# Cost-Effectiveness of Risdiplam Versus Nusinersen for Treating Patients with Spinal Muscular Atrophy Type 1 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[1,2]. SMA Type 1 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 (at-home 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-administrated 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 1 in China.

## METHODS

**Key model features**

- A six-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 FIREFISH study as proxy data.
- Model outcomes were costs, QALYs, life-years and incremental cost-effectiveness ratios (ICERs).
- Each cycle length was 1 month.
- The modelled time horizon was 10 years, considering the unknown long-term benefits.
- Half-cycle correction was adopted.

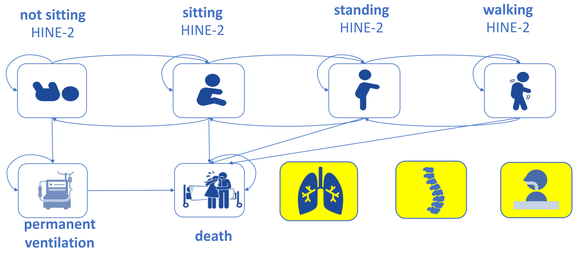



Figure 1. Markov Model for Type 1 Spinal Muscular Atrophy

**Treatment 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 FIREFISH study, which is an open-label, single-arm, multi-centre clinical study to evaluate the efficacy of Risdiplam.
- The model used baseline characteristics pooled from the FIREFISH Part 1 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 1. Summary of the Indirect Treatment Comparison

| Nusinersen | Estimate | Lower 95% CI | Upper 95% CI |
|---|---|---|---|
| HR for Ventilation-Free Survival | 0.197 | 0.056 | 0.415 |
| HR for OS | 0.261 | 0.028 | 0.665 |
| OR for Not Sitting to Sitting transition (based on OR for achievement of HINE-2 sitting milestone) | 1.499 | 0.715 | 3.129 |
| OR for Sitting to Standing transition (based on OR for achievement of HINE-2 standing milestone) | 0.538 | 0.205 | 2.132 |

HR: Hazard Ratio; OR: Odds Ratio; CI: Confidence Interval; OS: Overall Survival.

**Survival analysis:**

- OS and EFS survival curves were extrapolated using standard parametric models.
- LogNormal distribution for overall survival and Gompertz distribution for ventilation free survival were chosen in the base case analysis (figure 2&3).

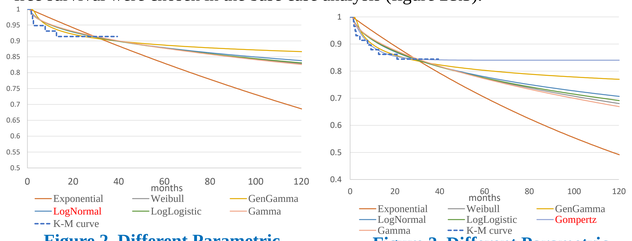



Figure 2. Different Parametric Extrapolations for Overall Survival




Figure 3. Different Parametric Extrapolations for Ventilation-Free 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[3].
- 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.

## Table 4. Costs Inputs per Disease State

| | Permanent Ventilation | Not Sitting | Sitting | Standing | Walking |
|---|---|---|---|---|---|
| **Baseline one-time cost** ¥30,800 | | | | | |
| **Outpatient** | ¥3,508 | ¥3,419 | ¥3,556 | ¥3,492 | ¥3,170 |
| **Inpatient** | ¥ 9,334 | ¥ 7,896 | ¥ 321 | ¥ 298 | ¥ 198 |
| **Medical devices** | ¥ 2,602 | ¥ 2,602 | ¥ 1,434 | ¥ 1,590 | ¥ 181 |
| **Total** | ¥ 15,444 | ¥ 13,917 | ¥ 5,311 | ¥ 5,380 | ¥ 3,549 |
| **Terminal care cost** ¥ 93,484 | | | | | |

**Utility**

- Utility values for patients were estimated from EQ-5D-3L responses from Chinese pediatric neurologists based on the case history descriptions of different disease states in the model.
- The 2018 Chinese utility value set for EQ-5D-3L was used in the base case analysis.
- Disutility of lumbar puncture, which was 0.071, was counted 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.

## Table 5. Summary Table of Utility Values

| | Permanent Ventilation | Not Sitting | Sitting | Standing | Walking |
|---|---|---|---|---|---|
| **Utility Based on 2018 EQ-5D-3L Chinese Value Set** | 0.1911 | 0.2853 | 0.3888 | 0.6020 | 0.7206 |

## RESULTS

**Base case analysis**

- Patients treated with Risdiplam gained 1.43 more life-years and 1.11 more QALYs compared to Nusinersen. (Table 6)
- The total direct medical costs of treating with Risdiplam is CNY 367,380 lower than treating with Nusinersen. The cost-saving is mainly resulted by lower outpatient costs in Risdiplam group. (Figure 2)

## Table 6. Base Case Analysis Results

| | Risdiplam | Nusinersen | Differences, Risdiplam vs Nusinersen |
|---|---|---|---|
| **Costs** | ¥4,119,395 | ¥4,486,776 | - ¥367,380 |
| **LYs** | 7.12 | 5.69 | 1.43 |
| **QALYs** | 2.83 | 1.72 | 1.11 |
| **ICER** | Risdiplam Dominant | | |

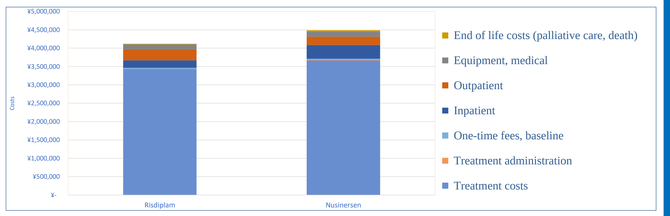


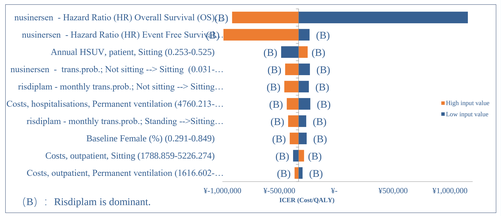

Figure 4. Results Summary Table in Base Case

**One-way sensitivity analyses**

- 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 in “sitting” state has the greateset 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(￥217,341) was 62.92%.
- The plots in incremental cost-effectiveness plan mainly located in first and fourth quadrant, which indicated that Risdiplam is more effective than Nusinersen.




(B)：Risdiplam is dominant.

Figure 3. One-way Sensitivity Results

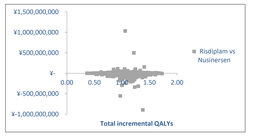



Figure 5. Incremental Cost-effectiveness Plane

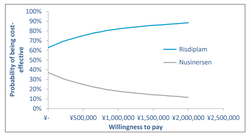



Figure 4. Cost-effectiveness Acceptability Curve

## LIMITATIONS

- In the absence of head-to-head trial data, Nusinersen treatment effects had to be estimated from an indirect comparison of Risdiplam and Nusinersen.
- The time horizon chosen in the study was relatively short as lacking long-term efficacy data. However, the chosen time horizon align with the nature history of SMA type 1.
- 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 caregiver had not been considered in this model, which might cause the underestimation of the utilities 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. The result was relatively robust in the sensitivity analysis.

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## DISCLOSURE

The study was funded by Shanghai Roche Pharmaceuticals Ltd & F. Hoffmann-La Roche Ltd , Basel, Switzerland.