

REVIEW ARTICLE OPEN



Gene-based therapy for the treatment of spinal muscular atrophy types 1 and 2 : a systematic review and meta-analysis

Bunchai Chongmelaxme¹, Varalee Yodsurang^{2,3}✉, Ponlawat Vichayachaipat², Thanate Srimatimanon² and Oranee Sanmaneechai^{4,5}✉

© The Author(s) 2024

Despite numerous studies identifying the advantages of therapies for spinal muscular atrophy (SMA), healthcare professionals encounter obstacles in determining the most effective treatment. This study aimed to investigate the effects of gene-based therapy for SMA. A systematic search was conducted from inception to May 2024 across databases, and all studies assessing the effects of gene-based therapy on patients with SMA types 1 and 2 were included. The outcomes measured were survival, the need for ventilatory support, improvements in motor function, and the occurrence of adverse drug reactions. Meta-analyses were performed using a random-effects model. A total of 57 studies ($n = 3418$) were included, and the meta-analyses revealed that onasemnogene abeparvovec showed the highest survival rate (95% [95% CI: 88, 100]), followed by risdiplam (86% [95% CI: 76, 94]) and nusinersen (60% [95% CI: 50, 70]). The number of patients needing ventilatory support was reduced after treatment with onasemnogene abeparvovec (risk ratio = 0.10 [95% CI: 0.02, 0.53]). Onasemnogene abeparvovec and risdiplam had similar proportions of patients with improvements in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders score of ≥ 4 points (92% [95% CI: 62, 100] vs 90% [95% CI: 77, 97]). In contrast, nusinersen had the smallest improvement (74% [95% CI: 66, 81]). The most frequently observed adverse drug reactions were headaches, vomiting, and gastrointestinal disorders. Gene-based therapy benefits patient survival and improves motor function. Onasemnogene abeparvovec and risdiplam appear highly effective, whereas nusinersen exhibits moderate effectiveness.

Gene Therapy (2024) 32:301–330; <https://doi.org/10.1038/s41434-024-00503-8>

INTRODUCTION

Spinal muscular atrophy (SMA) is a genetic anterior horn cell disorder triggered by homozygous or heterozygous deletions, accompanied by point mutations in the second allele of the survival motor neuron (SMN) 1 gene situated on chromosome 5q11.2–13.3 [1]. A deficiency in SMN protein leads to irreversible degeneration of motor neurons and subsequent muscle weakness. SMN2, an SMN1 homolog, generates low levels of functional SMN protein, which can partially compensate for the loss of SMN1. However, its copy number inversely correlates with the clinical severity of the disease in patients. Symptoms of SMA are characterized by weakness and atrophy in skeletal muscles used for movement. Disease onset varies from infancy to adulthood, with muscle weakness generally intensifying with age and potentially leading to paralysis in the most severe cases [2]. The International SMA Consortium categorizes SMA into five types, 0–4, based on the age of onset and highest achieved motor function, with severity progressively decreasing from type 0 to type 4 [2]. The treatment regimen for SMA includes specific therapy for the disease and supportive multidisciplinary treatment to prevent and manage complications. Gene-based therapies such

as nusinersen, onasemnogene abeparvovec, and risdiplam have been investigated and approved for SMA treatment [3–5].

A systematic review and meta-analysis of randomized controlled trials published in 2022 by Abbas et al. [6] assessed the beneficial and adverse effects of nusinersen. The findings demonstrated a significant risk difference in motor milestone response (0.51, 95% CI: 0.39, 0.62) and improvement in the Hammersmith Infant Neurological Examination–Part 2 (HINE-2) score (risk difference = 0.26, 95% CI: 0.12, 0.40). A decrease in severe adverse events was observed (Risk ratio [RR] = 0.72, 95% CI: 0.57, 0.92). However, nonsignificant results were found for any adverse effects (RR = 0.93, 95% CI: 0.97, 1.01) and serious adverse effects (RR = 0.81, 95% CI: 0.60, 1.07). A recent systematic review and meta-analysis by Pascual-Morena et al. [7] estimated the effects of onasemnogene abeparvovec on motor function in patients with SMA type 1. The results showed that patients improved their the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores by 11.06 points (95% CI: 9.47, 12.65) at 3 months and by 14.14 points (95% CI: 12.42, 15.86) at 6 months post infusion. The proportions of patients who achieved scores >40 , >50 , and $>58/60$ points were

¹Social and Administrative Pharmacy Department, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand. ²Department of Pharmacology and Physiology, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand. ³Preclinical Toxicity and Efficacy, Assessment of Medicines and Chemicals Research Unit, Chulalongkorn University, Bangkok 10330, Thailand. ⁴Division of Neurology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. ⁵Center of Research Excellent in Neuromuscular disease, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

✉email: varalee.y@pharm.chula.ac.th; oranee141@gmail.com

Received: 24 October 2023 Revised: 24 October 2024 Accepted: 8 November 2024

Published online: 27 November 2024

87%, 51%, and 12%, respectively, and the proportion increased to 100% among presymptomatic patients with higher baseline scores.

Although the benefits of gene-based therapy for SMA have been demonstrated in various studies, healthcare professionals and policymakers still face numerous challenges in identifying the most effective treatment for individuals. The effects of gene-based therapy had been demonstrated in the abovementioned systematic reviews and meta-analyses. However, none of the studies provided comparative analyses of such treatments, on top of several new studies being published after the latest review. This presents a significant barrier affecting the integration of new medicine into clinical practice. This study aimed to determine the effects of gene-based therapy on patient survival, the need for ventilatory support, motor function improvement, and the incidence of adverse drug reactions (ADRs) in SMA types 1 and 2.

METHODS

Search strategy and selection criteria

A literature search was conducted from inception to May 2024 across the following databases: PubMed, CENTRAL, EMBASE, ClinicalTrials.gov, and Scopus. All search terms are detailed in Appendix: Table S1. Additionally, the bibliographies of retrieved articles were reviewed to identify relevant studies not indexed in the databases mentioned above. Initially, titles and abstracts were screened to identify potential studies. Clinical trials, cohort studies, and case-control studies that reported the effects of gene-based therapy on patients with SMA types 1 and 2 were selected. The outcomes of interest were patient survival, the number of patients requiring ventilatory support, motor function improvement, and ADRs. Only studies published in English were included. The meta-analysis incorporated studies featuring symptomatic SMA patients receiving one type of treatment at a time (or naive) and having similar outcome measures and definitions. Full texts were assessed by TS, PV, VY, and BC, with disagreements among the investigators resolved through discussion with OS. Our study protocol was registered in the PROSPERO database (CRD42021284231).

Definition of outcome measures

Patient or event-free survival was defined as the absence of death or permanent ventilation. Permanent ventilation was defined as tracheostomy or the requirement of ≥ 16 h non-invasive ventilatory support for ≥ 14 [3, 8–11] or 21 [4, 5, 12, 13] consecutive days in the absence of acute reversible illness. The motor function measures for SMA type 1 were CHOP-INTEND and HINE-2, while the Motor Function Measure scale, HFMSE, and the Revised Upper Limb Module (RULM) scale were used for SMA type 2. Motor function improvements of ≥ 4 points in CHOP-INTEND are considered clinically meaningful for infants with SMA, based on evidence showing this level of change reflects significant motor function gains [4, 14, 15].

Data extraction and study quality assessment

Data extraction was undertaken by TS, PV, VY, and BC using a standardized form. This form included the authors' names, year of publication, country of origin, study design, participant characteristics, interventions, outcome measurements, and study durations. The methodological quality of all eligible studies was assessed by TS and BC using the Methodological Index for Non-Randomized Studies (MINORS) tool [16] for non-randomized studies, and the Cochrane risk of bias tool for randomized-controlled trials (RCTs) [17]. Non-randomized studies were categorized as good (15–16 points), moderate (9–14 points), or poor (≤ 8 points) qualities based on the scoring for non-comparative studies [16, 18].

Data analysis

Only studies that provided data relevant to the effects of gene-based therapy for SMA types 1 and 2 were allowed to be grouped based on individual outcomes, and subsequently performed a meta-analysis. A meta-analysis was performed to provide pooled estimates and 95% CIs using the score statistic and the exact binomial method incorporating the Freeman–Turkey double arcsine transformation of proportions among the studies reporting binary outcomes (patient survival, and the number of patients improved their motor function) [19]. Only for the number of patients requiring ventilatory support, the proportions of patients requiring ventilatory support at baseline and at the conclusion were recorded. From these data, the risk ratio was calculated and pooled across the studies. In addition, the mean difference (MD) was determined by comparing baseline and final scores of motor function improvement among studies reporting continuous data and pooled across the studies. DerSimonian and Laird random-effects model's meta-analyses were utilized for all analyses to account for variability within and between studies. Heterogeneity among studies was assessed using I^2 and chi-square (χ^2) statistical tests [20]. A subgroup meta-analysis was also conducted to investigate the effects of gene-based therapy on patients with SMA type 1. Publication bias was assessed by using funnel plots and statistical Egger's test [21]. Analyses were performed using STATA Statistical Software, release 15.0 (Stata Corp LLC, College Station, TX, USA).

RESULTS

The initial search returned 12023 articles, from which 1442 duplicates were removed. The remaining articles underwent title and abstract screening, resulting in 9651 articles being excluded due to their irrelevance to SMA or mismatched study designs. A total of 930 articles were then assessed for eligibility, of which 57 were included in the systematic review, and 39 were incorporated into the meta-analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is illustrated in Fig. 1, while the initial search results are presented in Appendix: Table S1.

