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SMA is a rare genetic disease that leads to rapid and irreversible loss of motor neurons, affecting muscle functions.

Spinal muscular atrophy (SMA) is caused by a lack of a functional survival motor neuron (SMN1) gene. Severity varies by type and corresponds to the number of copies of the back-up gene (SMN2).

**Presymptomatic**
- Degeneration and loss of motor neurons start shortly before birth and escalates quickly.
- It is imperative to diagnose SMA and begin treatment as early as possible to halt disease progression.

**Type 1 (60%)**
- >95% motor neuron loss by 6 months of age.
- 90% of babies with untreated Type 1 need permanent breathing support or die by their second birthdays.
- 1,4

**Type 2 (30%)**
- 3-4 copies of SMN2
- Symptoms are disabling and appear between six and 18 months of age.
- More than 30% will die by age 25.

**Type 3 (10%)**
- 3-4 copies of SMN2
- Symptoms typically appear in early childhood to early adulthood.
- They may lose the ability to stand or walk without support.

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A one-time therapy designed to address the genetic root cause of SMA

Provides a functional copy of the human SMN gene to halt disease progression through SMN protein expression

Delivered as a single, one-time dose designed to provide long-term benefit

Clinically transformative impact, showing prolonged survival and achievement of motor milestones never seen in natural history of disease

Single administration may provide reduced burden on the caregiver

One-time infusion avoids long-term chronic therapy administration

MHLW approved Zolgensma in Japan with label consistent with the FDA

**Indication**
The treatment of spinal muscular atrophy (SMA) in patients under the age of two, including those who are pre-symptomatic at diagnosis.

**Target patient population**
- Genetic diagnosis of SMA (up to 3 copies of SMN2) regardless of type
- Symptomatic or pre-symptomatic
- Expect 15-20 patients to be eligible for treatment each year

**Next steps**
Reimbursement with MHLW is expected by the end of 1H20 and, pending agreement, Zolgensma will be available at that time.
CHMP recommended Zolgensma® for conditional approval for babies and young children with SMA

Indication
Patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or

Patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene

Target patient population
- Genetic diagnosis of SMA (up to 3 copies of SMN2) regardless of type
- Symptomatic or pre-symptomatic
- Product presentation at launch will cover patients weighing up to 21 kg
### Significant addressable population in Europe

#### Yearly incidence

<table>
<thead>
<tr>
<th>Type</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>330-360</td>
<td>165-180</td>
<td>55-60</td>
<td>1,540-1,680</td>
<td>5,610-6,120</td>
<td>3,850-4,200</td>
</tr>
</tbody>
</table>

#### Prevalent population

<table>
<thead>
<tr>
<th>Type</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,540-1,680</td>
<td>5,610-6,120</td>
<td>3,850-4,200</td>
</tr>
</tbody>
</table>

#### Weight by age (years) for SMA Type 2 according to PNCR

<table>
<thead>
<tr>
<th>Weight</th>
<th>N</th>
<th>Min</th>
<th>Median</th>
<th>Max</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 – &lt;9 kg</td>
<td>5</td>
<td>1</td>
<td>1.16</td>
<td>1.75</td>
<td>1.28</td>
</tr>
<tr>
<td>9 – &lt;12 kg</td>
<td>27</td>
<td>0.83</td>
<td>2.33</td>
<td>4.5</td>
<td>2.31</td>
</tr>
<tr>
<td>12 – &lt;15 kg</td>
<td>59</td>
<td>1.33</td>
<td>4.25</td>
<td>8.08</td>
<td>4.08</td>
</tr>
<tr>
<td>15 – &lt;18 kg</td>
<td>44</td>
<td>2.42</td>
<td>5.75</td>
<td>8.5</td>
<td>5.51</td>
</tr>
<tr>
<td>18 – &lt;21 kg</td>
<td>41</td>
<td>4.5</td>
<td>7.42</td>
<td>13.42</td>
<td>7.64</td>
</tr>
</tbody>
</table>

WHO growth charts indicate median age for 21 kg is approximately 6 years of age.

