
<td>24.0</td>
<td>6.9 (0.8)</td>
<td>0.5 (0.7)</td>
<td>0.5003</td>
</tr>
<tr>
<td></td>
<td>SRP-9001 vs. PBO</td>
<td>19.6 vs. 24.0</td>
<td>7.2 vs. 6.9</td>
<td>−0.7 (1.1)</td>
<td>0.5384</td>
</tr>
</tbody>
</table>

**Graph:**

The graph shows the LS mean (± SE) change from baseline starting from mean NSAA total score at baseline for SRP-9001 and placebo.

**Figure:**

- **Figure 1:** Kaplan-Meier survival analysis showing the percentage of patients remaining in the study over time.
- **Figure 2:** Time-to-first-event analysis showing the time to the first event among patients.
- **Figure 3:** Forest plot showing the efficacy of different treatments compared to placebo.

**References:**

NSAA score in the 6–7-year-old group compared to natural history matched in age and baseline NSAA

SRP-9001 patients had a positive ~3 point difference on NSAA compared to matched natural history group at 1 year

- SRP-9001 treated 6-7 YO (N=12) were matched to natural history patients (N=21) from LEUVEN, Telethon and CINRG
- Change from baseline in NSAA at Week 48 is -0.3 in SRP-9001 group vs. -3.2 in matched natural history controls with a p value of 0.0129

* Two sample T-test was used
Safety summary: SRP-9001-102 Part 1

• 85% of 20 patients of the treated group had treatment-related TEAEs vs. 43% of 21 patients in the placebo group
  – The most common treatment-related TEAE was vomiting
    • 60% (12/20) in treatment group vs. 19% (4/21) in placebo group
• 82% of patients with treatment-related TEAEs had only mild or moderate treatment-related TEAEs
• No clinically relevant complement activation was observed
• Total of four patients with five treatment-related SAEs
  – Four SAEs in the treated group and one in the placebo group
    • Three rhabdomyolysis (two in SRP-9001 treatment group and one in placebo) that resolved
    • Increased transaminases in one patient and liver injury in another (both in SRP-9001 treatment group)
• No other clinically significant laboratory findings

Conclusions

• No new safety signals observed
• Primary biological endpoint (micro-dystrophin expression at 12 weeks post-treatment) achieved
• Total NSAA score of treated patients vs. placebo demonstrated a positive increase at all post-treatment time points
  – The study did not achieve a statistical significance on the primary functional endpoint of improvement in total NSAA score compared to placebo at 48 weeks post-treatment
• Pre-specified analysis in the 4- to 5-year-old group showed a significant improvement in NSAA vs. placebo group at 48 weeks
• Imbalance in baseline functional characteristics in the 6-to 7-year-old group contributed to the lack of statistical significance on the functional endpoint
• A new analysis of SRP-9001-treated participants (n=12, ages 6 to 7) showed a positive 2.9-point difference on NSAA compared to a matched natural history cohort one year after treatment
• Data support future clinical development plans
Study design: SRP-9001-103*

- **Design:** Ongoing, multi-center open-label clinical trial
- **Objectives:** Evaluate the safety and expression of a single dose of SRP-9001 commercially representative material
- **Participants:** 38 boys with DMD, ages ≥4; expanded cohorts to include older ambulant and non-ambulant individuals, and younger participants
- **Dose:** Weight-based dosing, $1.33\times10^{14}$ (linear standard qPCR method)
- **Inclusion criteria:**
  - No mutation exclusions
  - Negative for AAVrh74 antibodies
- **Primary endpoint:**
  - Micro-dystrophin protein expression from Baseline to Week 12, as measured by western blot
- **Results to date:** Safety and expression results for first 11 of 20 ambulatory boys in Cohort 1 disclosed in May 2021; functional results from first 11 of 20 ambulatory boys in Cohort 1 disclosed in Oct. 2021

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**ClinicalTrials.gov Identifier:** NCT04626674.