Study characteristics

Out of the 57 studies, 37 were conducted in high-income countries [3, 9, 22–56], seven were undertaken in upper-middle-income countries [57–63], and another study was conducted in a low- and middle-income country [64]. Twelve studies [4, 5, 8, 10–13, 65–69] spanned multiple countries in their study settings. In total, the studies encompassed 3336 patients treated with nusinersen (39 studies: $n = 2592$) [4, 8, 12, 22–24, 26, 27, 29–34, 37, 38, 41, 43–51, 55–62, 64–66, 68, 69], onasemnogene abeparvovec (11 studies: $n = 276$) [3, 9–11, 28, 39, 40, 53, 54, 63, 67], and risdiplam (7 studies: $n = 468$) [5, 13, 25, 35, 36, 42, 52]. Most patients were naive to gene-based therapy (46 studies: $n = 2769$) [3–5, 8–13, 22–24, 26, 27, 29–34, 36–38, 41, 43–51, 55–62, 64–66, 68, 69], while the remainder had previously undergone other treatments (11 studies: $n = 567$) [25, 28, 35, 39, 40, 42, 52–54, 63, 67]. SMA type 1 was the most frequently reported (24 studies: $n = 790$) [3–5, 8–13, 27, 30, 33, 37–41, 44, 51, 55, 60, 64, 66, 68]. Other categories included a combination of types 1 and 2 (13 studies: $n = 628$) [22, 25, 28, 31, 32, 42, 47, 49, 52–54, 63, 67], type 1 and 3 (1 study: $n = 17$) [35] types 2 and 3 (4 studies: $n = 119$) [23, 24, 36, 61], types 1, 2, and 3 (13 studies: $n = 1023$) [26, 29, 34, 43, 45, 46, 50, 56–59, 62, 65], and type 1, 2, 3, and 4 (2 studies: $n = 759$) [48, 69]. Treatment durations ranged from 1 day [48] to 5.7 years [12] (Table 1). Key patient characteristics are presented in Appendix: Table S2.

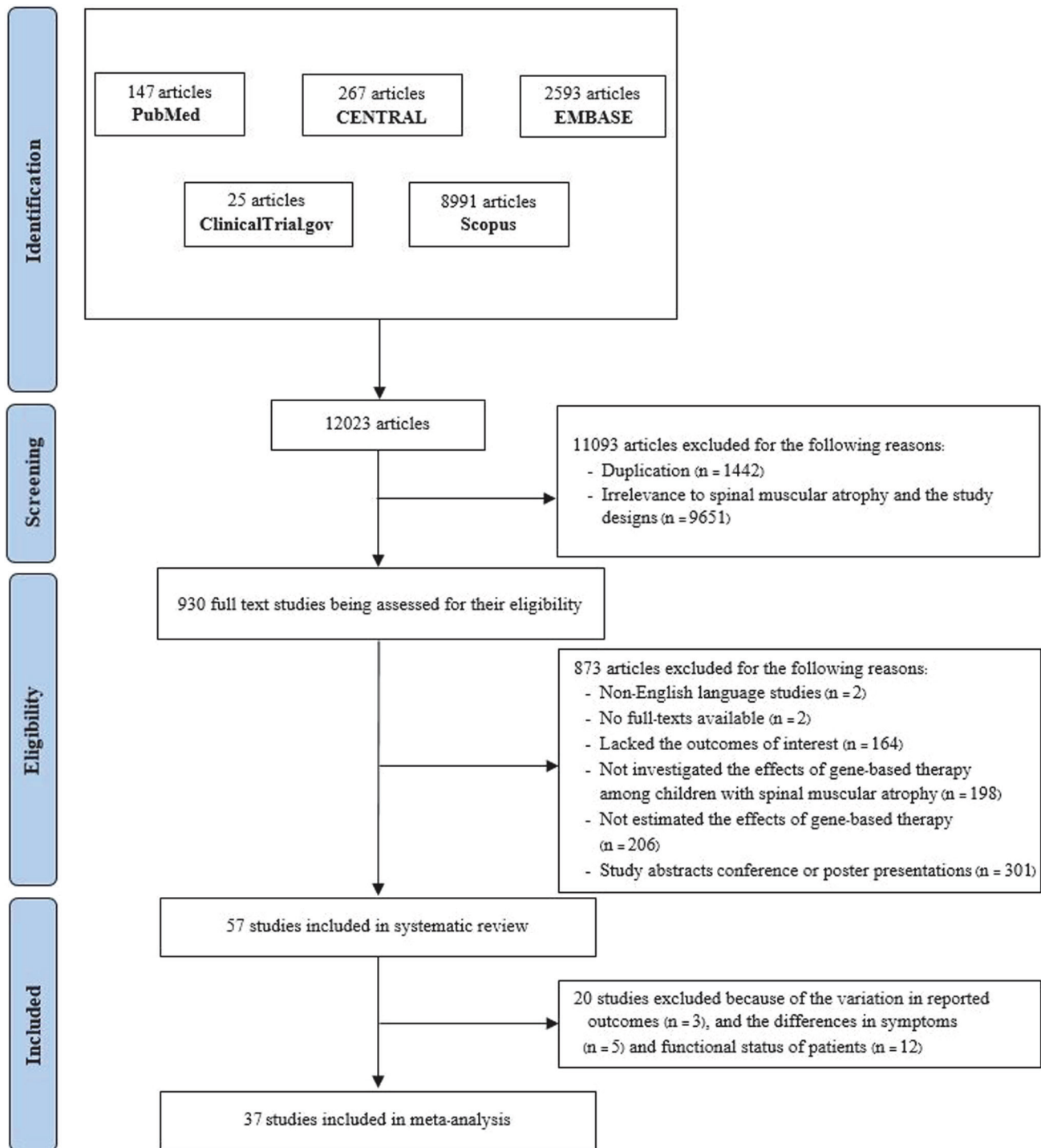


Fig. 1 PRISMA flow diagram illustrating the study selection process. n number of studies.

Effect of gene-based therapy

Among the 57 studies, 20 were excluded from the meta-analysis due to variations in participant characteristics [11, 12, 24, 25, 28, 35, 39, 40, 43, 52–54, 58, 63, 67], gene-based interventions, [33, 58] and outcome assessments [42, 57, 68]. Specifically, the studies by Crawford et al. [12] D'Silva et al. [28] Kotulska et al. [43] Strauss et al. [11] and Weiß et al. [67] were conducted among both asymptomatic and symptomatic patients, while the studies by Ali et al. [54] Artemyeva et al. [63] Belančić et al. [35] Bitetti et al. [39]

Cornell et al. [52] D'Silva et al. [28] Favia et al. [40] Kwon et al. [25] Tokatly Latzer et al. [53] and Weiß et al. [67] included patients previously treated with gene-based therapy. The gene-based interventions applied in the studies by Hully et al. [33] and Mirea et al. [58] combined nusinersen with physical therapy and nusinersen with palliative care, respectively. Last, the definition of motor improvement in the study by Aragon-Gawinska et al. [68] and the reported outcome in the study by Hahn et al. [42] differed from the others (Appendix: Table S3).

Table 1. Characteristics of the included studies.

First author (y)	Country	Setting	Study design	Patient characteristics		Sample size*	Gene-based therapy	Duration (mo.)
				Types of SMA	Age at first dose* (mo.)			
Acsadi (2021) [22]	US	Multicenter	RCT	1, 2	- Intervention = 16.7 (7.3, 48.6) - Control = 18.5 (15.3, 53.3)	14 vs 7	Nusinersen	24
Ali (2021) [54]	Qatar	Hamad Medical Corporation	Cohort	1, 2	18 (4, 23)	9 - Type 1 = 7 - Type 2 = 2	Onasemnogene Abepravovec *Previous treatment with nusinersen (n = 7)	10
Aragon-Gawinska (2018) [30]	France	Multicenter	Prospective cohort	1	21.3 (8.3, 113.1)	33	Nusinersen	6
Aragon-Gawinska (2020) [68]	Belgium and France	Multicenter	Cohort	1	- Type 1 "sitters" = 21.9 (2.7, 52.4) - Type 1 "non-sitters" = 23.3 (3.3, 102.8)	47 - Type 1 "sitters" = 15 - Type 1 "non-sitters" = 32	Nusinersen	14
Arslan (2023) [61]	Turkey	Hacettepe University	Cohort	2, 3	- Type 2 = 39 (25, 50) yr. - Type 3 "sitters" = 33.5 (20, 60) yr. - Type 3 "walkers" = 32 (21, 56) yr.	32 - Type 2 = 6 - Type 3 "sitters" = 16 - Type 3 "walkers" = 10	Nusinersen	23
Artemyeva (2022) [63]	Russia	Veltishev Research and Clinical Institute for Pediatrics	Cohort	1, 2	20.3 (5, 47)	41 - Type 1 = 31 - Type 2 = 10	Onasemnogene abepravovec *Previous treatment - Nusinersen (n = 17) - Risdiplam (n = 8) - Nusinersen and risdiplam (n = 1) - Branaplam (n = 3)	12
Audic (2024) [31]	France	Multicenter	Cohort	1, 2	16 (2, 34)	57 - Type 1 = 32 - Type 2 = 25	Nusinersen	36
Axente (2022) [57]	Romania	NR	Retrospective cohort	1, 2, 3	- Type 1 = 2, 76 - Type 2 = 13, 196 - Type 3 = 30, 185	34 - Type 1 = 11 - Type 2 = 16 - Type 3 = 7	Nusinersen	26
Baranello (2021) [5]	Multiple countries	Multicenter	Cohort	1	6.7 (3.3, 6.9)	21	Risdiplam	12
Belančić (2023) [34]	Croatia	NR	Retrospective cohort	1, 2, 3	- Type 1 = 6.3 (SD = 6.3) yr. - Type 2 = 8.8 (SD = 6.0) yr. - Type 3 = 24.5 (SD = 12.3) yr.	52 - Type 1 = 18 - Type 2 = 6 - Type 3 = 28	Nusinersen	1527 d.
Belančić (2024) [35]	Croatia	NR	Retrospective cohort	1, 3	- Type 1 = 8.0 (SD = 3.6) yr. - Type 3 = 26.1 (SD = 13.4) yr.	17 - Type 1 = 6 - Type 3 = 11	Risdiplam *Previous treatment - Nusinersen (n = 17)	12

