Evidence Base for Joint Clinical Assessment: A Clinical Systematic Literature Review of OAV101 IT and Comparators for Spinal Muscular Atrophy

Riley, N[1]; McCarthy G[2]; Drudge, C[3]; Kane, S[3]; Esguerra, J[3]; Kulinski, S[3]; Vo, P[4] • [1]Novartis, Basel, Switzerland; [2]Novartis, Dublin, Ireland; [3]EVERSANA®, Burlington, Ontario, Canada; [4]EVERSANA®, Basel, Switzerland

SA2

Scan QR code to access the poster:

INTRODUCTION

- Spinal muscular atrophy (SMA) is a rare genetic disorder leading to progressive muscle weakness and atrophy caused by survival of motor neuron (SMN) protein depletion resulting from the deletion of or mutations in the SMN1 gene.[1]
- Survival of motor neuron 2 (SNM2), a nearly identical gene to SMN1, thus serves as the only source of SMN protein for motor neurons.[2] As such, the severity of SMA is influenced by SMN2 copy number.
  - Generally, the fewer SMN2 copies, the more severe the symptoms.[1]
- Historically, SMA was classified by type and based on age of onset, motor abilities, and respiratory involvement.[1]
- Previously prognostic, this classification is less treatment-relevant in the era of disease-modifying therapies (DMTs), with recent clinical guidelines and publications supporting a shift toward motor function-based classification (**Table 1**).[3,4]

Table 1. SMA Classification Based on Milestones Achieved, SMN2 Copy Number, and Clinical Presentation

Motor Milestones Achieved	SMN2 Copy #	Clinical Presentation
No Sitting	1-3	• "Floppy infant" • Difficulties in breathing and coughing • Difficulties in swallowing • Fasciculations of tongue
Sitting, No Walking	2-3	• Delay in motor development • Weakness • Difficulties in coughing • Joint contractures • Scoliosis
Independent Walking	3+	• Variable degree of weakness • Joint contractures • Scoliosis • Loss of ambulation

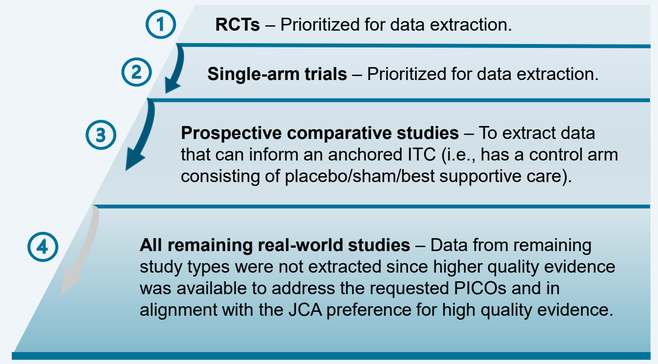
Adapted from Schorling et al. 2020[3]

- Recent advancements in DMTs and newborn screening have significantly improved clinical outcomes. These DMTs include nusinersen, risdiplam, and intravenous onasemnogene abeparvovec (OAV101 IV).[2,4]
- Intrathecal onasemnogene abeparvovec (OAV101 IT) is a newly developed single-dose gene replacement therapy that addresses the genetic root cause of SMA.[5,6]
- A systematic literature review (SLR) was conducted to understand the clinical evidence base for approved and upcoming therapies for patients with SMA.
- This SLR directly informed indirect treatment comparisons (ITCs) to support health technology assessments (HTAs), including the European Union Joint Clinical Assessment (JCA) for OAV101 IT (submitted on December 17, 2025).

METHODS

- Relevant records, published from January 14, 2014, to September 17, 2025, were searched via Ovid in MEDLINE, Embase, Cochrane Controlled Register of Trials, and Cochrane Database of Systematic Reviews.
- Grey literature searches were conducted including trial registries, conference abstracts and posters, and HTA reports.
- Broad inclusion criteria were applied to capture all relevant DMTs, and clinical outcomes anticipated to be relevant for the 30 European Economic Area Member States, in anticipation of the JCA.
- Data extraction followed an evidence hierarchy for each relevant population, intervention, comparator, and outcome (PICO) requested per the JCA scope, prioritizing randomized controlled trials (RCTs) as the highest level of evidence (**Figure 2**).
- Study quality was assessed per JCA guidelines.[7]
- This SLR was registered with PROSPERO (registration number: CRD42024627219).

