**Supplementary Table 1. PICOS framework and additional search criteria for the SLR.**

|  |  |
| --- | --- |
| **Category** | **Details** |
| **Population** | * Indication: SMA (Types 1, 2 and 3) * Age groups: Pediatrics and adults * Ethnicity: No restriction |
| **Intervention** | Studies assessing the following pharmacologic interventions in SMA were included:   * Risdiplam (Evrysdi®) * Nusinersen (SPINRAZA®) * Onasemnogene abeparvovec-xioi (AVXS-101; ZOLGENSMA®) * CK-107 * Branaplam (LMI070) * Olesoxime |
| **Comparator** | * Studies comparing interventions of interest either with each other or with placebo or SoC were included * Studies assessing interventions of interest without any comparator group (SA studies) were also included |
| **Outcomes** | * Efficacy: CHOP-INTEND; BSID-III; HINE-2; HFMS; HFMSE; MFM32; achievement of motor milestones; WHO motor milestones; survival rates; ventilation-free survival (time to death/use of permanent ventilation); ventilator use; ULM; RULM; 6MWT; CMAP amplitude; respiratory outcomes; scoliosis; hospitalization * HRQoL: PedsQL * Safety: AEs, discontinuations |
| **Study design** | Inclusion criteria:   * RCTs * Non-RCTs * SA trials * Real-world observational studies (prospective and retrospective)   Exclusion criteria:   * Cross-sectional studies * Case series/case reports   Previously published systematic reviews and meta-analyses were included for the purpose of bibliographic searches to identify relevant primary studies |
| **Language** | * English language only |
| **Country** | * No restriction |
| **Search timeframe** | * Database inception - 1st March 2021 |

6MWT: 6-Minute Walk Test; AE: adverse event; BSID-III: Bayley Scales of Infant and Toddler Development, third edition; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP: compound muscle action potential; HINE-2: Hammersmith Infant Neurological Examination, Section 2; HFMS, Hammersmith Functional Motor Scale; HFMSE: Hammersmith Functional Motor Scale –Expanded; HRQoL: health-related quality of life; MFM32: 32-item Motor Function Measure; PedsQL: Pediatric Quality of Life Inventory; PICOS: Population Intervention Comparison Outcomes and Study; RCT: randomized control trial; RULM: Revised Upper Limb Module; SA: single arm; SLR: systematic literature review; SMA: spinal muscular atrophy; SoC: standard of care; ULM: Upper Limb Module; WHO: World Health Organization.

|  |  |
| --- | --- |
| **Data sources** | |
| **Bibliographic**  **databases** | * Embase® * MEDLINE® * Cochrane CENTRAL |
| **Supplementary sources** | * Conference search (for 2016–2019)   + American Academy of Neurology (AAN)   + European Academy of Neurology (EAN)   + World Muscle Society (WMS)   + European Paediatric Neurology Society (EPNS)   + Cure SMA * Bibliography of recent reviews and primary studies * Grey literature search (for the following HTA bodies)   + National Institute for Health and Care Excellence (NICE)   + Canadian Agency for Drugs and Technologies in Health (CADTH)   + Pharmaceutical Benefits Advisory Committee (PBAC)   + La Haute Autorité de santé (HAS)   + Scottish Medicine Consortium (SMC)   + Institute for Quality and Efficiency in Healthcare (IQWiG)   + Federal Joint Committee (G-BA; Gemeinsamer Bundesausschuss)   + Institute for Clinical and Economic Review (ICER)   + Agency of Medicines and Medical Devices (AEMPS) * Trial registry search   + ClinicalTrials.gov of the US National Institute of Health   + WHO meta-registry: “International Clinical Trials Registry Platform Search Portal” |

**Supplementary Table 2. List of data sources used in the SLR.**

HTA: health technology assessment; SLR: systematic literature review; WHO: World Health Organization.