Table 1. continued

First author (y)	Country	Setting	Study design	Patient characteristics		Sample size*	Gene-based therapy	Duration (mo.)
				Types of SMA	Age at first dose* (mo.)			
Bitetti (2024) [39]	Italy	Department of Neurology, AORN Santobono-Pausilipon, Naples	Cohort	1	28.0 (SD = 20.0)	12	Onasemnogene Apeparvovec *Previous treatment with nusinersen (n = 9)	12
Chacko (2022) [26]	Australia	Queensland Children's Hospital Brisbane	Prospective cohort	1, 2, 3	- Type 1 = 0.42 (0.17, 5.00) yr. - Type 2 = 9.70 (3.60, 18.80) yr. - Type 3 = 7.50 (0.41, 15.10) yr.	28 - Type 1 = 7 - Type 2 = 12 - Type 3 = 9	Nusinersen	12
Chan (2021) [66]	Hong Kong Special Administrative Region, Republic of China and South Korea	Multicenter	Retrospective cohort	1	20.0 (0.35, 294.0)	40	Nusinersen	10
Chen (2021) [27]	Australia	Sydney Children's Hospital Network	Cohort	1	10.6 (2.7, 178.6)	9	Nusinersen	30-1
Chiriboga (2016) [24]	US	Multicenter	Phase-1 trial	2, 3	6.1 (2.0, 14.0) yr.	28 - Type 2 = 15 - Type 3 = 13	Nusinersen	9, 14
Cho (2023) [50]	South Korea	Multicenter	Cohort	1, 2, 3	- Type 1 = 2.3 (SD = 4.6) yr. - Type 2 = 15.4 (SD = 10.0) yr. - Type 3 = 24.4 (SD = 12.1) yr.	137 - Type 1 = 21 - Type 2 = 103 - Type 3 = 13	Nusinersen	34
Cornell (2024) [52]	UK	NR	Cohort	1, 2	2, 18 yr.	92 - Type 1 = 20 - Type 2 = 72	Risdiplam *Previous treatment - Nusinersen (n = 25) - Olesoxime (n = 2) - Unknown (n = 3)	11
Crawford (2023) [12]	Multiple countries	Multicenter	Phase-2 trial	1	22 (3, 42) d.	25	Nusinersen	5.7 yr.
Darras (2019) [23]	US	Multicenter	Cohort	2, 3	NR	28 - Type 2 = 11 - Type 3 = 17	Nusinersen	965.1 d.
Day (2021) [3]	US	Multicenter	Cohort	1	3.7 (0.5, 5.9)	22	Onasemnogene apearvovec	18
De Holanda Mendonca (2021) [64]	Brazil	Hospital das Clínicas	Cohort	1	NR	21	Nusinersen	24
D'Silva (2022) [28]	Australia	Sydney Children's Hospital Network	Cohort	1, 2	11 (0.65, 24)	21	Onasemnogene apearvovec *Previous treatment with nusinersen (n = 19)	15
Ergenekon (2022) [60]	Turkey	Marmara University School of Medicine	Retrospective cohort	1	11.3 (4.0, 34.8)	52	Nusinersen	6

Table 1. continued

First author (y)	Country	Setting	Study design	Patient characteristics		Sample size*	Gene-based therapy	Duration (mo.)
				Types of SMA	Age at first dose* (mo.)			
Favia (2024) [40]	Italy	Fondazione Policlinico Gemelli (FPG)	Cohort	1	NR	8	Onasemnogene abeparvovec *Previous treatment - Nusinersen (n = 6)	6
Finkel (2017) [4]	Multiple countries	Multicenter	RCT	1	- Intervention = 5.4 (1.7, 8.1) - Control = 6.0 (1.0, 8.7)	81 vs 41	Nusinersen	13
Finkel (2021) [8]	Multiple countries	Multicenter	Phase-2 trial	1	141 (36, 210)	20	Nusinersen	36.2
Gómez-García de la Banda (2021) [32]	France	Hôpital Raymond Poincaré and Hôpital Necker-Enfants malades	Cohort	1, 2	9.4 (7.1, 11.7)	16 - Type 1 = 2 - Type 2 = 14	Nusinersen	14
Gonski (2023) [29]	Australia	Sydney Children's Hospital Randwick and Children's Hospital Westmead	Retrospective cohort	1, 2, 3	- Type 1 = 0.54 (SD = 0.33) yr. - Type 2 = 8.90 (SD = 4.96) yr. - Type 3 = 8.33 (SD = 4.04) yr.	48 - Type 1 = 10 - Type 2 = 23 - Type 3 = 15	Nusinersen	2 yr.
Günther (2024) [69]	Austria, Germany, and Switzerland	Multicenter	Prospective cohort	1, 2, 3, 4	NR	237 - Type 1 = 5 - Type 2 = 67 - Type 3 = 156 - Type 4 = 9	Nusinersen	38
Hahn (2022) [42]	Germany	Multicenter	Retrospective cohort	1, 2	- Type 1 = 10.5 (3, 52) - Type 2 = 26.5 (3, 60)	111 - Type 1 = 31 - Type 2 = 80	Risdiplam *Previous treatment with nusinersen (n = 60)	12
Hepkaya (2022) [59]	Turkey	Istanbul University-Cerrahpasa	Clinical trial	1, 2, 3	- Type 1 = 8.81 (SD = 7.67) - Type 2 = 51.42 (SD = 44.55) - Type 3 = 141.38 (SD = 61.77)	43 - Type 1 = 18 - Type 2 = 12 - Type 3 = 13	Nusinersen	12
Hully (2020) [33]	France	Multicenter	Retrospective cohort	1	NR	7	Nusinersen with palliative care	4 yr.
Iwayama (2023) [47]	Japan	Aichi Medical University Hospital	Retrospective cohort	1, 2	23 (12, 40) yr.	7 - Type 1 = 1 - Type 2 = 6	Nusinersen	3.55 yr
Kim (2020) [49]	Korea	Kyungpook National University Hospital	Retrospective cohort	1, 2	44.7 (1.1, 265)	4 - Type 1 = 1 - Type 2 = 3	Nusinersen	24
Kotulska (2022) [43]	Poland	Narodowy Fundusz Zdrowia	Retrospective cohort	1, 2, 3	6.9 yr.	298 - Presymptomatic = 4 - Type 1 = 127 - Type 2 = 68 - Type 3 = 93	Nusinersen	12

Table 1. continued

First author (y)	Country	Setting	Study design	Patient characteristics		Sample size*	Gene-based therapy	Duration (mo.)
				Types of SMA	Age at first dose* (mo.)			
Kwon (2022) [25]	US	Multicenter	Cohort	1, 2	11 (0, 50) yr.	155 - Type 1 = 73 - Type 2 = 82	Risdiplam *Previous treatment - Naïve (n = 26) - Nusinersen (n = 101) - Onasemnogene approves (n = 9) - Both (n = 11) - Unknown (n = 8)	4-8
Łusakowska (2023) [45]	Poland	Multicenter	Prospective cohort	1, 2, 3	- Type 1 = 29 (13, 45) yr. - Type 2 = 24 (5, 41) yr. - Type 3 = 34 (6, 66) yr.	120- Type 1 = 12 - Type 2 = 19 - Type 3 = 89	Nusinersen	30
Masson (2022) [13]	Multiple countries	Multicenter	Cohort	1	5-3 (4-2, 6-8)	41	Risdiplam	24
Mendell (2017) [9]	US	Nationwide Children's Hospital	Cohort	1	- Cohort 1 (low dose) = 6-3 (5-9, 7-2) - Cohort 2 (high dose) = 3-4 (0-9, 7-9)	- Cohort 1 (low dose) = 3 - Cohort 2 (high dose) = 12	Onasemnogene abeparvovec	24
Mercuri (2021) [10]	Multiple countries	Multicenter	Phase-3 trial	1	- Intervention = 4-1 (SD = 1-3) - Control = 28-9 (SD = 41-7)	33 vs 23	Onasemnogene abeparvovec	14
Mirea (2022) [58]	Romania	National Teaching Center for Children's Neuro-psychomotor Rehabilitation "Dr. Nicolae Robanescu"	Retrospective cohort	1, 2, 3	NR	55 - Type 1 = 20 - Type 2 = 26 - Type 3 = 9	1) Nusinersen with physical therapy 2) Nusinersen	12
Modrzejewska (2021) [44]	Poland	Multicenter	Prospective cohort	1	23-00 (12-25, 41-25)	26	Nusinersen	26
Olsson (2019) [55]	Sweden	Queen Silvia Children's Hospital	Cohort	1	- Exposure = 14-4 (1-2, 92-4) - Nonexposure = 27-3 (3-0, 96-0)	12 vs 11	Nusinersen	NR
Osredkar (2021) [65]	Czech Republic and Slovenia	Multicenter	Prospective cohort	1, 2, 3	8-6 (0-2, 18-8) yr.	61 - Type 1 = 16 - Type 2 = 32 - Type 3 = 13	Nusinersen	14
Pane (2023) [37]	Italy	Multicenter	Cohort	1	3-3 (SD = 3-6) yr.	48	Nusinersen	48
Pechmann (2018) [41]	Germany	Multicenter	Prospective cohort	1	21-08 (1, 93)	61	Nusinersen	6
Sansone (2020) [38]	Italy	Multicenter	Retrospective cohort	1	NR	118	Nusinersen	10

