Matching-adjusted indirect comparison of risdiplam versus nusinersen in Type 1 spinal muscular atrophy: 2-year update

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*Presenter
Disclosures

- NH, RE and DAS are current employees of Visible Analytics
- VAR was an employee of F. Hoffmann-La Roche Ltd at the time of this study
- KG, MD and YM are current employees of F. Hoffmann-La Roche Ltd
- AM is a current employee of Bridge Medical Consulting

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Introduction

- Type 1 SMA is a severe, progressive, genetic neuromuscular disease, with untreated infants failing to achieve major motor milestones and typically dying before 2 years of age\(^1\)

- There are three approved treatments for SMA:
  - nusinersen (SPINRAZA\(^\text{®}\))
  - onasemnogene abeparvovec (ZOLGENSMA\(^\text{®}\))
  - risdiplam (EVRYSDI\(^\text{®}\))

- In the absence of head-to-head trials directly comparing treatments in SMA, ITC can be used to estimate the relative effectiveness and safety of available treatments\(^2\)

- A previous ITC based on 12 months of data supported risdiplam as a superior alternative to nusinersen in Type 1 SMA\(^3\)
  - Analyses did not provide sufficient evidence to draw concrete conclusions between risdiplam and onasemnogene abeparvovec

- The objective of this study was to conduct an updated ITC to evaluate relative efficacy and safety of risdiplam versus relevant comparators in Type 1 SMA using longer-term data covering at least 24 months of treatment

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Valid indirect treatment comparisons adjust for important trial differences that impact outcomes\textsuperscript{1,2}

- Trials may have different characteristics (enrollment criteria, different baseline characteristics, different outcome measures, etc.) that may impact treatment outcomes
  - Therefore, naïve ITCs have a high risk of bias if they are not adjusted for key observed differences
- Methodologies exist to adjust for differences in prognostic factors and effect modifiers across two different clinical trials\textsuperscript{3,4}

Identification of studies included in this analysis

- Studies reporting long-term data (>1 year) in Type 1 SMA were identified from an SLR, using a search strategy described previously:
  - nusinersen: data from the integrated ENDEAR (NCT02193074)/SHINE (NCT02594124) analyses (~3.5 years of follow-up) were extracted from the submission dossier to the public health agency in Germany
  - risdiplam: IPD were available from FIREFISH* (NCT02913482) covering at least 2 years of data

Risdiplam data from 58 infants from FIREFISH* were compared with nusinersen data from 81 infants in ENDEAR/SHINE using a MAIC
MAIC* was used to compare data from FIREFISH with data from ENDEAR/SHINE

- MAIC is a methodology that reduces bias in ITCs resulting from differences in prognostic factors and effect modifiers across two different clinical trials1,2*


*The comparison of FIREFISH and ENDEAR/SHINE uses an unanchored MAIC. Unanchored MAICs require that effect modifiers and prognostic factors are balanced between the population.

1. Risdiplam IPD are weighted so that selected baseline characteristics match the average characteristics in the comparator population.

2. Increasing similarity with comparator 

3. Weighted risdiplam outcomes are compared with published comparator outcomes

- Prognostic factors and effect modifiers for SMA were identified in a published literature review3
  - Matching factors used in this analysis were age at first dose, disease duration at baseline and baseline motor function
Endpoints of interest

The following outcomes of interest were compared:* 

- time to death 
- time to death or permanent ventilation 
- time to a HINE-2 motor milestone response 
- time to ≥4-point improvement in CHOP-INTEND from baseline 
- time to first SAE 

*HRs of risdiplam versus nusinersen were estimated using Cox proportional-hazards models, which handle differences in follow-up time across studies and allow comparisons over time. 
CHOP-INTEND, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Module 2; HR, hazard ratio; SAE, serious adverse event.
**FIREFISH* baseline characteristics were matched to ENDEAR/SHINE**

<table>
<thead>
<tr>
<th></th>
<th>Pre-matching: FIREFISH* (risdiplam unweighted)</th>
<th>Post-matching: FIREFISH* (risdiplam re-weighted)</th>
<th>ENDEAR/SHINE† (average of nusinersen and BSC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (ESS)</td>
<td>58*</td>
<td>58* (36.5)</td>
<td>121</td>
</tr>
<tr>
<td>Female, %</td>
<td>57</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Mean age at first dose, days</td>
<td>163</td>
<td>69</td>
<td>55</td>
</tr>
<tr>
<td>Mean age at symptom onset, weeks</td>
<td>7.2</td>
<td>7.9</td>
<td>8.5</td>
</tr>
<tr>
<td>Mean age at diagnosis, weeks</td>
<td>12.7</td>
<td>14.3</td>
<td>14.3</td>
</tr>
<tr>
<td>Mean disease duration at screening, days</td>
<td>91</td>
<td>94</td>
<td>~94</td>
</tr>
<tr>
<td>Mean CHOP-INTEND score</td>
<td>22.47</td>
<td>27.24</td>
<td>27.24</td>
</tr>
<tr>
<td>Mean HINE-2 score</td>
<td>0.93</td>
<td>1.28</td>
<td>1.37</td>
</tr>
<tr>
<td>Patients with nutritional support, %‡</td>
<td>9</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Patients requiring ventilatory support, %</td>
<td>29</td>
<td>18</td>
<td>22</td>
</tr>
</tbody>
</table>