**Supplementary Table 3. Key deviations from statistical analysis plan and justification**

|  |  |
| --- | --- |
| **Deviation** | **Justification** |
| For the ITC of risdiplam against nusinersen and BSC in Type 1 SMA, follow-up time adaptations were implemented for the analysis of motor milestones (as assessed by the HINE-2) and motor function (as assessed by CHOP-INTEND) outcomes:   * Any assessments occurring in the 6 months preceding the clinical cut-off date (Part 1: February 2019; Part 2: November 2019) were removed. This resulted in a modified FIREFISH dataset with a median time on study of 283 days, which is similar to the median time on study reported for the nusinersen arm in ENDEAR (280 days) | Reduces biases from differences in follow-up time across studies that would favor risdiplam in the analysis of HINE-2 and CHOP-INTEND outcomes. |
| STRIVE-US study data have been published after the protocol was written and were used instead of the START study for the ITC of risdiplam against onasemnogene abeparvovec in Type 1 SMA [29, 67, 68]. | STRIVE-US is a larger multicenter single-arm trial, while START is a small single-center dose-escalation study. |
| Age of symptom onset was not included as a covariate in the STC against onasemnogene abeparvovec. | Age of symptom onset was not imbalanced across studies and was therefore not included to minimize the number of covariates in the models. |

BSC: best supportive care; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2: Hammersmith Infant Neurological Examination, Section 2; ITC: indirect treatment comparison; SMA: spinal muscular atrophy; STC: simulated treatment comparison.

**Supplementary Table 4. Clinical trials excluded from the SLR.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study identifier** | **Intervention** | **Study type** | **Comparator** | **Sample size** | **SMA type** | **Status** | **Primary completion date (study completion date)** | **Reason for exclusion** |
| Finkel 2016 (NCT01839656) [44] | Nusinersen | DC/DE | NA | 20 | Type 1 | Complete | NA | DC/DE study\* |
| Mendell 2017 (NCT02122952) [27, 45] | Onasemnogene abeparvovec | DC/DE | NA | 15 | Type 1 | Complete | NA | DC/DE study\*  Single-center trial |
| STR1VE-AP (NCT03837184) [46] | Onasemnogene abeparvovec | SA | NA | 6 | Type 1 | Ongoing | Apr 1, 2021  (same date) | No data available |
| STR1VE-EU (NCT03461289) [47] | Onasemnogene abeparvovec | SA | NA | 33 | Type 1 | Ongoing | Sept 11, 2020  (same date) | Only early data were available |
| FIH study (NCT02268552) [48] | Branaplam | SA | NA | 39 | Type 1 | Ongoing | Jul 23, 2020  (same date) | Intervention not approved |
| Darras 2014 [50] | Nusinersen | DC/DE | NA | 25 | Types 2/3 | Complete | NA | DC/DE study\* |
| Chiriboga 2016 (NCT01494701/ NCT01780246) [51, 79, 80] | Nusinersen | DC/DE | NA | 28 | Types 2/3 (Amb/NAmb) | Complete | NA | DC/DE study\* |
| CS2 and CS12  (NCT01703988; CS2) [52]; (NCT02052791; CS12) [53] | Nusinersen | DC/DE | NA | 28 | Types 2/3 (Amb/NAmb) | Complete | NA | DC/DE study\* |
| STRONG (NCT03381729) [63] | Onasemnogene abeparvovec | DC/DE | NA | 51 | Type 2 | Ongoing | Jun 1, 2021  (same date) | Formulation not approved  Enrollment for the older cohort (24–60 months) is not complete |
| Bertini 2017 (NCT01302600 [54]) [81] | Olesoxime | RCT | Placebo only | 165 | Types 2/3 (Amb/NAmb) | Complete | NA | Intervention not approved |
| OLEOS (NCT02628743 [62, 82]) | Olesoxime | NA | NA | 131 | Types 2/3 (Amb/NAmb) | Complete | NA | Intervention not approved |
| TOPAZ (NCT03921528) [56] | SRK-015 | RCT | NA | 58 | Types 2/3 (Amb/NAmb) | Complete | Jan, 2021  (April, 2021) | Intervention not approved |
| DEVOTE (NCT04089566) [57] | Nusinersen | RCT | Active (12 mg nusinersen) & sham procedure | 125 | Types 1/2/3 | Ongoing | September 26, 2022 (same date) | Dose not approved |
| EMBRACE (NCT02462759) [58] | Nusinersen + sham procedure; Nusinersen | RCT | Sham procedure | 21 | Types 1/2/3 | Complete | NA | Insufficient data reported |
| SHINE (NCT02594124) [59] | Nusinersen | SA | - | 292 | Types 1/2/3 | Ongoing | August 29, 2023 (same date) | OLE study of ENDEAR and CHERISH (already included for comparison up to 12 months) |
| NCT04042025 [60] | Onasemnogene abeparvovec | DC/DE | - | 308 | Types 1/2/3 | Ongoing | December 31, 2034 (same date) | No data available |
| Rudnicki 2016 [61] | CK-107 | RCT | Placebo only | 70 | Type 2/3/4 (Amb/Namb) | Complete | NA | Intervention not approved |
| JEWELFISH (NCT03032172) [55] | Risdiplam | SA | NA | 174 | Types 1/2/3 (previously treated) | Ongoing | Dec 31, 2021  (Dec 27, 2024) | Patients previously received another therapy for SMA† |