Table 1. continued

First author (y)	Country	Setting	Study design	Patient characteristics		Sample size*	Gene-based therapy	Duration (mo.)
				Types of SMA	Age at first dose* (mo.)			
Sitas (2024) [36]	Croatia	Clinical hospital Center Zagreb	Cohort	2, 3	30 (18, 65) yr.	31 - Type 2 = 15 - Type 3 = 16	Risdiplam	30
Strauss (2022) [11]	Multiple countries	Multicenter	Prospective cohort	1	21-0 (8, 34) d.	14	Onasemnogene abeparvovec	18
Szabo (2020) [46]	Hungary	Multicenter	Retrospective cohort	1, 2, 3	0-78 (0-4, 1-5) yr.	57 - Type 1 = 13 - Type 2 = 21 - Type 3 = 23	Nusinersen	551 d.
Tachibana (2023) [48]	Japan	NR	Cohort	1, 2, 3, 4	NR	522 - Type 1 = 153 - Type 2 = 208 - Type 3 = 154 - Type 4 = 7	Nusinersen	785 d.
Tokatly Latzer (2023) [53]	Israel	Multicenter	Cohort	1, 2	6-1 (3-3, 17-0)	25	Onasemnogene abeparvovec *Previous treatment - Nusinersen (n = 8) - Risdiplam (n = 1)	24
Tscherter (2022) [56]	Switzerland	Multicenter	Prospective cohort	1, 2, 3	- Type 1 = 1-4 (0-1, 16-1) yr. - Type 2 = 7-8 (1-2, 31-4) yr. - Type 3 = 16-6 (2-5, 44-6) yr.	44 - Type 1 = 11 - Type 2 = 21 - Type 3 = 12	Nusinersen	1-9 yr.
Weiß (2022) [67]	Austria and Germany	Multicenter	Prospective cohort	1, 2	16-8 (0-8, 59-0)	76 - Presymptomatic = 6 - Type 1 = 51 - Type 2 = 19	Onasemnogene abeparvovec *Previous treatment - Naïve (n = 18) - Nusinersen (n = 58)	6
Weststrate (2022) [51]	UK	Great Ormond Street Hospital for Children	Retrospective cohort	1	11 (1, 90)	24	Nusinersen	24
Yang (2023) [62]	China	The West China Second University Hospital, Sichuan University and The Second Affiliated Hospital of Xi'an Jiaotong University	Retrospective cohort	1, 2, 3	0-7, 15-3 yr.	46 - Type 1 = 8 - Type 2 = 31 - Type 3 = 7	Nusinersen	63 d.

Table 2. Summary of study outcomes regarding patient survival.

First author (y)	Types of SMA	Gene-based therapy	Definitions of survival	No. of pts.	
				Survived	Total
Baranello (2021) [5]	1	Risdiplam	Being alive without the use of permanent ventilation; tracheostomy or ventilation (bilevel positive airway pressure) for ≥ 16 h per day continuously for >3 wk or continuous intubation for >3 wk, in the absence of, or after the resolution of, an acute reversible event	19	21
Chan (2021) [66]	1	Nusinersen	No death	38	39
Crawford (2023) [12]	1	Nusinersen	Alive and none required permanent ventilation; tracheostomy or ≥ 16 h/d ventilation continuously for > 21 days in the absence of an acute reversible event	25	25
Day (2021) [3]	1	Onasemnogene abeparvovec	Absence of death or permanent ventilation; tracheostomy or ≥ 16 h daily noninvasive ventilation support for ≥ 14 d, in the absence of acute reversible illness or perioperative ventilation	20	22
Ergenekon (2022) [60]	1	Nusinersen	No death	46	52
Finkel (2017) [4]	1	Nusinersen	No death or use of permanent ventilation; tracheostomy or ventilatory support for ≥ 16 h per day for >21 continuous days in the absence of an acute reversible event	49	80
Finkel (2021) [8]	1	Nusinersen	Alive without the need for permanent ventilation; tracheostomy or the need for ≥ 16 h of ventilation/d continuously for ≥ 2 wk in the absence of an acute reversible illness	11	20
Masson (2022) [13]	1	Risdiplam	Being alive without the use of permanent ventilation; tracheostomy or ventilation (bilevel positive airway pressure for ≥ 16 h/d continuously for > 3 wk or continuous intubation for >3 wk, in the absence of, or after the resolution of an acute reversible event)	34	41
Mendell (2017) [9]	1	Onasemnogene abeparvovec	Number of survived patients who did not required permanent ventilation; ≥ 16 h of respiratory assistance per day continuously for ≥ 14 days in the absence of an acute, reversible illness or a perioperative state	15	15
Mercuri (2021) [10]	1	Onasemnogene abeparvovec	Absence of death or permanent ventilation; tracheostomy or the requirement of ≥ 16 h daily non-invasive ventilatory support for ≥ 14 consecutive days in the absence of acute reversible illness (excluding perioperative ventilation)	31	33
Strauss (2022) [11]	1	Onasemnogene abeparvovec	Alive and none required of permanent ventilation; tracheostomy or ≥ 16 h/d respiratory assistance for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation	14	14

META-ANALYSIS

Patient- or event-free survival

Seven studies [3–5, 8–10, 13] investigating the effects of gene-based therapy on patient or event-free survival were included in our meta-analysis. Of these, two each employed nusinersen [4, 8] and risdiplam [5, 13], while three utilized onasemnogene abeparvovec [3, 9, 10] (Table 2). The results showed that patients undergoing gene-based therapy demonstrated an 84% survival rate (95% CI: 70, 95, $P = 0.00$, $I^2 = 82.77\%$, $\chi^2 = 34.82$, $P = 0.00$). Onasemnogene abeparvovec proved to be the most effective treatment, evidencing the highest survival rate (95% [95% CI: 88, 100], $I^2 = 0\%$, $P = 0.44$), followed by risdiplam (86% [95% CI: 76, 94], $I^2 = 0\%$, $P = 0.99$) and nusinersen (60% [95% CI: 50, 70], $I^2 = 0\%$, $P = 0.99$) (Fig. 2). The significant difference of head-to-head comparisons between gene-based therapy are presented in Appendix: Table S4; onasemnogene abeparvovec (95% [95% CI: 88, 100], $P = 0.00$) versus nusinersen (60% [95% CI: 50, 70], $P = 0.00$), $P = 0.00$; risdiplam (86% [95% CI: 76, 94], $P = 0.00$) versus nusinersen (60% [95% CI: 50, 70], $P = 0.00$), $P = 0.61$; onasemnogene abeparvovec (95% [95% CI: 88, 100], $P = 0.00$) versus risdiplam (86% [95% CI: 76, 94], $P = 0.00$), $P = 0.10$.

Number of patients needing ventilatory support

Sixteen studies examined the number of patients requiring ventilatory support after receiving nusinersen [4, 26, 27, 30, 31, 37, 38, 41, 44, 49, 51, 56, 59, 64–66], onasemnogene abeparvovec (2 studies), [9, 10] or risdiplam (2 studies) [5, 13]

(Table 3). The results indicated that only onasemnogene abeparvovec reduced the number of patients needing ventilatory support (RR = 0.10 [95% CI: 0.02, 0.53], $I^2 = 0\%$, $P = 0.909$). Risdiplam (RR = 0.39 [95% CI: 0.09, 1.76], $I^2 = 34.4\%$, $P = 0.22$) and nusinersen (RR = 1.06 [95% CI: 0.97, 1.16], $I^2 = 29.0\%$, $P = 0.12$) did not demonstrate a significant effect (Fig. 3); onasemnogene abeparvovec (0.10 [95% CI: 0.02, 0.53], $P = 0.01$) versus nusinersen (1.06 [95% CI: 0.97, 1.16], $P = 0.20$), $P = 0.01$; risdiplam (0.39 [95% CI: 0.09, 1.76], $P = 0.22$) versus nusinersen (1.06 [95% CI: 0.97, 1.16], $P = 0.20$), $P = 0.19$; onasemnogene abeparvovec (0.10 [95% CI: 0.02, 0.53], $P = 0.01$) versus risdiplam (0.39 [95% CI: 0.09, 1.76], $P = 0.22$), $P = 0.25$ (Appendix: Table S4).