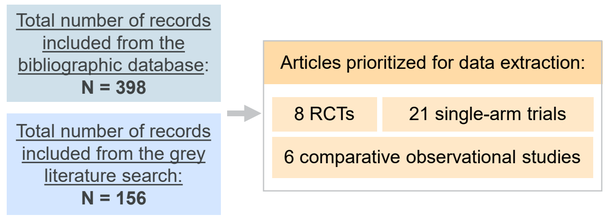
Figure 2. Systematic Approach to Data Extraction



RESULTS

- Utilizing the evidence hierarchy (**Figure 2**), a total of **8 RCTs** and **21 single arm trials** were prioritized for data extraction (**Figure 3**).
  - Included RCTs were phase II trials, phase II/III trials or phase III trials, with most comparing nusinersen to sham control.
  - Most included single-arm trials assessed OAV101 IV (7 studies), followed by nusinersen (9 studies), risdiplam (3 studies), and other emerging therapies (e.g., OAV101 IT, 3 studies).
- No head-to-head RCTs were identified for SMA DMTs including nusinersen, risdiplam, or OAV101 (IV or IT).
- Most clinical trials involved SMA DMT-naïve patients while few involved SMA DMT-experienced populations.
- Of the 324 included observational studies, **6 were prioritized** for data extraction due to their comparative study design and potential usability for ITCs (**Figure 3**).

Figure 3. Identification of Studies via Bibliographic Database Searches and Grey Literature Searches



- All prioritized observational studies assessed nusinersen compared to standard of care (SoC), palliative care, or against a historical untreated control arm.
- Key efficacy outcomes identified in this SLR included motor function, respiratory function, survival, and safety.
  - Hammersmith Functional Motor Scale–Expanded (HFMSE) and Revised Upper Limb Module (RULM) were the most reported motor function scales used throughout (**Tables 2** & **3**).

Table 2. Examples of Key Efficacy Outcomes Reported by Select RCTs and Single-arm Trials

Study type	Author, Year	Intervention	Measure	Timepoint	Value
Motor function					
RCT *SUNFISH part 2*	Oskoui, 2023[8]	Risdiplam	Mean CFB in HFMSE score	12 months	1.20
		Placebo			0.00
Single-arm trial *SMART*	McMillan, 2025[9]	OAV101 IV	Median CFB in HFMSE score	12 months	4.00
RCT *SUNFISH part 2*	Oskoui, 2023[8]	Risdiplam	Mean CFB in RULM score	12 months	1.90
		Placebo			0.90
Single-arm trial *SMART*	As per Clinicaltrials.gov[10]	OAV101 IV		12 months	2.00
Respiratory function					
RCT *SUNFISH part 2*	Oskoui, 2023[8]	Risdiplam	Mean CFB in FVC (L)	12 months	-5.20
		Placebo			-3.40
Single-arm trial *RAINBOWFISH*	Finkel, 2025[11]	Risdiplam	% patients requiring PAV	24 months	88.0%
Safety					
RCT *SUNFISH part 2*	Oskoui, 2023[8]	Risdiplam	% patients experiencing any AE	24 months	91.7%
		Placebo			80.0%
Single-arm trial *SMART*	McMillan, 2025[9]	OAV101 IV		12 months	100%

- Included RCTs and single-arms trials were generally of good or fair quality as per study quality assessments.

Table 3: Examples of Key Efficacy Outcomes Reported by Select Comparative Observational Studies

Author, Year	Intervention	Measure	Timepoint	Value
Motor function				
Pandey, 2025[12]	Nusinersen	Mean CFB in HFMSE score	12 months	39.9
	SoC			29.9
Vasquez-Costa, 2022[13]	Nusinersen		6 months	2.43
	SoC			0.160
	Nusinersen	Mean CFB in RULM score	6 months	1.67
	SoC			-0.580
Respiratory function				
Gomez-Garcia de la Banda, 2021[14]	Nusinersen	Mean CFB in FVC (L)	12 months	66.0
	Historical control		14 months	45.0
Safety				
Pandey, 2025[12]	Nusinersen	% patients experiencing any AE	12 months	NR
	SoC			NR
Vasquez-Costa, 2022[13]	Nusinersen		≥6 months	77.0%
	SoC			NR
Pandey, 2025[12]	Nusinersen	% discontinuations due to an AE	12 months	0.00%
	SoC			0.00%
Vasquez-Costa, 2022[13]	Nusinersen		≥6 months	5.00%
	SoC			NR

- Overall, observational studies presented limited clinical evidence and had critical risk-of-bias.