\*As Phase III RCTs and SA studies were available for the interventions of interest, DC/DE studies were excluded. †Patients in JEWELFISH had previous enrollment in Study BP29420 (MOONFISH) with the splicing modifier RO6885247 or previous treatment with nusinersen, olesoxime or onasemnogene abeparvovec.

Amb: ambulatory; DC: dose comparison; DE: dose escalation; NA: not applicable; NAmb: non-ambulatory; NCT: national clinical trial; RCT: randomized controlled trial; SA, single arm; SLR: systematic literature review; SMA, spinal muscular atrophy.

**Supplementary Table 5. Availability of endpoints of interest in Type 1 SMA.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome** | **Type of outcome** | **Risdiplam**  **FIREFISH** | **Nusinersen**  **ENDEAR\*** | **Onasemnogene abeparvovec STR1VE-US** |
| **Motor milestone endpoints** | | | | |
| Percentage of infants sitting without support for ≥30 seconds, as classified by Item 26 of BSID-III | Binary | Yes | No | Yes† |
| Percentage of infants with head control (classified by BSID-III) | Binary | Yes | No | Yes‡ |
| Percentage of infants that can roll over (classified by BSID-III) | Binary | Yes | No | Yes‡ |
| Percentage of infants that can stand with assistance (classified by BSID-III) | Binary | Yes | No | Yes‡ |
| Percentage of infants that achieve full head control (classified by HINE-2) | Binary | Yes | Yes | No |
| Percentage of infants sitting without support (classified by HINE-2) | Binary | Yes | Yes | No |
| Percentage of infants sitting with or without support (classified by HINE-2) | Binary | Yes | Yes§ | No |
| Percentage of infants rolling (classified by HINE-2) | Binary | Yes | Yes | No |
| Percentage of infants standing (classified by HINE-2) | Binary | Yes | Yes | No |
| Motor milestone response according to HINE-2 | Binary | Yes | Yes | No |
| **Motor function endpoints** | | | | |
| Percentage of infants who achieve a CHOP-INTEND score ≥40 | Binary | Yes | Yes | Yes† |
| Percentage of infants with a ≥4-point improvement in CHOP-INTEND score from baseline | Binary | Yes | Yes | Yes† |
| **Survival endpoints** | | | | |
| EFS (death or permanent ventilation) | Time to event | Yes|| | Yes||,\*\* | Yes¶,\*\* |
| OS | Time to event | Yes | Yes\*\* | No |
| **Safety endpoints** | | | | |
| Proportion of patients with any SAE | Binary | Yes | Yes | Yes |

\*At latest available data cut of 6–13 months for ENDEAR. †At 18 months of age visit for STR1VE-US and at 12 months from baseline visit for FIREFISH. ‡By the 18 months of age visit for STR1VE-US and at 12 months from baseline visit for FIREFISH. §Only available interim efficacy dataset (n=51). Analysis of this outcome assumes that the baseline characteristics for the interim population are the same as for the ITT population (n=80). ||EFS was defined as the absence of death or permanent ventilation, defined as either tracheostomy or ≥16 hours ventilation per day continuously for >21 days in the absence of an acute reversible event. ¶EFS was defined as the absence of death or permanent ventilation, as a tracheostomy or the requirement of ≥16 hours of respiratory assistance per day for ≥14 consecutive days, in the absence of an acute reversible illness, excluding perioperative ventilation. \*\*Published Kaplan–Meier curves were digitized.