Motor function improvement

Among patients with SMA type 1, 19 studies [3–5, 8–10, 13, 22, 23, 27, 30, 37, 41, 46, 47, 49, 57, 64, 66] reported the number of patients who improved their motor function (Table 4). Twelve of these studies [4, 8, 9, 13, 27, 34, 41, 45–47, 49, 66] investigated patients who improved their CHOP-INTEND score by 4 points or more, revealing that 78% of gene therapy patients were able to improve their score (78% [95% CI: 69, 85], $I^2 = 41.67\%$, $\chi^2 = 18.86$, $P = 0.06$). Onasemnogene abeparvovec was associated with the greatest number of improved patients (92% [95% CI: 62, 100]), [9] followed by risdiplam (90% [95% CI: 77, 97]) [13] and nusinersen (74% [95% CI: 66, 81], $I^2 = 12.11\%$, $P = 0.33$) [4, 8, 27, 41, 46, 47, 49, 66] (Fig. 4); onasemnogene abeparvovec (92% [95% CI: 62, 100], $P = 0.00$) versus nusinersen (74% [95% CI: 66, 81], $P = 0.00$), $P = 0.14$; risdiplam (90%

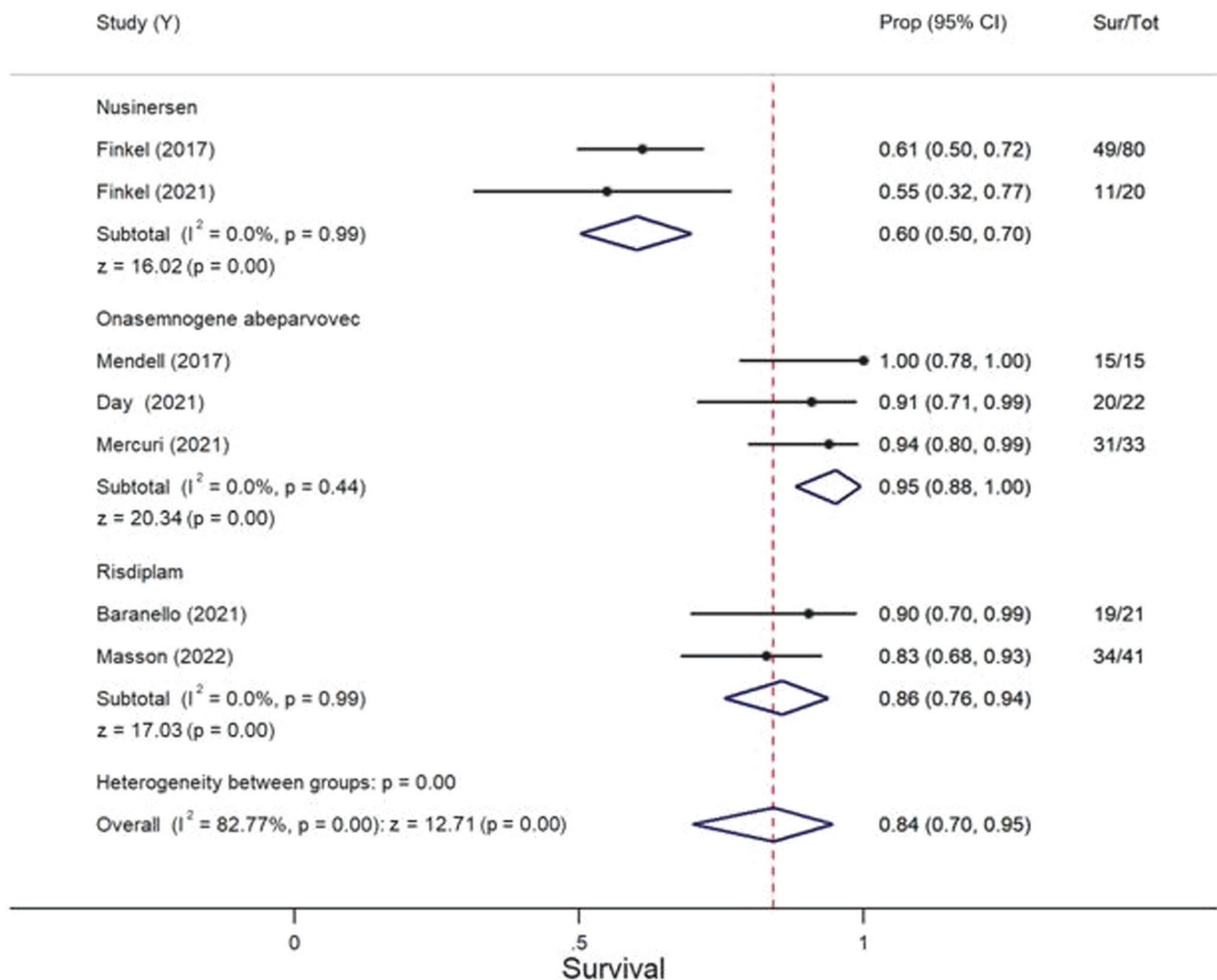


Fig. 2 Forest plot depicting patient survival. prop proportion; sur survival; tot total.

[95% CI: 77, 97], $P = 0.00$) versus nusinersen (74% [95% CI: 66, 81], $P = 0.00$), $P = 0.01$; onasemnogene abeparvovec (92% [95% CI: 62, 100], $P = 0.00$) versus risdiplam (90% [95% CI: 77, 97], $P = 0.00$), $P = 0.96$ (Appendix: Table S4). The order was maintained when examining those who improved their HINE-2 score, as per 7 studies [3, 4, 8, 13, 22, 37, 41]: onasemnogene abeparvovec (86% [95% CI: 65, 97]), [3] risdiplam (61% [95% CI: 45, 76]), [13] and nusinersen (58% [95% CI: 41, 73], $I^2 = 80.48\%$, $P = 0.00$) [4, 8, 22, 41] (Appendix: Fig. S1); onasemnogene abeparvovec (86% [95% CI: 65, 97], $P = 0.00$) versus nusinersen (58% [95% CI: 41, 73], $P = 0.00$), $P = 0.02$; risdiplam (61% [95% CI: 45, 76], $P = 0.00$) versus nusinersen (58% [95% CI: 41, 73], $P = 0.00$), $P = 0.76$; onasemnogene abeparvovec (86% [95% CI: 65, 97], $P = 0.00$) versus risdiplam (61% [95% CI: 45, 76], $P = 0.00$), $P = 0.03$ (Appendix: Table S4).

Twenty-one studies [3, 8–10, 13, 23, 26, 27, 30–32, 37, 41, 44, 46, 47, 51, 55, 56, 64, 66] investigated motor function in patients using a variety of measurements. CHOP-INTEND was the most frequently used tool (17 studies) [3, 8, 10, 13, 26, 27, 30, 37, 39, 41, 44, 46, 47, 54–56, 66]. Other tools were HINE-2 (7 studies) [8, 12, 30–32, 37, 41], HFMSE (3 studies) [23, 26, 46], the Motor Function Measure scale (2 studies) [30, 32], and the RULM scale (2 studies) [26, 47] (Table 5). Gene-based therapy improved patients' CHOP-INTEND scores (MD = 15.25 [95% CI: 10.91, 19.59], $I^2 = 0\%$, $\chi^2 = 9.35$, $P = 0.929$). Both nusinersen (MD = 15.56 [95% CI: 10.68, 20.45], $I^2 = 0\%$, $P = 0.863$) [8, 26, 27, 30, 37, 41, 44, 46, 47, 55, 56, 66] and

onasemnogene abeparvovec (MD = 14.07 [95% CI: 4.63, 23.50], $I^2 = 0\%$, $P = 0.917$) [3, 10] showed a significant improvement (Appendix: Fig. S2); onasemnogene abeparvovec (14.07 [95% CI: 4.63, 23.50], $P = 0.00$) versus nusinersen (15.56 [95% CI: 10.68, 20.45], $P = 0.00$), $P = 0.78$. The outcomes for the change in HINE-2 score (limited to nusinersen) are shown in Appendix: Fig. S3, and that for the change in HFMSE and RULM scores are in Figs. 5, 6, respectively.

Adverse drug reactions

The ADRs were reported in 12 studies: nusinersen, 4 studies [12, 22, 24, 59]; onasemnogene abeparvovec, 5 studies [3, 9, 10, 28, 39]; and risdiplam, 2 studies [25, 42]. For nusinersen, ADRs ranged from 10 [22] to 40% [12] across studies. Headaches were the most frequently observed, affecting approximately 10% of patients [59], and vomiting was 7% [59]. Other observed ADRs were proteinuria (4%); and subfebrile fever (7%) [12, 59]. A study by Acsadi et al. [22] did not report the details of ADRs. For onasemnogene abeparvovec, vomiting was reported, ranging from 9 [10] to 100% [28]. Elevations in aminotransferase levels, including alanine and aspartate, were reported, ranging from 18% [10] to 27% [3] for mild symptoms and from 3 [10] to 5% [3] for severe symptoms. For risdiplam, gastrointestinal disorders were frequently reported, including serious constipation [25] and serious gastrointestinal disorders (3.8%) [42]. All reported ADRs are presented in Table 6. Serious adverse events, such as liver

Table 3. Summary of study outcomes regarding the need for ventilatory support.