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*ClinicalTrials.gov identifier: NCT04626674.
Micro-dystrophin transduction by vector genome count in first 11 patients

QUESTION

What was the safety and tolerability experience?

Is the transgene DNA inside muscle cells?

Is the desired protein made?

Is the protein at the cell membrane? How much is there?

BASED ON MUSCLE BIOPSIES FROM THE GASTROCNEMIUS MUSCLE AT WEEK 12

Safety

Vector Genome Copies/Nucleus

Western Blot

Immunofluorescence

Consistent with previous experience with SRP-9001 (Study 101 and 102); an additional SAE observed in Cohort 2; no clinically relevant complement activation observed

Mean of 3.87³ vector genome copies/nucleus

55.4%⁴ mean percent normal micro-dystrophin protein expression

70.5%⁵ mean dystrophin-positive fibers observed with 116.9%⁵ intensity

Micro-dystrophin gene transfer therapy is investigational and has not been reviewed or approved by any regulatory authority.


2. Safety
   • An additional SAE observed in Cohort 2 (immune mediated myositis)
   • Most common AE is vomiting (64% of patients)
   • Increase in liver enzymes were transient and responsive to steroids
   • No signs of impaired liver function in any patient
   • The SAEs reported in 2 patients in cohort 1 fully resolved

3. Standard deviation (SD) of 2.44.

4. SD of 43.4%.

5. SD of 23.4% for mean dystrophin positive fibers and 44.6% for intensity; mean baseline values were 12.8% and 41% for dystrophin positive fibers and intensity, respectively.
Study 102 Part 2 placebo crossover patients (clinical process material) and Study 103 patients (commercially representative process material) show consistent results

### Micro-dystrophin Clinical Process Material

*Study 102 Part 2 Placebo Crossover Patients, Mean (n=11)*

<table>
<thead>
<tr>
<th>Vector Genome Copies per Nucleus</th>
<th>% of Normal Expression</th>
<th>% Dystrophin Positive Fibers</th>
<th>% Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.62</td>
<td>51.7%</td>
<td>79.2%</td>
<td>100.6%</td>
</tr>
</tbody>
</table>

### Micro-dystrophin Commercially Representative Process Material

*Study 103 Patients, Mean (n=11)*

<table>
<thead>
<tr>
<th>Vector Genome Copies per Nucleus</th>
<th>% of Normal Expression</th>
<th>% Dystrophin Positive Fibers</th>
<th>% Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.87</td>
<td>55.4%</td>
<td>70.5%</td>
<td>116.9%</td>
</tr>
</tbody>
</table>
SRP-9001-103: Mean NSAA score from cohort 1 (first 11 patients)

SRP-9001 patients improved **3 points** on NSAA at 6 months

- First 11 patients improved 3 points from baseline
- 6 to 7-year-olds (n=9) improved 2.9 points from baseline
Vast compendium of clinical data for SRP-9001

*SRP-9001 is the only candidate in development with results from a randomized, placebo-controlled trial*

**Broadest patient experience**
- Sarepta has dosed the largest number of DMD patients with a gene therapy
- Dosed 77 patients with SRP-9001 in three ongoing studies (101, 102 and 103)
  - 45 dosed with clinical process material (study 101 and 102) and 32 dosed with commercially representative process material (study 103)
  - 59 are ambulatory boys who were ≥4 and < 8 years of age at time of dosing
  - 12 are ambulatory boys who were ≥ 8 years of age at time of dosing
  - 6 are non-ambulatory boys
  - Youngest patient dosed is age 4 with oldest patient aged 19
  - Weight range at time of dosing to date is 13.7 kg to 80.1 kg

**Durable clinical activity**
- Sustained functional improvements as compared to natural history
- Consistently positive expression results observed
- All patients are at least 6 weeks post dosing with longest now in Year 4 of follow-up

**Consistent tolerability profile**
# Study design: SRP-9001-301

**KEY FEATURES OF SRP-9001-301**

- **N=120**
- **Stratification**
  - Age
  - Baseline NSAA
- **Homogenous Trajectory**
  - Time to Rise <5 sec
- **Balance between age cohorts**
  - Minimum of 50% patients enrolled 4 to 5-year-old group