*Includes patients from the ‘high-dose’ (pivotal dose) cohort of Part 1 (n=17) and all patients from FIREFISH Part 2 (n=41). †The ENDEAR/SHINE cohort includes one additional patient who was never dosed in ENDEAR, but participated in SHINE (N=122). Hence, weighting was conducted on the baseline characteristics of the original ENDEAR population (N=121). ‡Unable to swallow, or gastrointestinal tube feeding required.

MAIC suggests prolonged overall survival in infants treated with risdiplam compared with infants treated with nusinersen

**Naïve comparison**
risdiplam vs. nusinersen
HR* 0.33  
(95% CI 0.07–0.86)

**MAIC**
risdiplam vs. nusinersen
HR* 0.19  
(95% CI 0.02–0.54)

MAIC suggests infants with Type 1 SMA treated with risdiplam may have a 81% reduction in the rate of death compared with infants treated with nusinersen

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*HRs of risdiplam versus nusinersen were calculated using Cox proportional-hazards models. An HR <1 favors risdiplam over comparator. 95% CIs that do not span 1 indicate a statistically significant difference. †Sum of weights. CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; SMA, spinal muscular atrophy.*
**MAIC suggests prolonged event-free survival with risdiplam compared with nusinersen**

<table>
<thead>
<tr>
<th>Treatment (study)</th>
<th>Number at risk</th>
<th>Time (months)</th>
<th>Event-free survival probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risdiplam unadjusted</td>
<td>58</td>
<td>51</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>50</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>46</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>41</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>42</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>50</td>
<td>0.00</td>
</tr>
<tr>
<td>Risdiplam re-weighted</td>
<td>44</td>
<td>40</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>39</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>37</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>38</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>38</td>
<td>0.00</td>
</tr>
<tr>
<td>Nusinersen</td>
<td>81</td>
<td>42</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>38</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>38</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>38</td>
<td>0.00</td>
</tr>
</tbody>
</table>

- **Naïve comparison**
  - Risdiplam vs. nusinersen
    - HR* 0.23
    - (95% CI 0.10–0.44)

- **MAIC**
  - Risdiplam vs. nusinersen
    - HR* 0.19
    - (95% CI 0.07–0.39)

MAIC suggests infants with Type 1 SMA treated with risdiplam may have an 81% reduction in the rate of death or permanent ventilation compared with infants treated with nusinersen.

*HRs of risdiplam versus nusinersen were calculated using Cox proportional-hazards models. An HR <1 favors risdiplam over comparator. 95% CIs that do not span 1 indicate a statistically significant difference. †Sum of weights.*

CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; SMA, spinal muscular atrophy.
MAIC suggests risdiplam treatment may be associated with a higher likelihood of a HINE-2 motor milestone response* compared with nusinersen

*Infant classed as responder if more motor milestones show improvement than show worsening. Improvement defined as a ≥2-point increase in ability to kick (or maximal score) or a ≥1-point increase in head control, rolling, sitting, crawling, standing or walking. Worsening defined as a ≥2-point decrease in ability to kick (or lowest score) or a ≥1-point decrease in head control, rolling, sitting, crawling, standing or walking. HRs of risdiplam versus nusinersen were calculated using Cox proportional-hazards models. Infants were censored at latest recorded visit. Three infants in FIREFISH died before any post-baseline visit and were therefore censored at time 0. An HR >1 favors risdiplam over comparator. 95% CIs that do not span 1 indicate a statistically significant difference.

Naïve comparison

risdiplam vs. nusinersen

HR† 1.15
(95% CI 0.79–1.73)

MAIC

risdiplam vs. nusinersen

HR† 1.50
(95% CI 1.07–2.14)

MAIC suggests infants with Type 1 SMA treated with risdiplam may be more likely to have a HINE-2 motor milestone response compared with infants treated with nusinersen

<table>
<thead>
<tr>
<th>Treatment (study)</th>
<th>Number at risk</th>
<th>Time (months)</th>
<th>Proportion of infants with a HINE-2 motor milestone response*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risdiplam unadjusted</td>
<td>58</td>
<td>0, 6, 12, 18, 24</td>
<td>0.00, 0.25, 0.50, 0.75, 1.00</td>
</tr>
<tr>
<td>Risdiplam re-weighted‡</td>
<td>44</td>
<td></td>
<td>0.00, 0.25, 0.50, 0.75, 1.00</td>
</tr>
<tr>
<td>Nusinersen</td>
<td>81</td>
<td></td>
<td>0.00, 0.25, 0.50, 0.75, 1.00</td>
</tr>
</tbody>
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CI, confidence interval; HINE-2, Hammersmith Infant Neurological Examination, Module 2; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; SMA, spinal muscular atrophy.
MAIC suggests infants treated with risdiplam may be more likely to see an earlier CHOP-INTEND response* compared with nusinersen treatment