Positive regulatory action based on robust Zolgensma clinical trial program, updated at MDA

<table>
<thead>
<tr>
<th>STR1VE</th>
<th>START</th>
<th>Cumulative Safety</th>
<th>SPR1NT</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/22 event-free survival at 14 mos &amp; 13 patients sat for ≥30 secs at 18 months.</td>
<td>Long-term follow-up</td>
<td>Safety data from 335 patients across all clinical investigations of IV Zolgensma, the U.S. managed access program, commercial patients, and the RESTORE global registry was consistent with previously observed safety data.</td>
<td>Nearly all patients were free of ventilatory support of any kind. All patients were fed orally and most were within gender &amp; age-appropriate weight range. All 2-copy patients achieved or maintained a CHOP INTEND score of ≥50, and 13 patients achieved a score ≥58. Remaining patients are still within the normal development window for these milestones.</td>
</tr>
<tr>
<td>9/22 achieved “ability to thrive” - the most stringent endpoint for SMA Type 1</td>
<td>Mean age was 4.8 years (4.3 –5.6) and the mean time since gene therapy was 4.5 years (4.1 –5.2). No patient who was free of ventilatory support at the end of the study has initiated new mechanical respiratory support. 6/10 patients (60%) do not require regular, daily respiratory support more than four years after dosing.</td>
<td>Sustained durability now up to 5 years post-dosing and up to 5+ years of age</td>
<td>6/10 patients (60%) do not require regular, daily respiratory support more than four years after dosing.</td>
</tr>
<tr>
<td>• 19 patients (86.4%) did not receive nutrition through any non-oral method</td>
<td>14 patients (63.6%) maintained weight</td>
<td>Safety profile consistent with previously-reported safety information</td>
<td>12 patients (54.5%) were able to tolerate thin liquids.</td>
</tr>
<tr>
<td>• 14 patients (63.6%) maintained weight</td>
<td>12 patients (54.5%) were able to tolerate thin liquids.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 12 patients (54.5%) were able to tolerate thin liquids.</td>
<td></td>
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</tr>
</tbody>
</table>

Completed study met co-primary efficacy endpoints and demonstrated the “ability to thrive”

Presymptomatic babies achieved age-appropriate motor milestones
In the 2-copy cohort of SPR1NT, so far nearly all patients achieved independent sitting and 4 achieved independent walking within the age-appropriate windows.

**Sits independently**

Primary Endpoint

**Walks independently**

- Eight patients have so far achieved independent sitting (5.7–11.8 months of age).
- The other 6 patients have not yet passed the WHO developmental window.

- Four patients have so far achieved independent walking (12.2–18.3 months of age).
- The other 10 patients have not yet passed the WHO developmental window.

*Age visit when milestone was confirmed*

*Age at last visit prior to data cut, milestone not yet confirmed*

WHO-MGRS window, 1st–99th percentile for milestone

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One-time gene therapy may replace burden of chronic treatment on healthcare systems in Europe

- Cumulative estimated healthcare costs per child ranges between €2.5 to €4 million within the first 10 years alone
- Chronic therapy can cost healthcare systems tens of millions of dollars over a patient’s lifetime
- In many cases in Europe the current cost of care, including chronic treatments, are already being covered/reimbursed by health systems

Zolgensma® could reduce the long-term financial burden on healthcare systems by replacing repeat, lifelong therapies with a single, one-time treatment

To support urgent need to treat, AveXis offering innovative “Day One” access program in Europe

The “Day One” access program offers ministries of health and reimbursement bodies (in countries without pre-existing early access pathways) a variety of flexible, payment options that can be implemented immediately at time of approval. Program is meant to ensure the continued integrity of local pricing and reimbursement frameworks.