Randomization 1:1 active to placebo and stratified by age group (≥ 4 to < 6 years vs. ≥ 6 to < 8 years) and NSAA total score (≤ 22 vs. > 22) at screening

<table>
<thead>
<tr>
<th>Randomization (n=120)</th>
<th>Single IV infusion SRP-9001 (n=60)</th>
<th>Single IV infusion placebo (n=60)</th>
<th>Single IV infusion SRP-9001</th>
<th>Extension study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1: 52 weeks</td>
<td>Biopsy at 12 weeks</td>
<td>Biopsy at 12 weeks</td>
<td>Part 2: 52 weeks</td>
<td>Part 3: 5 years post-SRP-9001 infusion</td>
</tr>
</tbody>
</table>

- **Design**: Global, multi-center (~43 sites in ~10 countries) randomized double-blind, placebo-controlled clinical trial
- **Objectives**: Evaluate effect of a single dose of SRP-9001 commercially representative material on physical function as assessed by North Star Ambulatory Assessment (NSAA) score
- **Participants**: 120 boys with Duchenne, ≥ 4 to < 6 years vs. ≥ 6 to < 8 years
- **Dose**: Weight-based dosing, 1.33x10^14 (linear standard qPCR method)
- **Inclusion criteria**:
  - Time to Rise from Floor < 5 seconds
  - Stable daily dose of oral corticosteroids for at least 12 weeks before screening
  - rAAVrh74 antibody titers < 1:400
- **Exclusion criteria**:
  - Mutations between or including exons 1-17 and mutations fully contained within exon 45 (inclusive) are not eligible
- **Primary endpoint**:
  - Change in NSAA total score from Baseline to Week 52
- **Secondary endpoints**:
  - Number of skills gained or improved at Week 52 as measured by NSAA
  - Quantity of micro-dystrophin protein expression at Week 12 (Part 1) as measured by western blot
  - Timed function tests
  - Safety
Gene therapy pipeline program:

SRP-9003 for limb-girdle muscular dystrophy Type 2E
INHERITANCE
The LGMDs are a group of genetically heterogeneous, autosomal inherited (recessive more common than dominant) muscular dystrophies with a childhood to adult onset.\(^1,2,3\)

SYMPTOMS
Individuals may first notice a problem when they begin to walk with a “waddling” gait because of weakness of the hip and leg muscles. They may have trouble getting out of chairs, rising from a toilet seat or climbing stairs. As this weakness progresses, the person may require the use of assistive mobility devices.\(^4\)

POPULATION
Approximate global prevalence of LGMDs as a group is 1.63 per 100,000 (prevalence estimates range from 0.56 to 5.75 per 100,000).\(^1\) Over 30 subtypes exist.\(^3\) Both genders are affected equally.\(^4\)

TREATMENT
No cause-specific treatment is available for any of the LGMD subtypes.

Genetic Root of Disease
Broad range of mutations in various genes responsible for protein production\(^3\)

Missing Proteins
Depends on specific subtype, such as proteins involved in the dystrophin associated protein complex (DAPC), sarcolemma, dystroglycan complex, as well as intracellular proteins\(^3\)

Cellular Alteration
These critical proteins are responsible for muscle function, regulation and repair\(^4\)

Affected muscles
Affects skeletal muscle and in some cases affects cardiac and/or diaphragm\(^3,4\)

Function Loss
Progressive weakness and wasting of hip or shoulder girdle muscles\(^1\); in some cases cardiac abnormalities and respiratory decline\(^4\)

Sarepta’s gene therapy engine at work

Lead clinical development program, SRP-9003, in limb-girdle muscular dystrophy type 2E

VECTOR

AAVrh74

• Chosen for efficient transduction to muscles (cardiac and skeletal)\(^1,2\)

PROMOTER

MHCK7

• Selective for cardiac and skeletal transgene muscle expression\(^2,3,4\)

