Cost-Effectiveness of Risdiplam Versus Nusinersen for Treating Patients with Spinal Muscular Type I in China

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BACKGROUND
• Spinal muscular atrophy (SMA) is a neurodegenerative disease included in the Chinese Rare Diseases List, leading to progressive, symmetrical muscle weakness and muscular atrophy[1]. SMA Type I is the most severe subtype, which refers to individuals who have symptom onset prior to 6 months and would die before 2 years old without any intervention[3].
• Risdiplam (oral oral therapy, approved in China in 2021) and Nusinersen (intrathecal injection; approved in China in 2019) were the only two available disease-modifying treatments for SMA in China. Risdiplam is the first orally-administered small molecule, directly targeting the underlying molecular deficiency of SMA by increasing of functional SMN protein.

OBJECTIVES
• To evaluate the cost-effectiveness of Risdiplam versus Nusinersen in treating patients with SMA type I in China.

METHODS
Key model features
• The state Markov model based in Microsoft Excel was adapted to the Chinese healthcare system perspective[4] (Figure 1).
• Time related proportions of scoliosis were derived from literature[5], whilst that of respiratory/bulbar impairment were based on FIREISH study as proxy data.
• Model outcomes were costs, QALYs, life-years and incremental cost-effectiveness ratios (ICER).
• Each cycle length was 1 month.
• The modelled time horizon was 10 years, considering the unknown long-term benefit.
• Half-cycle correction was adopted.

RESULTS
• The utility values for patients were estimated from EQ-5D-3L responses from Chinese pediatric neurologists based on the case history descriptions of different disease stages in the model.
• The 2018 Chinese utility value set for EQ-5D-3L was used in the base case analysis. Individuals of lung function, which was 0.01, was used in the cycle of administration in Nusinersen group [8].
• The utility values were be summarized and presented as table 5. Standard error was estimated as 20% of mean.

LIMITATIONS
• In the absence of head-to-head trial data, Nusinersen treatment had to be estimated from an indirect comparison of Risdiplam and Nusinersen.
• The time horizon chosen in the study was relatively short as lack of long-term efficacy data. However, the chosen time horizon align with the half-life of SMA type I.
• Utilities had to be estimated from a vignette study as no preference-based quality of life measures were included in the clinical trials owing to the very young age of the patients.
• Further, the utilities of caregivers had not been considered in this model, which might cause the underestimation of the utility benefit of Risdiplam arm as it is a convenient oral formulation.

CONCLUSION
• Risdiplam is a dominant alternative over Nusinersen for patients with SMA type I in China, with more QALYs gained and less costs.

Table 1. Summary of the Indirect Treatment Comparison

<table>
<thead>
<tr>
<th></th>
<th>Nusinersen</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR for Ventilation-Free Survival</td>
<td>0.397</td>
<td>0.056</td>
<td>0.415</td>
<td></td>
</tr>
<tr>
<td>HR for OS</td>
<td>0.261</td>
<td>0.028</td>
<td>0.665</td>
<td></td>
</tr>
<tr>
<td>OR for Sitting to Standing transition (based on OR for achievement of HINE-2 sitting milestone)</td>
<td>1.499</td>
<td>0.715</td>
<td>3.129</td>
<td></td>
</tr>
<tr>
<td>OR for Sitting to Standing transition (based on OR for achievement of HINE-2 sitting milestone)</td>
<td>0.538</td>
<td>0.205</td>
<td>2.132</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Base Case Analysis Results

<table>
<thead>
<tr>
<th></th>
<th>Risdiplam</th>
<th>Nusinersen</th>
<th>Differences, Risdiplam vs Nusinersen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs</td>
<td>¥4,119,395</td>
<td>¥4,486,776</td>
<td>- ¥377,380</td>
</tr>
<tr>
<td>LVA</td>
<td>7.12</td>
<td>5.69</td>
<td>1.43</td>
</tr>
<tr>
<td>ICER</td>
<td>2.83</td>
<td>1.72</td>
<td>1.11</td>
</tr>
</tbody>
</table>

Table 3. Summary Table of Utility Values

<table>
<thead>
<tr>
<th></th>
<th>Permanent Ventilation</th>
<th>Not Sitting</th>
<th>Sitting</th>
<th>Standing</th>
<th>Walking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal cost per QALY</td>
<td>¥3,484</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Markov Model for Type 1 Spinal Muscular Atrophy

Treatement effects of Risdiplam and Nusinersen
• Modelling of survival and motor-milestones (defined according to the Hammersmith Infant Neuromuscular Examination Module 2 [HINE-2]) with Risdiplam were based on data from the FIREISH study, which is an open-label, single-arm, multicentre clinical study to evaluate the efficacy of Risdiplam.
• The model used baseline characteristics pooled from the FIREISH Part I and Part 2 population[6].
• Modelling of outcomes with Nusinersen was based on relative effects estimated from a matching-adjusted indirect comparison (MAIC) and assumptions (table 1).
• Transition probabilities between some states of Nusinersen group (sitting to non-sitting, standing to sitting, walking to standing) were assumed to be equal as that of Risdiplam group, as there were no other available data.

Table 4. Costs Inputs per Disease State

<table>
<thead>
<tr>
<th></th>
<th>Permanent Ventilation</th>
<th>Not Sitting</th>
<th>Sitting</th>
<th>Standing</th>
<th>Walking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline one-time cost</td>
<td>¥13,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>¥3,508</td>
<td>¥3,419</td>
<td>¥3,556</td>
<td>¥3,492</td>
<td>¥3,170</td>
</tr>
<tr>
<td>Inpatient</td>
<td>¥6,334</td>
<td>¥7,096</td>
<td>¥5,321</td>
<td>¥288</td>
<td>¥191</td>
</tr>
<tr>
<td>Medical devices</td>
<td>¥2,602</td>
<td>¥3,602</td>
<td>¥1,438</td>
<td>¥9,360</td>
<td>¥1,181</td>
</tr>
<tr>
<td>Total</td>
<td>¥15,447</td>
<td>¥19,317</td>
<td>¥9,311</td>
<td>¥5,380</td>
<td>¥5,349</td>
</tr>
</tbody>
</table>

Figure 2. Different Parametric Extrapolations for Overall Survival

Cost parameters
• The drug acquisition costs after patient assistance program for Nusinersen and Risdiplam based on the drug recommended dosage by label were used in the model.
• Other direct medical costs including administration, inpatient, outpatient, and medical devices costs were estimated from expert clinical opinion and hospital information systems in China[6].
• The palliative care cost was extracted from literature[7].
• The medical costs of six disease state were presented in table 4, respectively. Standard error was estimated as 20% of mean.

Figure 3. One-way Sensitivity Results

Figure 4. Results Summary Table in Base Case

One-way sensitivity analysis
• One-way sensitivity analysis indicates that hazard ratio of overall survival in Nusinersen group, hazard ratio of ventilation-free survival in Nusinersen group and utility of "sitting" stage has the greatest impact on incremental cost-effectiveness ratio.

Probabilistic sensitivity analysis
• Probabilistic sensitivity analysis showed that the probability of Risdiplam being cost-effective at a willingness to pay of 3 times Chinese Gross Domestic Product (¥271,341) was 62.92%.

The results presented here are based on the use of the base case. The results of the sensitivity analysis are shown in the figures.