Nusinersen in treatment-naïve patients with later-onset spinal muscular atrophy (SMA): efficacy results from a phase 1b/2a multicentre study (CS2) and its open-label extension (CS12)

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Spinal muscular atrophy and nusinersen

**CS2 (phase 1b/2a, open-label study) and CS12 (multiple dose redosing study)**

<table>
<thead>
<tr>
<th>CS2 total cohort</th>
<th>Dose</th>
<th>Total dose</th>
<th>N&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 mg</td>
<td>9 mg</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>6 mg</td>
<td>18 mg</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>9 mg</td>
<td>18 mg</td>
<td>9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>12 mg</td>
<td>36 mg</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CS12 total cohort</th>
<th>Dose</th>
<th>Total dose</th>
<th>N&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12 mg</td>
<td>48 mg</td>
<td>47</td>
</tr>
</tbody>
</table>

- **Primary endpoint:**
  - Evaluate the safety and tolerability of nusinersen administered intrathecally

- **Exploratory endpoints include:**
  - HFMSE
  - ULM test (non-ambulatory patients)
  - 6MWT (ambulatory patients)

**6MWT = 6-minute walk test; AE = adverse event; D = day; HFMSE = Hammersmith functional motor scale – expanded; f/u, follow-up; ULM = upper limb module test. N<sup>a</sup> = overall enrollment. <sup>b</sup>Patients received treatment on Days 1 and 85 only. Data cut-off dates: 12 January 2015 (CS2), 07 April 2016 (CS12 interim analysis). Chiriboga CA, et al. AAN 2014; ClinicalTrials.gov NCT01703988; Clinicaltrials.gov NCT02052791.**
Baseline demographics for patients who received their first nusinersen dose in CS2

- 6 / 34 patients from CS2 who entered CS12 previously received nusinersen in CS1\(^a\)
- Patients naïve to drug in CS2 were identified and followed into CS12 for this analysis (N=28)

<table>
<thead>
<tr>
<th></th>
<th>SMA Type II n=11</th>
<th>SMA Type III n=17</th>
<th>Total N=28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age at screening in CS2, years</td>
<td>4.4 (4.0)</td>
<td>8.9 (4.4)</td>
<td>7.1 (4.7)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>8 (73)</td>
<td>7 (41)</td>
<td>15 (54)</td>
</tr>
<tr>
<td>Mean (SD) age at symptom onset, months</td>
<td>11.0 (3.4)</td>
<td>22.0 (13.5)</td>
<td>17.7 (11.9)</td>
</tr>
<tr>
<td>Mean (SD) age at SMA diagnosis, months</td>
<td>15.4 (6.3)</td>
<td>43.6 (32.4)</td>
<td>32.5 (28.9)</td>
</tr>
<tr>
<td>SMN2 copy number, n (%)(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1 (6)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>3</td>
<td>11 (100)</td>
<td>10 (59)</td>
<td>21 (75)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>6 (35)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Ambulatory status, n (%)(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulatory</td>
<td>0</td>
<td>13 (76)</td>
<td>13 (46)</td>
</tr>
<tr>
<td>Non-ambulatory</td>
<td>11 (100)</td>
<td>4 (24)</td>
<td>15 (54)</td>
</tr>
<tr>
<td>Motor function at screening in CS2, n (%)(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting without support</td>
<td>11 (100)</td>
<td>17 (100)</td>
<td>28 (100)</td>
</tr>
<tr>
<td>Standing without support</td>
<td>0</td>
<td>12 (71)</td>
<td>12 (43)</td>
</tr>
<tr>
<td>Walking with support</td>
<td>2 (18)</td>
<td>15 (88)</td>
<td>17 (61)</td>
</tr>
<tr>
<td>Walking independently</td>
<td>0</td>
<td>13 (76)</td>
<td>13 (46)</td>
</tr>
</tbody>
</table>

\(^a\)CS1 (NCT01494701) was a single ascending-dose, Phase 1, open-label study of nusinersen in patients with later-onset SMA. Patients from CS1 could enrol in CS2. \(^b\)Based on patients dosed with nonmissing data. Data cut-off dates:12 January 2015 (CS2), 07 April 2016 (CS12 interim analysis).
Change in HFMSE score over time: patients with Type II SMA

- Maximum possible HFMSE score is 66$^1$
- Mean (SE) Baseline HFMSE score: 21.3 (2.9)
- Mean (SE) change with nusinersen of:
  - 5.1 (1.2) points at Day 253
  - 12.3 (2.2) points at Day 1050
- In a natural history cohort of Type II and Type III SMA, mean change was –0.5 point over 24 months (730 days) and –1.7 points over 36 months (1095 days)$^2$

Change in ULM test total score over time: patients with Type II SMA

- Maximum possible ULM test total score is 18 in nonambulant patients with SMA\textsuperscript{1}
- Mean (SE) Baseline ULM test total score: 11.9 (0.9)
- Mean (SE) change with nusinersen of:
  - 1.9 (0.8) points at Day 253
  - 4.6 (1.4) points at Day 1050
- In a natural history, mean change was 0.04 points over 12 months\textsuperscript{2}

Change in HFMSE score over time: patients with Type III SMA

- Maximum possible HFMSE score is 66\(^1\)
- Mean (SE) Baseline HFMSE score: 48.9 (3.0)
- Mean (SE) change with nusinersen of:
  - 1.3 (0.5) points at Day 253
  - 1.6 (1.5) points at Day 1050
- In a natural history cohort of Type II and Type III SMA, mean change was –0.5 points over 24 months (730 days) and –1.7 points over 36 months (1095 days)\(^2\)

Change in 6MWT distances over time: patients with Type III SMA

- Mean (SE) Baseline 6MWT distance: 253.3 (50.7) metres
- Mean (SE) change with nusinersen of
  - 28.6 (13.6) metres at Day 253
  - 96.7 (17.3) metres at Day 1050
- Natural history is mean –1.5 metre change over 12 months¹
- One patient with Type II SMA gained the ability to walk independently
- Two patients with Type III SMA re-gained the ability to walk independently

Safety and tolerability for CS2 and CS12

• In the 28 patients who first received nusinersen in CS2, median (min, max) number of intrathecal doses was 6 (1, 7)
  - Mean (SD) time on study was 880.5 (328.5) days
• Overall, most AEs were mild to moderate and considered not related to study drug
  - No SAEs were reported as related to study drug
• The LP procedure was generally well tolerated
  - Some AEs (e.g., PLPS, headache, back pain) were possibly associated with the LP and are expected in the context of this procedure\textsuperscript{1,2}
• No clinically significant adverse changes in laboratory or neurological examinations considered related to nusinersen

LP = lumbar puncture; PLPS = post-lumbar puncture syndrome; SAE = serious AE. Data cut-off dates: 12 January 2015 (CS2), 07 April 2016 (CS12 interim analysis).

Summary

• Baseline characteristics for this cohort were consistent with expected natural history

• For patients with Type II SMA with up to ~3 years of treatment:
  - Improvements were observed in motor function over time, as measured by HFMSE scores and ULM test
  - One patient with Type II SMA gained the ability to walk independently

• For patients with Type III SMA with up to ~3 years of treatment:
  - HFMSE scores were stable over time
  - Increases were observed in 6MWT distances
  - Two patients with Type III SMA re-gained the ability to walk independently

• No new safety findings were reported during longer-term treatment with nusinersen
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