- **Retroactive rebates** ensuring early access costs are aligned with negotiated prices following local clinical and economic assessment processes
- **Deferred payments and installment options** allowing reimbursement bodies to manage budget impact during the early access phase
- **Outcomes-based rebates** negotiated following clinical and economic assessments can be applied to patients treated during the early access period
- **Robust training** for treating institutions on administration and follow-up care
- **Access to RESTORE**, a global SMA registry of patients who have been diagnosed with SMA that draws upon existing country registries
AVXS-101 IT / STRONG Trial
Significant unmet need for patients with later onset forms of SMA despite SMN2 modifying therapies

Existing therapies and those in development have limitations

- Work on the back-up SMN2 gene
- Not all patients achieve full clinically meaningful response
- Require chronic use for person’s lifetime
- Risks and compliance challenges with administration
- Unknown effects of long-term use
STRONG designed to evaluate safety and efficacy of AVXS-101 IT in patients with SMA Type 2

SMA patients with 3 copies of SMN2 who were between 6 and 60 months of age at the time of dosing

Dose A, n=3
6.0E13 vg (enrolled)

Dose B, n=25
1.2E14 vg (25 enrolled)

Dose C, n=4
2.4E14 vg (4 enrolled)

Follow-up for 12 months post-dose

Follow-up for 15 months post-dose

Primary Endpoints
- Safety (AEs)
- Efficacy
  - ≥6 months and <24 months
    Standing alone (Bayley #40)
  - ≥24 months and <60 months
    Change from baseline in HFMSE

Secondary Elements
- Efficacy
  - Both age groups:
    Walking alone, defined as taking at least 5 steps independently

End of study

Study currently on clinical hold
Hammersmith scale is “gold standard” for measurement of progress in SMA patients >2 years

### SMA Types 2 and 3 Motor Function tests

**HFMSE**
Hammersmith functional Motor Scale expanded for SMA
Measures functional motor abilities in non-ambulant and ambulant individuals, designed specifically for patients with SMA >2 years old¹⁻⁵

**MFM32**
Motor Function measure 32*
Measures motor function abilities and possible changes in very weak patients aged 6 – 60 years⁴,⁶

### SMA Type 2 Motor Function test

**BSID III**
Bayley Scales of infant and toddler development third edition Motor Scales*
Measures control of muscle groups and range of motor functions in children aged 1 – 42 months⁴,⁷,⁸

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AVXS-101 IT demonstrated remarkable 6-point increases in Hammersmith scores

Least Squares (LS) Mean Analysis: Baseline to 12-month change in HFMSE total score

Primary Endpoint met
P=0.0021
Difference between LS means: 5.6
95% CI: 2.1 – 9.1

*The LS mean analysis based on a mixed model with repeated measurements (MMRM) with unstructured mean and within-subject error correlation, provides an accurate estimate of treatment effect. The model includes the change from baseline as the dependent variable, fixed effect of cohort (AVXS-101 and PNCR), visit, covariates of baseline HFMSE and age at baseline, and interactions of cohort age at baseline, baseline HFMSE visit, baseline HFMSE cohort, and cohort visit. Each AVXS-101 dose was modeled separately. Original study assumption (for power/sample size calculation): mean increase of 8 points in AVXS-treated patients. The PNCR natural history control group is used as the primary “population matched” control cohort. CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale-Expanded; PNCR, Pediatric Neuromuscular Clinical Research. 1. Mallinckrodt CH, et al. J Biopharm Stat. 2001;11:9–21. 2. Barnes SA, et al. Pharm Stat. 2008;7:215–225.
Hammersmith scores were rapid and sustained with a 92% clinically meaningful response

A 3-point increase in HFMSE is agreed by experts to represent the minimum change considered clinically meaningful\(^1\text{–}^3\)

Hammersmith increases reflect the preservation of motor neurons connected to key muscle groups, allowing for motor development.