BSID-III: Bayley Scales of Infant and Toddler Development, third edition; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EFS: event-free survival; HINE-2: Hammersmith Infant Neurological Examination, Section 2; ITT: intent to treat; OS: overall survival; SAE: serious adverse event.**Supplementary Table 6. Baseline characteristics of FIREFISH pre- and post‑matching with STR1VE‑US (MAIC analysis).**

|  |  |  |  |
| --- | --- | --- | --- |
| **Baseline characteristic** | **Risdiplam**  **pre-matching:**  **(Pooled FIREFISH)** | **Risdiplam**  **post-matching:**  **(Pooled FIREFISH)** | **Onasemnogene abeparvovec**  **(STR1VE-US)** |
| Sample size (ESS) | 58 | 58 (2.1) | 22 |
| **Mean age at first dose, days** | **163** | **141** | **114** |
| Gender (Female, %) | 57 | 100 | 55 |
| **Mean age at symptom onset, days** | **51** | **73** | **60** |
| Mean age at diagnosis, days | 89 | 104 | 56 |
| **Mean score on CHOP-INTEND** | **22.47** | **31.01** | **32.00** |
| Patients with ventilatory support, % | 29 | 0 | 0 |

Matching factors are denoted in bold. Disease duration was not reported in the STR1VE-US trial, and therefore age at symptom onset was used as an alternative matching factor.

CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ESS: effective sample size; MAIC: matching-adjusted indirect comparison.

**Supplementary Table 7. STC model fit statistics of FIREFISH versus STR1VE-US.**

|  |  |  |
| --- | --- | --- |
| **Endpoint** | **Royston’s R2 [83]** | **McFadden's Pseudo-R2 [84]** |
| Ventilation-free survival | 0.042 | - |
| Sitting without support over 30 seconds | - | 0.110 |
| Head control for 3 seconds | - | 0.081 |
| Rolling back to sides | - | 0.069 |
| Standing with assistance | - | 0.194 |
| CHOP-INTEND score improvement ≥4 points | - | 0.128 |
| CHOP-INTEND score achievement ≥40 points | - | 0.189 |
| Any SAE | - | 0.010 |

Pseudo-R2 values between 0.2 and 0.4 are considered to provide an excellent fit [84].

CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; MEV: Measure of explained variation; SAE: serious adverse event; STC: simulated treatment comparison.

**Supplementary Table 8. BSID-III covariate estimates (STC FIREFISH vs STR1VE-US).**

|  |  |  |
| --- | --- | --- |
| **Endpoint** | **OR of 1-month increase in age at first dose (95% CI)** | **OR of 1-point increase in baseline CHOP-INTEND score (95% CI)** |
| Sitting without support over 30 seconds (Item 26) | 0.642  (0.282–1.005) | 1.118  (1.001–1.405) |
| Head control for 3 seconds  (Item 4) | 0.951  (0.572–1.523) | 1.112  (1.028–1.247) |
| Rolling back to sides  (Item 20) | 0.706  (0.432–1.043) | 1.076  (0.987–1.218) |
| Standing with assistance  (Item 33) | 0.878  (0.000–1.887) | 1.270  (1.000–5.46E+26) |

BSID-III: Bayley Scales of Infant and Toddler Development, third edition; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI: confidence interval; OR: odds ratio; STC: simulated treatment comparison.