<table>
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<th>Number at risk</th>
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<td>1</td>
</tr>
<tr>
<td>Risdiplam re-weighted†</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>Nusinersen</td>
<td>81</td>
<td>5</td>
</tr>
</tbody>
</table>

*Improvement of ≥4 points in CHOP-INTEND score from baseline. †HRs of risdiplam versus nusinersen were calculated using Cox proportional-hazards models. Patients were censored at latest recorded visit. Three patients in FIREFISH died before any post-baseline visit and were therefore censored at time 0. An HR >1 favors risdiplam over comparator. 95% CIs that do not span 1 indicate a statistically significant difference. ‡Sum of weights.

**Naïve comparison risdiplam vs. nusinersen**

HR† 1.92
(95% CI 1.36–2.80)

**MAIC risdiplam vs. nusinersen**

HR† 1.89
(95% CI 1.28–2.88)

MAIC suggests infants with Type 1 SMA treated with risdiplam may be more likely to see an earlier CHOP-INTEND response compared with infants treated with nusinersen.
MAIC suggests treatment with risdiplam may reduce the likelihood of experiencing an SAE compared with nusinersen treatment

*HRs of risdiplam versus nusinersen were calculated using Cox proportional-hazards models. Patients were censored at the earliest date from: CCOD, death date, study withdrawal date, and last treatment dose +30 days. An HR <1 favors risdiplam over comparator. 95% CIs that do not span 1 indicate a statistically significant difference.†Sum of weights.

CCOD, clinical cut-off date; CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; SAE, serious adverse event; SMA, spinal muscular atrophy.

Naïve comparison
risdiplam vs. nusinersen

HR* 0.45
(95% CI 0.29–0.65)

MAIC
risdiplam vs. nusinersen

HR* 0.41
(95% CI 0.26–0.66)

MAIC suggests infants with Type 1 SMA treated with risdiplam may be less likely to experience an SAE compared with infants treated with nusinersen
General limitations

- In order to avoid biased results, it is important to adjust for differences in identified effect modifiers and prognostic factors
  - In this study, we adjusted for imbalances in all identified factors in Type 1 SMA; however, results may still be biased by unreported or unknown factors
- One factor that it was not possible to control for was potential changes in SoC over time
  - Improvements in survival with risdiplam treatment may have been influenced by updates in the SoC around respiratory support
  - However, both studies recruited patients globally from a large number of sites that were specialized centers and the two studies were not conducted far enough apart from each other to expect significant changes in the SoC that could have resulted in improvements in survival
    - There were a number of sites that participated in both FIREFISH and ENDEAR/SHINE clinical trials
Comparisons of motor milestones are limited by differences between the assessment schedule of the trials

- HRs calculated for motor function endpoints may be biased due to differences in assessment schedules between the FIREFISH and ENDEAR trial

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Day 56</th>
<th>Day 119</th>
<th>Day 182</th>
<th>Day 245</th>
<th>Day 301</th>
<th>Day 364</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIREFISH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP-INTEND</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>HINE-2</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ENDEAR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHOP-INTEND &amp; HINE-2</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

**FIREFISH had more frequent assessments of CHOP-INTEND.** To remove bias in favor of risdiplam, analyses of CHOP-INTEND were performed using only visits where both FIREFISH and ENDEAR had assessments (FIREFISH CHOP-INTEND assessments at Day 119 and Day 245 were not included).

**ENDEAR had earlier and more frequent assessments of HINE-2 response and an earlier first assessment of HINE-2 response, which may bias results in favor of nusinersen.**
Conclusions

Results from this updated MAIC analysis of risdiplam (FIREFISH) compared with nusinersen (ENDEAR/SHINE) suggested that infants with Type 1 SMA treated with risdiplam may see greater improvements compared with infants treated with nusinersen over at least 2 years of follow-up.

- Infants treated with risdiplam may have an 81% reduction in rate of death and an 81% reduction in rate of death or permanent ventilation compared with infants treated with nusinersen.
- Treatment with risdiplam may increase the likelihood of experiencing a HINE-2 motor milestone response compared with treatment with nusinersen.
- Treatment with risdiplam may lead to earlier improvements in motor function* compared with treatment with nusinersen.
- Treatment with risdiplam may also reduce the likelihood of experiencing an SAE versus treatment with nusinersen.

*Assessed by the achievement of a ≥4-point increase in CHOP-INTEND total score.

CHOP-INTEND, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Module 2; MAIC, matching-adjusted indirect comparison; SAE, serious adverse event; SMA, spinal muscular atrophy.

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