6-point change in HFMSE from baseline impacts between 3 and 6 skills

An increase in HFMSE can impact skills ranging from:

- Inability → Partial (0 → 1)
- Partial → Complete (1 → 2)
- Inability → Complete (0 → 2)

3 completely achieved skills (2 points per skill)
6 partially achieved skills (1 point per skill)

<table>
<thead>
<tr>
<th>Sitting</th>
<th>Rolling</th>
<th>Transitions/Crawling</th>
<th>Transitions/Kneeling</th>
<th>Standing/Stepping</th>
</tr>
</thead>
</table>

Gains were seen across all five domains of motor function

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Baseline (Years)</th>
<th>HFMSE Total Score</th>
<th>Bayley-III Milestone Gained</th>
<th>HFMSE item score gain during study (0→1, 1→2)</th>
<th>HFMSE item score gain was 1 or 2 at baseline</th>
<th>HFMSE item score gain, specifically from a 0→2 during study</th>
<th>Bayley-III milestone gained during study (video confirmed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-3</td>
<td>4.2</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rolls from back to sides (item 20)</td>
</tr>
<tr>
<td>O-6</td>
<td>3.7</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stands with assistance (item 33)</td>
</tr>
<tr>
<td>O-9</td>
<td>2.3</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Walks with assistance (item 37)</td>
</tr>
<tr>
<td>O-4</td>
<td>4.5</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O-1</td>
<td>2.5</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O-5</td>
<td>3.0</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>O-8</td>
<td>2.2</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>O-2</td>
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<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O-11</td>
<td>4.4</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O-12</td>
<td>3.1</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O-10</td>
<td>2.3</td>
<td>4</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>O-7</td>
<td>2.6</td>
<td>3</td>
<td></td>
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</tr>
</tbody>
</table>

HFMSE Test items 28–33 Scored 0 in all patients. Patients ordered from highest to lowest baseline HFMSE. Bayley-III, Bayley Scales of Infant Development, Version 3; HFMSE, Hammersmith Functional Motor Scale Expanded; vg, vector genome.
STRONG reinforces potential best-in-category profile for AVXS-101 IT for older SMA

- **Transformational efficacy** with a mean 6-point increase in Hammersmith, twice the clinically meaningful threshold
- **Robust response** with nearly all (92%) achieving a clinically meaningful response
- **Replaces chronic administration** with a single, one-time dose
- **Safety profile consistent** with IV AVXS-101 program
Next steps for the AVXS-101 IT program

- FDA (27th March) requested additional pre-clinical data to release the partial clinical hold
- Additional pre-clinical data requested expected to be generated in studies planned / initiated
- We plan to engage with FDA during Q2 to clarify scope of data required
- We plan to approach FDA for pre-BLA meeting based on recently presented STRONG data, which confirms the positive benefit/risk of the IT formulation
- BLA submission timing: dependent on FDA feedback, could range from H2 2020 to 2021
**Form 483 complete**

FDA completed review of its August 2019 Form 483 response and classified the inspection as Voluntary Action Indicated with no further enforcement action necessary.

**Zolgensma®**

- **EC decision confirming approval expected by June 2020**
- **Reimbursement expected by the end of 1H20, pending agreement**
- **Others** Decisions anticipated late 2020 or early 2021 in Switzerland, Canada, Australia, Argentina, South Korea, Brazil
Appendix
MDA data continue to demonstrate efficacy of Zolgensma® across broad spectrum of SMA

**Presymptomatic**

**Sprint**
Ph 3, open-label, single-arm, multi-center trial to evaluate safety and efficacy of IV Zolgensma® in pre-symptomatic SMA patients with 2 or 3 copies of SMN2 <6 weeks

**Type 1**

**Strive**
Ph 3, open-label, single-arm, single-dose, multi-center trial to evaluate efficacy and safety of IV Zolgensma® in SMA Type 1 patients <6 months

**Type 2**

**Strong**
Ph 1, open-label, dose-comparison, multi-center trial to evaluate safety and tolerability of intrathecal (IT) AVXS-101 in SMA Type 2 patients 6 months – 5 years

**Start**
Long-term follow-up
Voluntary, ongoing, observational, long-term follow up study in patients from the Ph 1 open-label, single-site trial to evaluate safety and efficacy of IV Zolgensma® in SMA Type 1 patients <6 months