A Phase 2 clinical trial evaluating the safety and efficacy of SRP-9001 for treating patients with Duchenne muscular dystrophy

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What does this study mean for the DMD community?

Findings from this study suggest that rAAVrh74.MHCK7.micro-dystrophin (SRP-9001) has a biological effect that may be clinically relevant to people with DMD.

Conclusions

• Findings from Part 1 of SRP-9001 Study 102 reinforce an acceptable safety profile consistent with previous studies.
• Study 102 achieved the primary biological endpoint of change in micro-dystrophin expression (baseline to 12 weeks post-treatment).
• Change in NSAA total score of patients who received SRP-9001 did not achieve statistical significance compared with that of patients who received placebo.
• Analysis of the 4-5 to 7-year-old subgroup, with well-matched functional measures at baseline, showed a statistically significant difference between patients who received SRP-9001 and those who received placebo at Week-48.
• These results provide important information for ongoing clinical development.

Methods

Randomisation was only stratified by age group at baseline (4-5 vs. 6-7 years).

Results

Safety endpoints: TEAEs and SAEs

<table>
<thead>
<tr>
<th></th>
<th>SRP-9001 (n=20)</th>
<th>Placebo (n=20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any TEAE</td>
<td>16 (80.0)</td>
<td>12 (60.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Vasoconstriction/narrowing</td>
<td>13 (65.0)</td>
<td>9 (45.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (25.0)</td>
<td>2 (10.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (30.0)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>g-Dystrophin/Reversion</td>
<td>1 (5.0)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (15.0)</td>
<td>2 (10.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1 (5.0)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (15.0)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>2 (10.0)</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

TEAEs were transient and manageable.

- 85% of patients with treatment-related TEAEs had mild or moderate treatment-related TEAEs.
- No clinically relevant complement activation was observed.
- There were four patients with five treatment-related SAEs, four treatment-related SAEs were reported in the SRP-9001-treated group and one was reported in the placebo group. There were three instances of rhabdomyolysis (two in the SRP-9001-treated group and one in the placebo group) that were resolved.
- In SRP-9001 group, one patient had hepatic enzymes increased and one had liver injury.
- There were no deaths or discontinuations in Part 1 of Study 102.

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Age subgroup

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Baseline</th>
<th>LSM change at Week 48 (SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-5 years-old</td>
<td>SRP-9001</td>
<td>20.5 (0.7)</td>
<td>1.9 (0.6)</td>
<td>0.0126</td>
</tr>
<tr>
<td>placebo</td>
<td>20.4 (0.7)</td>
<td>2.3 (0.6)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>6-7 years-old</td>
<td>SRP-9001</td>
<td>15.5 (0.7)</td>
<td>-0.8 (0.7)</td>
<td>0.7897</td>
</tr>
<tr>
<td>placebo</td>
<td>20.5 (0.7)</td>
<td>0.8 (0.6)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

In 4-5-year-olds, functional measures were well matched at baseline.

However, in 6-7-year-olds, NSAA scores were not well matched at baseline.

Improvements in NSAA scores reached statistical significance in a subgroup analysis of 4- to 5-year-olds.

- In 4-5-year-olds, the change in NSAA total score from baseline was +1.7 points in the SRP-9001 treated group and +0.3 points in the placebo group, which was not statistically different (P=0.37).

Biological endpoints

- Patients suppressed micro-dystrophin at 12 weeks post-SRP-9001 treatment.

Micro-dystrophin expression and vector genome copies

Week 12 (n=20)

<table>
<thead>
<tr>
<th></th>
<th>Percentage of normal, %</th>
<th>SE (2.0x10^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRP-9001</td>
<td>39.4 (1.1)</td>
<td>SE (4.2x10^6)</td>
</tr>
<tr>
<td>placebo</td>
<td>28.1 (2.2)</td>
<td>SE (4.2x10^6)</td>
</tr>
</tbody>
</table>

*Method developed by Nationwide Children’s Hospital and used previously in Study 101. For patients who received a dose in this study, the dose used was 2.0x10^11 vg/kg for the SRP-9001 group, 2.0x10^11 vg/kg for the placebo group.

Conclusions

- In 4-5-year-olds, the change in NSAA total score from baseline was +1.7 points in the SRP-9001 treated group and +0.3 points in the placebo group, which was not statistically different (P=0.37).

Abbreviations

- 4.2x10^11: Vector genome copies (vg) per 10^11 cells (poly nucleotide)
- 50%: Percentage of normal dystrophin expression level
- 70%: Percentage of normal dystrophin expression level
- 5’UTR: 5’ untranslated region
- CP: Copy number
- DMD: Duchenne muscular dystrophy
- EP: End point
- ITR: Intron
- KDEL: Karosin, disulfide, endoplasmic reticulum localization signal
- LSM: Least squares mean
- MHCK7: Myosin heavy chain kinase 7
- NSAA: North Star Ambulatory Assessment
- PDPF: Percentage of day to patient follow up
- P: Probability
- PolyA: Polyadenylation
- PolyA: Polyadenylation
- 1.5: Vector genome copy number, mean
- 2.0: Vector genome copy number, mean
- 1.33: Vector genome copy number, mean
- IV: Intravenous

References


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