First author (y)	Types of SMA	Gene-based therapy	Definitions of ventilatory support	No. of pts. with ventilatory support		
				Baseline	Final	Total
Aragon-Gawinska (2018) [30]	1	Nusinersen	Invasive ventilation or noninvasive ventilation	17	23	33
Audic (2024) [31]	1, 2	Nusinersen	Tracheostomy or noninvasive ventilation for > 12 h/d	9	19	54
Baranello (2021) [5]	1	Risdiplam	Permanent ventilation; tracheostomy or ventilation (bilevel positive airway pressure) for ≥16 h/d continuously for > 3 wk or continuous intubation for > 3 wk, in the absence of, or after the resolution of, an acute reversible event	5	0	21
Chacko (2022) [26]	1, 2	Nusinersen	Respiratory-related hospitalizations	10	4	18
Chan (2021) [66]	1	Nusinersen	A decreased or increased ventilation need	27	27	38
Chen (2021) [27]	1	Nusinersen	Noninvasive ventilation	2	6	9
Crawford (2023) [12]	1	Nusinersen	Permanent ventilation; tracheostomy or ≥16 h/d ventilation continuously for > 21 days in the absence of an acute reversible event	0	0	25
Day (2021) [3]	1	Onasemnogene abeparvovec	Requiring no daily ventilator support excluding acute reversible illness and perioperative ventilation	0	4	22
De Holanda Mendonca (2021) [64]	1	Nusinersen	Invasive mechanical ventilation or noninvasive ventilation	21	21	21
D'Silva (2022) [28]	1, 2	Onasemnogene abeparvovec	Noninvasive ventilation	7	5	21
Ergenekon (2022) [60]	1	Nusinersen	Invasive mechanical ventilation or noninvasive ventilation	30	35	52
Favia (2024) [40]	1	Onasemnogene abeparvovec	Noninvasive ventilation	1	0	8
Finkel (2017) [4]	1	Nusinersen	Permanent ventilation; tracheostomy or ventilatory support for ≥16 h/d for > 21 continuous days in the absence of an acute reversible event	21	18	80
Gonski (2023) [29]	1, 2	Nusinersen	Noninvasive ventilation at night	17	14	33
Hepkaya (2022) [59]	1, 2	Nusinersen	Tracheostomy or noninvasive ventilation	5	11	30
Hully (2020) [33]	1	Nusinersen with palliative care	Noninvasive ventilation	4	5	37
Kim (2020) [49]	1, 2	Nusinersen	Invasive mechanical ventilation for 24 h/d or noninvasive ventilation	4	4	7
Masson (2022) [13]	1	Risdiplam	Permanent ventilation; tracheostomy or ventilation, i.e., bilevel positive airway pressure for ≥16 h/d for >3 wk or have continuous intubation for >3 wk, in the absence of or after the resolution of an acute reversible pulmonary event	12	7	41
Mendell (2017) [9]	1	Onasemnogene abeparvovec	Permanent ventilation; ≥16 h/d of respiratory assistance continuously for ≥ 14 days in the absence of an acute, reversible illness or a perioperative state	5	0	15
Mercuri (2021) [10]	1	Onasemnogene abeparvovec	Permanent ventilation; tracheostomy or the requirement of ≥ 16 h/d non-invasive ventilatory support for ≥14 consecutive days in the absence of acute reversible illness (excluding perioperative ventilation)	9	1	33
Modrzejewska (2021) [44]	1	Nusinersen	Tracheostomy or noninvasive ventilation for >16 h/d	18	21	26
Osredkar (2021) [65]	1, 2	Nusinersen	Invasive ventilation or noninvasive ventilation (at night or day and night)	16	19	48
Pane (2023) [37]	1	Nusinersen	Tracheostomy or noninvasive ventilation	34	37	48
Pechmann (2018) [41]	1	Nusinersen	Tracheostomy or noninvasive ventilation	35	42	61
Sansone (2020) [38]	1	Nusinersen	Tracheostomy, invasive and noninvasive ventilation	109	103	118
Strauss (2022) [11]	1	Onasemnogene abeparvovec	Permanent ventilation; tracheostomy or ≥16 h/d respiratory assistance for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation	0	0	14
Tokatly Latzer (2023) [53]	1, 2	Onasemnogene abeparvovec	Noninvasive ventilation	5	12	25
Tscherter (2022) [56]	1	Nusinersen	Noninvasive ventilation for >16 h/d	4	7	11
Weiß (2022) [67]	1	Onasemnogene abeparvovec	Chronic respiratory failure and ventilation	24	23	76
Weststrate (2022) [51]	1	Nusinersen	Noninvasive ventilation as needed, at night, or for >16 h/d	13	13	24

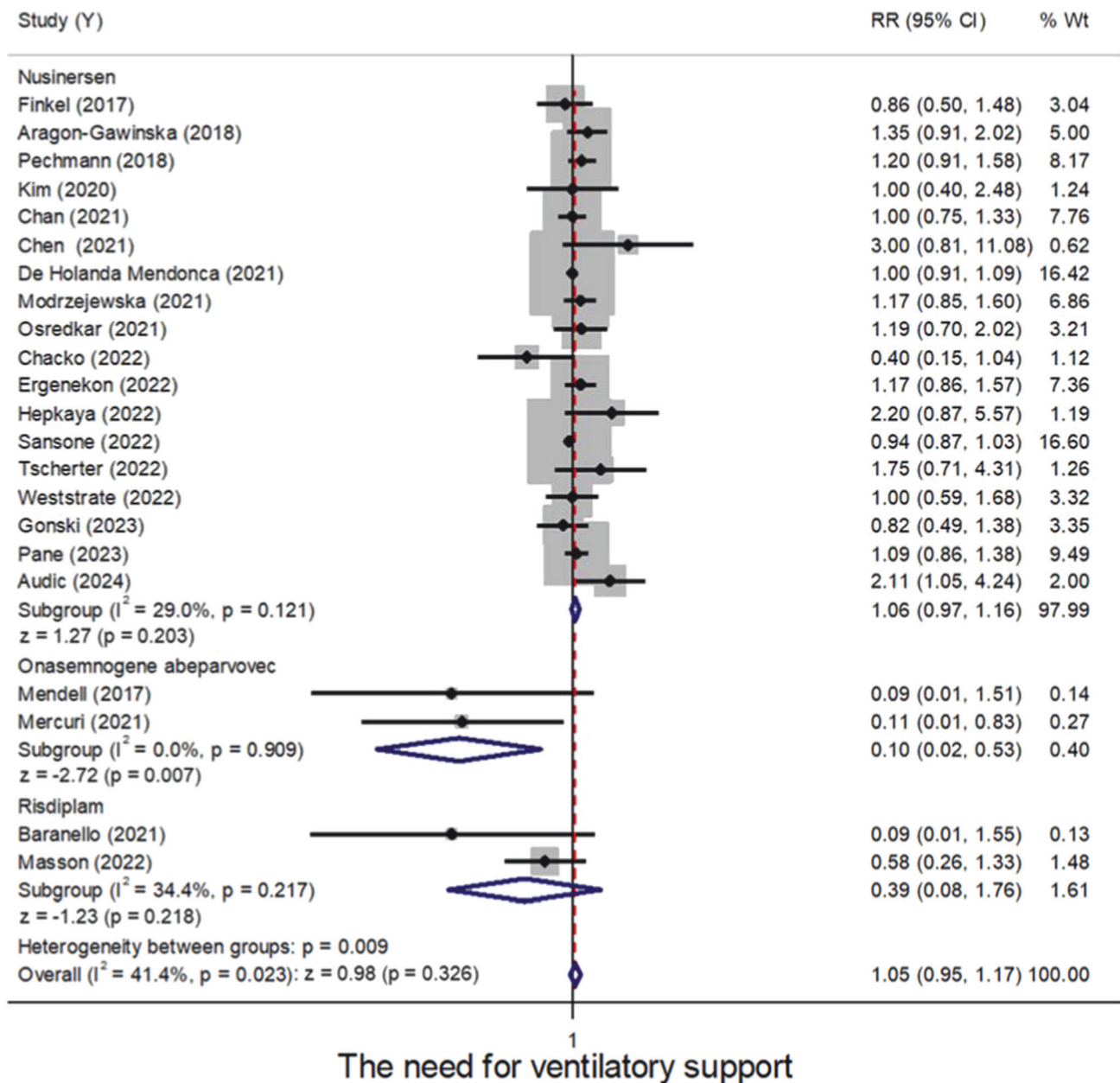


Fig. 3 Forest plot illustrating the need for ventilatory support. rr relative risk; wt weight.

failure or thrombotic microangiopathy, which are rarely reported in case reports, were not mentioned in this studies reviewed in the systematic review or meta-analysis

Subgroup analyses among patients with only type 1 SMA revealed similar trends to patients with types 1 and 2 SMA, and the results of these are presented in Appendix: Figs. S4–S6.

Study quality assessment

According to the MINORS tool used to assess the quality of 55 included non-randomized studies, overall findings of these ranged from moderate (47 studies) [8–10, 12, 13, 23–25, 27–36, 38, 40–60, 62–64, 66–69] to good (8 studies) [3, 5, 11, 26, 37, 39, 61, 65]. In summary, almost all clearly stated study aim (54 studies), [3, 5, 8–13, 23–40, 42–69], and reported their inclusion criteria that fit all patients (54 studies) [3, 5, 8–13, 23–63, 65–69]. Most studies applied appropriate study endpoints (52 studies) [3, 5, 9–13, 23–40, 42, 44–69], and follow-up period of the study (45 studies)

[3, 5, 10–13, 23–26, 29–48, 50–52, 56–61, 63–66, 68, 69]. In addition, approximately two thirds of included studies (34 studies) [3, 9, 11, 12, 23, 24, 26–29, 31, 34, 35, 37–41, 43, 45–47, 50, 52, 56–58, 61, 62, 64–66, 68, 69] did not blind outcome assessor when assessing the study endpoints, prospectively collected the data before starting the study (33 studies) [3, 5, 8–13, 23–27, 30, 32, 36, 37, 39, 44, 45, 48, 52–56, 59, 61, 64, 65, 67–69], and lost to follow up less than 5% of participants (33 studies) [5, 9, 11, 12, 25–30, 32, 36, 37, 39, 40, 42–44, 47–49, 51–54, 57–59, 61, 64, 65, 67–69]. However, only less (5 studies) [3, 5, 10, 11, 26] provided adequate details of sample size calculation (Appendix: Table S5). For the quality of included RCTs, both of the studies [4, 22] had a low risk of bias due to deviations from intended interventions, bias due to missing outcome data, and bias in measurement of the outcomes, while demonstrated some concern risk of bias arising from the randomization process, and bias in selection of the reported results (Appendix: Table S6).

