How does risdiplam compare with other treatments for Types 1–3 spinal muscular atrophy: A systematic literature review and indirect treatment comparison

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- No head-to-head clinical trials have directly compared the efficacy of risdiplam, nusinersen and onasemnogene abeparvovec in SMA
- Comparative efficacy and safety information is needed to inform treatment choice for patients with SMA
- Risdiplam trial data were indirectly compared with data from published nusinersen and onasemnogene abeparvovec studies using population-adjustment methodologies

Population-adjustment methodology

Pre-adjustment: Studies differ in terms of enrollment criteria and patient characteristics at baseline

Risdiplam IPD

Increasing similarity with comparator

Prognostic factors and effect modifiers are **unbalanced**

Comparator study (Aggregate data)

Align risdiplam study IPD with comparator aggregate data

Post-adjustment: Risdiplam data are adjusted to reduce cross-study imbalances in prognostic factors and effect modifiers

Adjusted risdiplam outcomes **Comparator study outcomes**

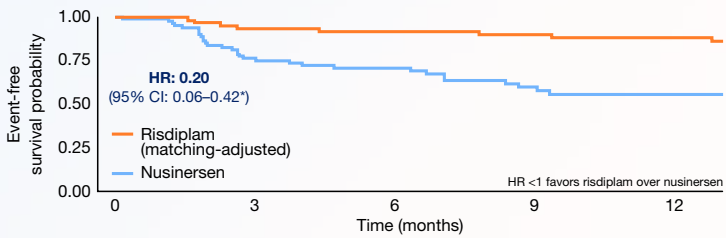
Adjusted risdiplam outcomes are compared with published comparator outcomes

Type 1 SMA: risdiplam versus nusinersen

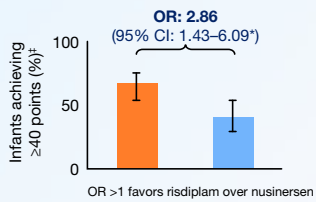
- FIREFISH and ENDEAR enrolled patient populations with similar baseline characteristics
- MAIC methodology was applied to further reduce differences in prognostic factors and effect modifiers

Baseline characteristics	Pre-matching: Risdiplam (FIREFISH)	Post-matching: Risdiplam (FIREFISH)	Average of nusinersen & BSC (ENDEAR)
Sample size (ESS)	58	58 (36.5)	121
Mean age at first dose, days	163	169	169
Mean disease duration at screening, days	91	94	94
Mean score on CHOP-INTEND	22.47	27.24	27.24

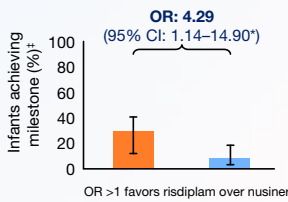
Event-free survival



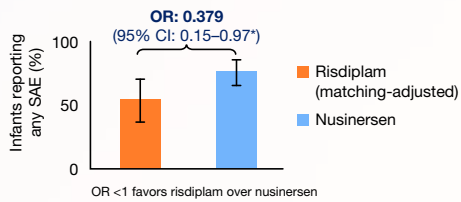
CHOP-INTEND (achieving score of ≥40 points)



Sitting without support (HINE-2)



Serious adverse events†



Type 1 SMA: risdiplam versus onasemnogene abeparvovec

- FIREFISH and STR1VE-US were indirectly compared using STC methodology; MAIC was not feasible due to insufficient population overlap (ESS was 2.1)
- Results exhibited large uncertainty around the relative effect estimates due to population differences and small samples

Types 2 and 3 SMA: risdiplam versus nusinersen

- SUNFISH enrolled a broader population compared with CHERISH; MAIC methodology was applied to adjust for population differences
- Results exhibited large uncertainty around the relative effect estimates due to substantial differences across populations

Limitations

- Population-adjustment methodologies assume that all prognostic and predictive factors are balanced post-adjustment and cannot account for differences in study design or changes in standard of care

Conclusions

- MAIC analyses suggested significantly prolonged survival, improvements in motor function, and reduced likelihood of SAEs with risdiplam versus nusinersen in Type 1 SMA
- No concrete conclusions could be drawn in comparisons of risdiplam with onasemnogene abeparvovec in Type 1 SMA and of risdiplam with nusinersen in Types 2 and 3 SMA

*95% CIs that do not span 1 indicate a statistically significant difference. †SAEs reported in the studies were reflective of the underlying disease. The most frequent SAEs were pneumonia for risdiplam and respiratory distress for nusinersen.
‡CHOP-INTEND and HINE-2 outcomes were compared at a median follow-up of ~9 months.
BSC, best supportive care; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval; ESS, effective sample size; HINE-2, Hammersmith Infant Neurological Examination, Section 2; HR, hazard ratio; IPD, individual patient data; MAIC, matching-adjusted indirect comparison; OR, odds ratio; SAE, serious adverse event; SMA, spinal muscular atrophy; STC, simulated treatment comparison.

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