STRENGTHS & LIMITATIONS

- **Strengths**: This SLR adhered to the best practices set forth by the HTA coordination group. The detailed search strategy, broad inclusion criteria, and systematic approach to data extraction underscores the robust nature of this review.
- **Limitations**: The systematic approach to data extraction may have excluded data from lower quality evidence sources (e.g., case reports); however, the impact of this is expected to be minor since it allowed prioritization of data extraction from high-quality evidence sources, in alignment with JCA guidelines.

CONCLUSIONS

Studies identified in this SLR comprised a foundational high-quality evidence base resulting from the evidence hierarchy applied.

Given the lack of head-to-head SMA trials identified in this SLR, ITCs were required. Evidence from the SLR was therefore used to evaluate the feasibility of conducting ITCs to generate comparative effectiveness data for OAV101 IT versus relevant SMA DMTs in support of the JCA submission.

ABBREVIATIONS: AE = adverse event; CFB = change from baseline; DMT = disease modifying therapy; FVC = forced vital capacity; HFMSE = Hammersmith Functional Motor Scale–Expanded; HTA = health technology assessments; ITC = indirect treatment comparison; IV = intravenous; JCA = Joint Clinical Assessment; L = liter; NR = not reported; OAV101 IT = onasemnogene abeparvovec; OAV101 IV = intravenous onasemnogene abeparvovec; PAV = permanent assisted ventilation; PICO = population, intervention, comparator, and outcome; RCT = randomized controlled trial; RULM = Revised Upper Limb Module; SoC = standard of care; SLR = systematic literature review; SMA = spinal muscular atrophy; SMN = survival of motor neuron; SMN2 = survival of motor neuron 2.

REFERENCES: 1. Kostera-Pruszczyk A, et al. (2021) *Neurol Neurochir Pol* 55 (5). **2.** Nishio H, et al. (2023) *Int J Mol Sci* 24 (15). **3.** Schorling et al. (2020) *J Neurol Diseases*, 7(1), 1-13. **4.** Schroth M, et al. (2024) *Neurol Clin Pract* 14 (4). **5.** Cure SMA (Web Page) SMA Drug Pipeline. Updated Available online at: https://www.curesma.org/sma-drug-pipeline/. Accessed: March 8, 2025. **6.** Finkel RS, et al. (2023) *J Neuromuscul Dis* 10 (3). **7.** HTA CG (2024). Guidance on filling in the joint clinical assessment (JCA) dossier template – Medicinal products. Available online at: https://health.ec.europa.eu/publications/guidance-filling-joint-clinical-assessment-jca-dossier-template-medicinal-products_en. Accessed: January 21, 2025. **8.** Oskoui M et al. (2023) *J Neurol* 270 (5). **9.** McMillan HJ et al. (2025) *J Neurol* 104 (2). **10.** ClinicalTrials.gov (2024). Safety and Efficacy of Intravenous OAV101 (AVXS-101) in Pediatric Patients With Spinal Muscular Atrophy (SMA) (SMART). Available online at: https://clinicaltrials.gov/study/NCT04851873. **11.** Finkel RS et al. (2025) *N Engl J Med* 393 (7). **12.** Pandey A, et al. (2025) *Eur J Paediatr Neurol* 54(12). **13.** Vázquez-Costa JF, et al. (2022) *Eur J Neurol* 29 (11). **14.** Gómez-García de la Banda M, et al. (2021) *Pediatr Pulmonol* 56 (1).

DISCLOSURES: This study was funded by Novartis. C Drudge, S Kane, J Esguerra, S Kulinski & P Vo are employees of EVERSANA. EVERSANA receives consultancy fees from pharmaceutical and medical device companies, including Novartis. N Riley & G McCarthy are employees and shareholders of Novartis.

ACKNOWLEDGMENTS: We thank Maria Cavaco of EVERSANA for her support in the development of this poster. Graphic design was provided by Elizabeth Willis of EVERSANA.

PRESENTED AT 2026 ISPOR US CONFERENCE – MAY 17 to 20, 2026 – PHILADELPHIA, PA, USA