Table 4. Summary of study outcomes regarding the number of patients with improved motor functions.

First author (y)	Types of SMA	Gene-based therapy	Measurement		Duration (mo.)	No. of pts.	Total
			Tools	Definitions of motor function improvement			
Acsadi (2021) [22]	1, 2	Nusinersen		Response: 1) Improvement in ≥ 1 category (i.e., an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥ 1 point; an increase in the score for kicking of ≥ 2 points; or achievement of the maximal score for kicking); and 2) More categories with improvement than categories with worsening (i.e., a decrease in the score for head control, rolling, sitting, crawling, standing, or walking of ≥ 1 point or a decrease in the score for kicking of ≥ 2 points)	24	13	14
			HINE-2: sitting	The increase by ≥ 1 point from baseline	14	9	14
			HINE-2: standing	The increase by ≥ 1 point from baseline	14	2	14
			HINE-2: walking	The increase by ≥ 1 point from baseline	14	1	14
Aragon-Gawinska (2018) [30]	1	Nusinersen	HINE-2: sitting	The ability to sit independently for >30 s.	6	5	30
Aragon-Gawinska (2020) [68]	1	Nusinersen	HINE-2	The increase by ≥ 2 points from baseline in sitters	6	11	14
			HINE-2	The increase by ≥ 2 points from baseline in non-sitters	6	13	30
Audic (2024) [31]	1, 2	Nusinersen	WHO criteria: sitting	The ability to sit independently at least 10 s	36	53	57
			WHO criteria: standing	The ability to stand with assistance at least 10 s	36	27	57
			WHO criteria: standing	The ability to stand independently at least 10 s	36	12	57
			WHO criteria: walking	The ability to walk with assistance at least five steps	36	11	57
			WHO criteria: walking	The ability to walk independently at least five steps	36	5	57
Axente (2022) [57]	1, 2	Nusinersen	NR	The ability to sit in non-sitters (SMA 1)	26	5	11
			NR	The ability to walk in sitters (SMA 2)	26	4	16
Baranello (2021) [5]	1	Risdiplam	BSID-3: sitting	The ability to sit independently for ≥ 5 s	12	7	21
Belančić (2023) [34]	1	Nusinersen	CHOP-INTEND	The increase by ≥ 4 points from baseline	307 d.	10	14
Bitetti (2024) [39]	1	Onasemnogene abeparvovec	WHO criteria: sitting	The ability to sit independently for >1 min (all)	12	11	12
			WHO criteria: standing	The ability to stand with assistance (all)	12	5	12
			WHO criteria: standing	The ability to stand independently for >1 min (all)	12	1	12
			WHO criteria: walking	The ability to walk with assistance (all)	12	1	12
			WHO criteria: sitting	The ability to sit independently for >1 min (nusinersen-naïve patients)	12	2	3
			WHO criteria: standing	The ability to stand with assistance (nusinersen-naïve patients)	12	2	3
			WHO criteria: standing	The ability to stand independently for >1 min (nusinersen-naïve patients)	12	0	3
			WHO criteria: walking	The ability to walk with assistance (nusinersen-naïve patients)	12	0	3
			WHO criteria: sitting	The ability to sit independently for >1 min (patients who received nusinersen prior to study enrollment)	12	9	9
			WHO criteria: standing	The ability to stand with assistance (patients who received nusinersen prior to study enrollment)	12	3	9
			WHO criteria: standing	The ability to stand independently for >1 min (patients who received nusinersen prior to study enrollment)	12	1	9
			WHO criteria: walking	The ability to walk with assistance (patients who received nusinersen prior to study enrollment)	12	1	9
Chan (2021) [66]	1	Nusinersen	CHOP-INTEND	The increase by ≥ 4 points from baseline	10	13	19
Chen (2021) [27]	1	Nusinersen	CHOP-INTEND	The increase by ≥ 4 points from baseline	24	8	9
Chiriboga (2016) [24]	2	Nusinersen	HFMSE	The increase by ≥ 3 points from baseline	85 d.	5	7
Crawford (2023) [12]	1	Nusinersen	WHO criteria: sitting	The ability to sit without support	5-7 yr.	25	25

Table 4. continued

First author (y)	Types of SMA	Gene-based therapy	Measurement		Duration (mo.)	No. of pts.	Total
			Tools	Definitions of motor function improvement			
Darras (2019) [23]	2	Nusinersen	6MWT: walking	The ability to walk independently for ≥ 15 ft.	36	1	11
Day (2021) [3]	1	Onasemnogene abeparvovec	CHOP-INTEND	1) The achievement of ≥ 40 points 2) The achievement of ≥ 50 points 3) The achievement of ≥ 60 points	18	1) 21 2) 14 3) 5	22
			HINE-2	Response: Improvement in ≥ 1 category	18	19	22
			BSID-3: sitting	The ability to sit independently for ≥ 30 s.	18	13	22
De Holanda Mendonca (2021) [64]	1	Nusinersen	HINE-2	The increase by ≥ 3 points from baseline	6–24	6	21
			HINE-2: sitting	The ability to sit independently	6–24	2	21
			HINE-2: sitting with support	The ability to sit with support	6–24	1	21
D'Silva (2022) [28]	1, 2	Onasemnogene abeparvovec	WHO motor milestone	≥ 1 WHO gross motor developmental milestone	15	6	21
			WHO criteria: sitting	The ability to sit without support	15	6	8
			WHO criteria: walking	The ability to walk with assistance	15	1	8
			BSID-3: sitting and walking	≥ 1 functional motor skill based on items 26, 37, and 43 on the BSID-3	15	11	13
Favia (2024) [40]	1	Onasemnogene abeparvovec	CHOP-INTEND	The increase by ≥ 4 points from baseline	6	5	8
Finkel (2017) [4]	1	Nusinersen	CHOP-INTEND	The increase by ≥ 4 points from baseline	13	52	73
			HINE-2	Response: 1) Improvement in ≥ 1 category (i.e., an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥ 1 point; an increase in the score for kicking of ≥ 2 points; or achievement of the maximal score for kicking); and 2) More categories with improvement than categories with worsening (i.e., a decrease in the score for head control, rolling, sitting, crawling, standing, or walking of ≥ 1 point or a decrease in the score for kicking of ≥ 2 points)	13	37	73
Finkel (2021) [8]	1	Nusinersen	CHOP-INTEND	1) The increase by ≥ 4 points from baseline 2) The achievement of ≥ 40 points 3) The achievement of ≥ 50 points	36	1) 7 2) 8 3) 6	13
			HINE-2	Response: 1) The increase by ≥ 2 points from baseline or the ability to pincer grasp in the category of voluntary grasp; or 2) The increase by ≥ 2 points in the ability to kick or ability to touch toes from baseline; or 3) The increase by 1 point in any of the remaining 6 categories (head control, rolling, sitting, crawling, standing, or walking)	36	12	20
Günther (2024) [69]	2	Nusinersen	HFMSE	The increase by ≥ 3 points from baseline	38	2	33
			RULM	The increase by ≥ 2 points from baseline	38	12	32
Iwayama (2023) [47]	1, 2	Nusinersen	CHOP-INTEND	The increase by ≥ 4 points from baseline	3–55 yr.	4	7
Kim (2020) [49]	1, 2	Nusinersen	CHOP-INTEND	The increase by ≥ 4 points from baseline	24	3	4
			HFMSE	The increase by ≥ 2 points from baseline	24	3	3
Kotulska (2022) [43]	1, 2	Nusinersen	CHOP-INTEND	The increase by ≥ 4 points from baseline	12	129	170
Łusakowska (2023) [45]	1, 2	Nusinersen	CHOP-INTEND	The increase by ≥ 4 points from baseline	26, 30	5	9
Masson (2022) [13]	1	Risdiplam	CHOP-INTEND	The increase from baseline for ≥ 4 points	24	37	41
			CHOP-INTEND	The achievement of ≥ 40 points	24	31	41
			HINE-2	Response: 1) Improvement in ≥ 1 category (i.e., an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥ 1 point; an increase in the score for kicking of ≥ 2 points; or achievement of	24	25	41