**Supplementary Table 9. CHOP-INTEND covariate estimates (STC FIREFISH vs STR1VE-US).**

|  |  |  |
| --- | --- | --- |
| **Endpoint** | **OR of 1-month increase in age at first dose (95% CI)** | **OR of 1-point increase in baseline CHOP-INTEND score (95% CI)** |
| CHOP-INTEND score improvement ≥4 points | 0.575  (0.000–1.089) | 1.123  (0.913–1.737) |
| CHOP-INTEND score achievement ≥40 points | 0.619  (0.288–0.977) | 1.176  (1.077–1.412) |

CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI: confidence interval; OR: odds ratio; STC: simulated treatment comparison.

**Supplementary Table 10. Availability of endpoints of interest in Types 2 and 3 SMA.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Type of outcome** | **Risdiplam**  **SUNFISH\*** | **Nusinersen**  **CHERISH** |
| **Efficacy endpoints** | | | |
| HFMSE, change from baseline | Continuous | Yes | Yes† |
| HFMSE, OR/proportion of patients showing improvement ≥3 points‡ | Binary | Yes | Yes§ |
| RULM, change from baseline | Continuous | Yes | Yes† |
| RULM, OR/proportion of patients showing improvement ≥2 points|| | Binary | Yes | Yes¶ |
| **Safety endpoints** | | | |
| OR/proportion of patients with any SAE | Binary | Yes | Yes |

\*At 12 months from baseline. †12-month data derived from digitized charts of imputed data. ‡A change in the HFMSE score of 2–3 points is considered to be clinically meaningful [81, 82]. §At Month 15 (adjusted OR). ||A response on the RULM is defined as an increase of at least 2 points [20]. ¶Proportion at Month 12 derived from digitized charts of non-imputed data. Analysis of this outcome assumes that the baseline characteristics for the “completer” population are the same as for the ITT population.

HFMSE: Hammersmith Functional Motor Scale – Expanded; ITT: intent-to-treat; OR: odds ratio; RULM: Revised Upper Limb Module; SAE: serious adverse event; SMA: spinal muscular atrophy.

**Supplementary Table 11. Analyses of HFMSE outcomes in SUNFISH and CHERISH at Month 12.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome** | **Comparator**  **(STUDY)** | **MAIC in SUNFISH subset\*** | | | | | **Bucher adjusted indirect comparison in SUNFISH subset\*** | | | | |
| **ESS** | **Change from baseline** | | **Difference against control** | **Mean difference against comparator**  **(95% CI)** | **N** | **Change from baseline** | | **Difference against control** | **Mean difference against comparator (95% CI)** |
| **Intervention** | **Control** | **Intervention** | **Control** |
| HFMSE change from baseline | Risdiplam  (SUNFISH subset\*) | 43.4 | 2.2 | 2.1 | 0.1 | Not applicable† | 68 | 1.9 | 1.7 | 0.3 | Not applicable† |
| Nusinersen  (CHERISH) | 126 | 3.3 | 0.2 | 3.1 | Reference | 126 | 3.3 | 0.2 | 3.1 | Reference |
| **Outcome** | **Comparator**  **(STUDY)** | **ESS** | **Proportion responders** | | **OR against control** | **OR against comparator**  **(95% CI)** | **N** | **Proportion responders** | | **OR against control** | **OR (95% CI) against comparator** |
| **Intervention** | **Control** | **Intervention** | **Control** |
| HFMSE responders‡ | Risdiplam  (SUNFISH subset\*) | 43.4 | 66% | 49% | 2.2 | Not applicable† | 68 | 58% | 48% | 1.5 | Not applicable† |
| Nusinersen  (CHERISH)§ | 126 | 57% | 26% | 5.6 | Reference | 126 | 57% | 26% | 5.6 | Reference |

\*Defined as patients from SUNFISH Part 2 who were 2–9 years of age at screening, with HFMSE total score ≥10 at baseline and without severe scoliosis. †This is an anchored indirect comparison; relative effects cannot be computed due to lack of match in control arms. ‡A change from baseline in HFMSE total score of ≥3 points. §At 15 months.

AIC: adjusted indirect comparison; CI: confidence interval; ESS: effective sample size; HFMSE: Hammersmith Functional Motor Scale – Expanded; MAIC: matching-adjusted indirect comparison; OR: odds ratio.