TRANSGENE

\(\beta\)-SARCglycan

• Designed to deliver a full copy of the SGCB gene that codes for the \(\beta\)-sarcoglycan protein\(^2,3\)


LGMD2E is investigational and has not been FDA reviewed or approved.
SRP-9003: Lead gene therapy candidate in clinical development for LGMD2E

Only compound in development for LGMD2E; encouraging clinical data generated to date

**SRP-9003**
Gene construct (AAVrh74.MHCK7.SGCB) that transduces skeletal and cardiac muscle, delivering a gene that codes for the full-length β-sarcoglycan protein, the absence of which causes progressive degeneration

**Clinical Study***
First-in-human, open-label, Phase 1/2 trial with two cohorts – three patients in each cohort:
- Cohort 1 (1.85×10^{13} vg/kg)^a
- Cohort 2 (7.41×10^{13} vg/kg)^b

**Primary Endpoint**
Safety

**Secondary Endpoint**
β-sarcoglycan protein expression at week 8**

**Other Endpoints**
- Change in creatine kinase (CK) from baseline
- Functional endpoints:
  - North Star Ambulatory Assessment for Dysferlinopathy (NSAD): 100-meter walk-run; 10-meter walk-run, 4-stair climb, and time to rise

**Next Milestones**
- Seek FDA confirmation of pivotal trial study design

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*ClinicalTrials.gov Identifier: NCT03652259.

**Based on pre-clinical studies, the goal was to achieve expression levels of ≥20%.


^a 1.85×10^{13} vg/kg measured using linear reference plasmid DNA qPCR; supercoiled reference DNA equivalent is 5×10^{13} vg/kg

^b 7.41×10^{13} vg/kg measured using linear reference plasmid DNA qPCR; supercoiled reference DNA equivalent is 2×10^{14} vg/kg
Clinical results: SRP-9003-101 (N=3)* Cohort 1 (1.85 x 10^{13} \text{vg/kg})^{2,3}

**QUESTION**

What was the safety and tolerability experience with SRP-9003?

- 2 subjects had elevated liver enzymes, 1 of which was designated an SAE^{4}

Is the transgene DNA inside muscle cells?

- Mean vector copies/nucleus
  - 0.59 at day 60
  - 0.13 at 24 months

Is the desired protein made?

- 36% at day 60
- 54% at 24 months
- Mean β-sarcoglycan protein expression vs normal by western blot

Is the protein at the cell membrane? How much is there?

- 51% at day 60
- 48% at 24 months
- Mean β-sarcoglycan positive fibers observed with intensity of

Is muscle function improved?

- Subjects experienced mean 5.7-POINT IMPROVEMENT on NSAD from baseline to 18 months, this improvement was sustained through 24 months

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*ClinicalTrials.gov identifier: NCT03652259.
4. Safety as of January 14, 2021:
   - 1 patient experienced mild vomiting, which resolved 1 day without treatment
   - No other laboratory abnormalities were suggestive of safety concerns
     o No decreases in platelet counts observed outside the normal range
     o No clinical sequelae associated with complement activation
Clinical results: SRP-9003-101 (N=3)* Cohort 2 (7.41 x 10^{13} \text{ vg/kg})^{2,3}

**QUESTION**

- **What was the safety and tolerability experience with SRP-9003?**
  - Majority of AEs were mild to moderate (e.g., vomiting, pain in extremity), which resolved\(^4\)

- **Is the transgene DNA inside muscle cells?**
  - Mean of \(4.2\) vector copies/nucleus at day 60

- **Is the desired protein made?**
  - \(62.1\%\) mean β-sarcoglycan protein expression vs normal by western blot at day 60

- **Is the protein at the cell membrane? How much is there?**
  - \(72\%\) mean β-sarcoglycan positive fibers observed with \(73\%\) intensity at day 60

- **Is muscle function improved?**
  - Subjects experienced mean of \(3.7\)-POINT IMPROVEMENT on NSAD from baseline to 6 months
  - \(4.0\)-POINT IMPROVEMENT at 1 year

