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Interim Efficacy and Safety Results from the Phase 2 NURTURE Study Evaluating Nusinersen in Presymptomatic Infants With Spinal Muscular Atrophy

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Introduction

- Spinal muscular atrophy (SMA)
  - Autosomal recessive neuromuscular disorder
  - Caused by mutations in the SMN1 gene
  - SMA Type I: onset by age 6 months, never rolls or sits independently
  - SMA Type II: onset by age 6–18 months, sits, but never walks independently

- Nusinersen
  - Antisense oligonucleotide
  - Modifies splicing of the homologous SMN2 precursor mRNA
  - Leads to increased production of full-length SMN protein

- NURTURE
  - Phase 2, open-label, multicenter, multinational, single-arm study
  - 12-mg scaled equivalent dose of intrathecal nusinersen
  - Infants with genetically diagnosed and presymptomatic SMA (most likely to develop Type I or II)
  - Previous interim analysis:
    - Infants treated were achieving motor milestones generally consistent with normal development in contrast to the natural history of SMA Type I

Study Overview: Interim Analysis
(Data Cut-off: October 31, 2016)

NURTURE study interim analysis data cut-off date: October 31, 2016.

**Participant disposition**

**Key eligibility criteria:**
- Age ≤6 weeks at first dose
- Presymptomatic SMA
- Genetic diagnosis of 5q SMA
- 2 or 3 SMN2 copies

25 infants screened
5 failed screening
20 infants dosed
- 2 SMN2 copies, n=13
- 3 SMN2 copies, n=7

- Discontinued treatment, n=0
- Withdrawn from study, n=0

**Identification**
- Affected sibling, n=15
- Newborn screening initiative, n=3
- Prenatal screening, n=1
- Known carrier status, n=1

**Study schematic**

Efficacy set: 18 infants who have reached Day 64 or longer

Infants completing visit
- n=20
- n=18
- n=16
- n=11
- n=9
- n=5

Screening period (≤21 days)

Nusinersen 12-mg scaled equivalent dose

Dosing schedule

Study day

- 1
- 15
- 29
- 64

183
302
365
421
540
659
778

- 4 loading doses with follow-up evaluations
- Maintenance dose and follow-up evaluation every 119 days
- D868 post-treatment follow-up visit

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Primary Endpoint: Time to Death or Respiratory Intervention\(^a\)

- At the time of the interim analysis, infants had been enrolled for a median (range) 317.5 (2.0–524.0) days
- All infants were alive and none had required respiratory intervention

<table>
<thead>
<tr>
<th>Nusinersen-treated infants, n (%)</th>
<th>2 SMN2 copies n=13</th>
<th>3 SMN2 copies n=7</th>
<th>Total n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>13 (100%)</td>
<td>7 (100%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>Required invasive ventilation or tracheostomy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Required noninvasive ventilation for (\geq 6) hours/day continuously for (\geq 7) days</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NURTURE study interim analysis data cut-off date: October 31, 2016. \(^a\)Respiratory intervention was defined as invasive or noninvasive ventilation for \(\geq 6\) hours/day continuously for \(\geq 7\) days or tracheostomy.
# HINE Motor Milestone\textsuperscript{1} Achievements\textsuperscript{a}

<table>
<thead>
<tr>
<th>Motor function</th>
<th>Full head control</th>
<th>Independent sitting (stable sit, pivot [rotates])</th>
<th>Stands with support/ Stands unaided</th>
<th>Cruising/ Walking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total infants achieving, n</td>
<td>15</td>
<td>12</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Expected age of attainment, mo\textsuperscript{a}</td>
<td>5</td>
<td>7</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Infants achieving at expected age, n/N (%)</td>
<td>15/16 (94%)</td>
<td>10/12 (83%)</td>
<td>7/11 (64%)</td>
<td>5/9 (56%)</td>
</tr>
</tbody>
</table>

- Three of 9 infants ≥12 months of age had achieved standing unaided (expected age, 12 months)
- Two infants ~13 months of age had achieved independent walking (expected age, 15 months)

\textsuperscript{1}HINE = Hammersmith Infant Neurological Examination
\textsuperscript{a}Among 18 Infants With Day 64 Assessment. NUPTURE study interim analysis data cut-off date: October 31, 2016


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Summary of Safety

- The lumbar puncture procedure was generally well tolerated
- There were no clinically significant adverse changes in laboratory or neurological examinations considered related to nusinersen
- All AEs considered by the investigator to be possibly related to study drug resolved during study follow-up

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Total n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>16 (80%)</td>
</tr>
<tr>
<td>SAEa</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>AE related to study drugb</td>
<td>0</td>
</tr>
<tr>
<td>AE possibly related to study drugb</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Muscular weakness and weight-bearing difficulty</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Hyperreflexia and tachycardia</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Pyrexia, increased ALT, increased AST with increased eosinophil count, lymphocyte count, and WBC count</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>SAE related to study drug</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation or withdrawal</td>
<td>0</td>
</tr>
</tbody>
</table>

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; SAE = serious adverse event; WBC = white blood cell. NURTURE study interim analysis data cut-off date: October 31, 2016. aSAEs were bronchitis, choking, and pneumonia (n=1); pneumonia (n=1); urinary tract (n=1); failure to thrive (n=1); pyrexia (n=1); and abdominal distension, respiratory distress, dehydration, and rhinovirus infection (n=1). bAssessed by the investigator.
Conclusions

- These results from the second interim analysis of NURTURE extend those from a June 2016 interim analysis
  - Continued beneficial effects of nusinersen in infants with presymptomatic SMA on survival and achievement of motor milestones over the expected natural history of SMA Type I
  - All infants are alive without requiring chronic respiratory support and are exhibiting improvements in motor function and/or motor milestones
  - Most infants are achieving motor milestones generally consistent with normal development
  - Achievement of motor milestones not acquired by infants with SMA Type I or II

- Nusinersen was well tolerated and no specific safety concerns were identified
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