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*ClinicalTrials.gov Identifier: NCT03652259.
4. Safety as of January 14, 2021:
   - 1 treatment-related SAE observed
   - 1 patient had mildly elevated GGT
   - No stopping/discontinuation rules were triggered by AEs
   - One of the participants in this trial died unexpectedly due to a recreational accident unrelated to the study
   - No other laboratory abnormalities were suggestive of safety concerns
     - No decreases in platelet counts observed outside the normal range
     - No clinical sequelae associated with complement activation
SRP-9003–treated patients display an improvement in total NSAD score vs natural history

Patients treated with SRP-9003 demonstrated clinically meaningful improvements in functional outcomes in an exploratory comparison vs an LGMD2E/R4 natural history cohort, as measured by NSAD


LGMD2E/R4=limb-girdle muscular dystrophy type 2E/R4; LS=least-squares; MMRM=mixed-model repeated measures; NSAD=North Star Assessment for Limb-girdle Type Muscular Dystrophies. MMRM analysis included fixed effects for treatment arm, visit, and treatment arm by visit interaction, and baseline NSAD, baseline 100m, and baseline 10m as continuous covariates; the first-order autoregressive structure was used for variance-covariance matrix of within-patient errors.
Conclusions

• This interim analysis reinforces the favorable safety profile of systemically administered SRP-9003
• SRP-9003 showed efficient transduction and drove robust, dose-dependent SGCB protein expression in all patients at Day 60, resulting in reconstitution of the sarcoglycan complex; SGCB expression was sustained up to 2 years
• Creatine kinase decreased by 77% at Year 2 in Cohort 1 and 74% at Year 1 in Cohort 2 (data not presented)
• Patients treated with SRP-9003 demonstrated improvements over baseline in NSAD and timed function tests that were sustained up to 2 years in Cohort 1 and 1 year in Cohort 2
• Exploratory post hoc analysis showed SRP-9003–treated patients had clinically meaningful improvements in functional outcomes, as measured by NSAD, compared with a natural history cohort
• The observed durable treatment effect provides proof of concept and supports further clinical assessment of SRP-9003 gene transfer therapy in patients with LGMD2E/R4

KEY TAKEAWAY:
Persistence of SRP-9003 in transduced muscle continues to drive meaningful levels of SGCB expression over time, leading to sustained functional improvements

Gene therapy engine at work across the entire LGMD portfolio

OPPORTUNITY TO GENERATE A STEADY STREAM OF GENE THERAPY CANDIDATES IN FIVE ADDITIONAL SUBTYPES WHICH TOGETHER REPRESENT MORE THAN 70% OF ALL KNOWN LGMDS

Setting the standard in gene therapy manufacturing
Sarepta’s hybrid strategy - external thought leaders complement our internal expertise
Sarepta’s manufacturing expertise
Advancing the gold standard in gene therapy manufacturing

A deliberate and strategic move to

*iCELLis® adherent mammalian*
Advancing the gold standard in gene therapy manufacturing

Benefits

• Mitigated Risk
• Increased Speed
• Expanded Scale
• Improved Cost Efficiency

A deliberate and strategic move to
iCELLis® adherent mammalian
Sarepta’s sustainable model for one-time transformational therapies
One-time gene therapy model vs. chronic therapy model

**One-Time Gene Therapy**

- Only dose

**Chronic Therapy**

- Dose 1
- Dose 2
- Dose 3
- Dose 4
- Dose 5
- Dose 6
- Dose 7

**LIFETIME THERAPY COSTS**

For illustrative purposes
Traditional drug development forecast curve

Chronic dosing model . . .

For illustrative purposes
Gene therapy forecast curve

One-time treatment model . . .

For illustrative purposes
Sarepta’s forecast curve

Creating a viable business model for gene therapy

For illustrative purposes
Establishing a distinct partnership model to drive future success
Patients can’t wait so neither will we
Dragging tomorrow into today

#DraggingTomorrowIntoToday