Table 4. continued

First author (y)	Types of SMA	Gene-based therapy	Measurement		Duration (mo.)	No. of pts.	Total
			Tools	Definitions of motor function improvement			
				the maximal score for kicking); and 2) More categories with improvement than categories with worsening (i.e., a decrease in the score for head control, rolling, sitting, crawling, standing, or walking of ≥ 1 point or a decrease in the score for kicking of ≥ 2 points)			
			BSID-3: sitting	The ability to sit independently for ≥ 5 s.	24	25	41
				The ability to sit independently for ≥ 30 s.	24	18	41
			BSID-3: standing	The ability to stand independently	24	0	41
			BSID-3: walking	The ability to walk independently	24	0	41
			CHOP-INTEND	The increase by ≥ 4 points from baseline	21–33	11	12
Mendell (2017) [9]	1	Onasemnogene abeparvovec	1) BSID-3: sitting (≥ 5 s.) 2) WHO criteria: Sitting (≥ 10 s.) 3) BSID-3: (≥ 30 s.)	The ability to sit independently for, 1) ≥ 5 s. 2) ≥ 10 s. 3) ≥ 30 s.	21–33	1) 11 2) 10 3) 9	12
			BSID-3: walking	The ability to crawl, pull to stand, stand independently, and walk independently	21–33	2	12
			WHO criteria: sitting	The ability to sit independently for ≥ 10 s.	18	14	32
Mercuri (2021) [10]	1	Onasemnogene abeparvovec	HINE-2	Improvement in ≥ 1 category (i.e., an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥ 1 point; an increase in the score for kicking of ≥ 2 points; or achievement of the maximal score for kicking)	48	28	48
			CHOP-INTEND	The increase by ≥ 4 points from baseline	6	47	61
			HINE-2	Response: 1) Improvement in ≥ 1 category (i.e., an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥ 1 point; an increase in the score for kicking of ≥ 2 points; or achievement of the maximal score for kicking); and 2) More categories with improvement than categories with worsening	6	21	61
Pechmann (2018) [41]	1	Nusinersen	HINE-2	1) The increase by ≥ 3 points from baseline 2) The increase by 2–4 points from baseline 3) The increase by ≥ 5 points from baseline	6	1) 19 2) 15 3) 4	61
			HFMSE	The increase by ≥ 3 points from baseline	785 d.	28	97
Tachibana (2023) [48]	2	Nusinersen	WHO criteria: sitting	The ability to sit independently for ≥ 30 s.	18	14	14
			WHO criteria: standing	The ability to stand with assistance	18	14	14
			WHO criteria: standing	The ability to stand independently for >1 min	18	10	14
			WHO criteria: walking	The ability to walk with assistance	18	12	14
			WHO criteria: walking	The ability to walk independently	18	10	14
			BSID-3 criteria: sitting	The ability to sit independently	18	14	14
			BSID-3 criteria: standing	The ability to stand with assistance	18	14	14
			BSID-3 criteria: standing	The ability to stand independently	18	11	14
			BSID-3 criteria: walking	The ability to walk with assistance	18	11	14
			BSID-3 criteria: walking	The ability to walk independently	18	9	14
Szabo (2020) [46]	1, 2	Nusinersen	CHOP-INTEND	The increase by ≥ 4 points from baseline	10	7	7
Weiß (2022) [67]	1, 2	Onasemnogene abeparvovec	CHOP-INTEND	The increase by ≥ 4 points from baseline	6	49	60
			HFMSE	The increase by ≥ 3 points from baseline	6	49	60

BSID-3 Bayley Scales of Infant and Toddler Development, third edition, CHOP-INTEND Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HINE-2 Hammersmith Infant Neurological Examination-2, WHO World Health Organization, 6MWT 6-Minute Walk Test.

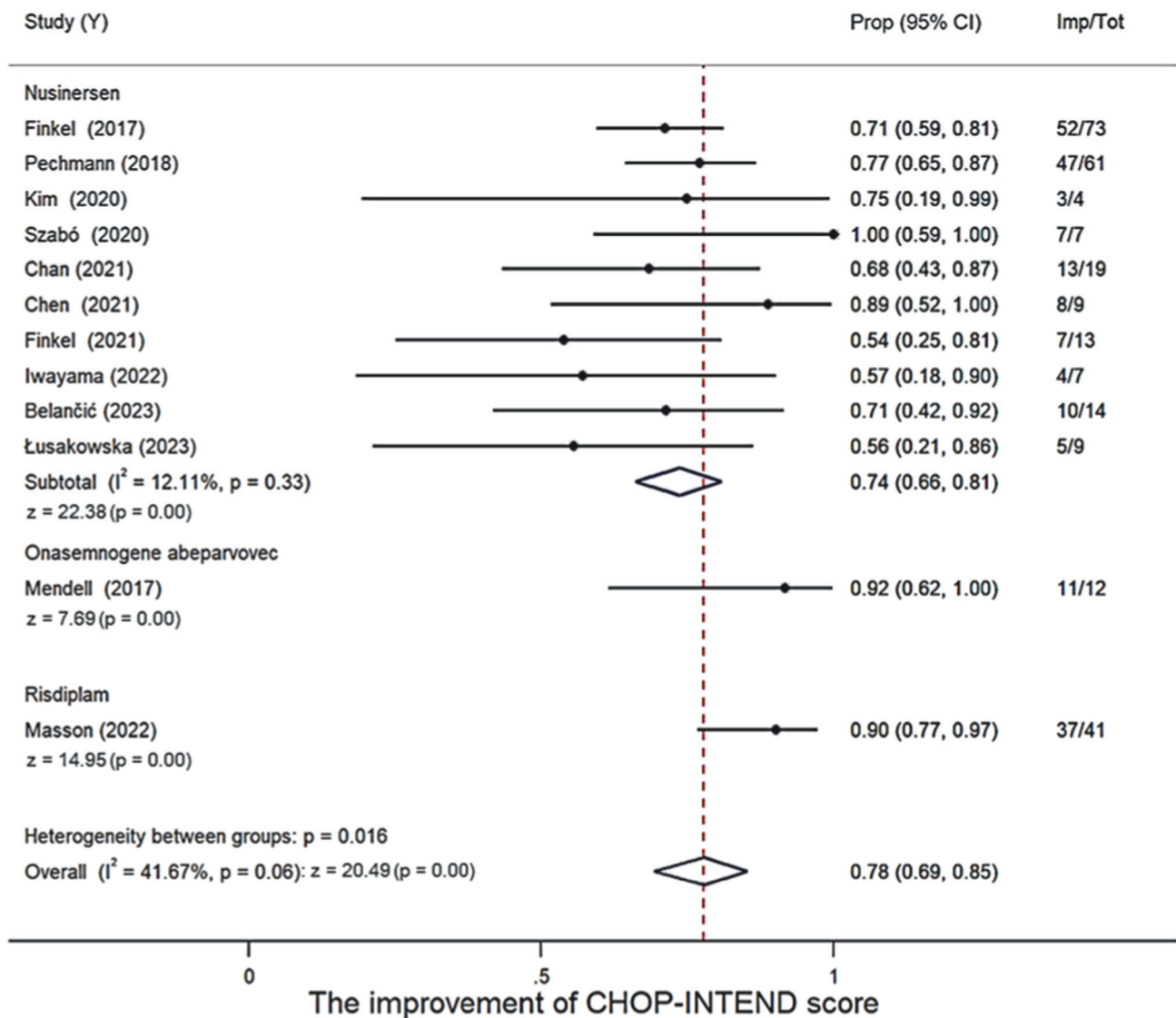


Fig. 4 Forest plot displaying the number of patients with an improvement of their CHOP-INTEND score ≥ 4 . prop proportion; imp improve; tot total.

Publication bias

Non-significant publication bias were observed for all studies evaluating the outcomes, including patient survival ($P = 0.149$), the number of patients requiring ventilatory support ($P = 0.838$), the number of patients improved their CHOP-INTEND scores ≥ 4 ($P = 0.822$), and the mean CHOP-INTEND score improvement ($P = 0.975$). All funnel plots are presented in Appendix: Figs. S7–S10.

DISCUSSION

Despite several studies evaluating gene-based therapy's effects on SMA, none have provided a comprehensive summary. The present work is the first systematic review and meta-analysis to evaluate the effects of gene-based therapy for SMA types 1 and 2, and our findings demonstrate their benefits on patient survival and motor function improvement. Onasemnogene abeparvovec and risdiplam appear highly effective, while nusinersen is moderately effective. Only onasemnogene abeparvovec reduced the number of patients who needed ventilatory support. The most frequently

observed ADRs with gene-based therapy were headache, vomiting, and gastrointestinal disorders.

Our meta-analysis results indicate that onasemnogene abeparvovec is highly effective in treating SMA types 1 and 2, resulting in the highest patient survival and motor function improvement instances. Additionally, it is the only gene-based therapy that reduces the number of patients needing ventilatory support. Onasemnogene abeparvovec is an SMN-enhancing therapy that replaces the missing or nonfunctional SMN1 gene with a new, functional one. Adeno-associated virus 9 conveys the replacement gene into the body and infects target cells with new DNA. Consequently, patients can produce their own SMN protein, leading to a more normal life. Gene therapy was proposed over 50 years ago, and its use among humans has increased steadily [70]. The therapy offers the potential to address specific mutations and repair or ameliorate diseases using various methods. They include replacing a mutated gene with a healthy one, inactivating a malfunctioning gene, and introducing a missing gene. The use of adeno-associated virus 9 also ensures that after the virus enters the host cell, the gene of interest is transported to the nucleus,

Table 5. Summary of study outcomes regarding the improvement in motor function scores.

First author (y)	Types of SMA	Gene-based therapy	Sample size*	Duration (mo.)	Measurement	Measuring score	
						Baseline visit	Final visit
Ali (2021) [54]	1, 2	Onasemnogene abeparvovec	9 - Type 1 = 7 - Type 2 = 2	10	CHOP-INTEND	NR	NR
Aragon-Gawinska (2018) [30]	1	Nusinersen	33	6	CHOP-INTEND	Med (range) Mo. 0 - All (n = 20) = 31.5 (6, 45)	Med (range) Mo. 6 - All (n = 22) = 35 (19, 51)
					HINE-2	Med (range) Mo. 0 - All (n = 33) = 1 (0, 6)	Med (range) Mo. 6 - All (n = 30) = 3.5 (0, 11)
					MFM 20	Med (range) Mo. 0 - All (n = 4) = 22.5 (16.67, 25)	Med (range) Mo. 6 = 30 (13.33, 48.33)
					MFM 32	Med (range) Mo. 0 - All (n = 2) = 25 (19.79, 30.2)	Med (range) Mo. 6 - All (n = 1) = 4.16
Aragon-Gawinska (2020) [68]	1	Nusinersen	46	14	HINE-2	Med, mean (range) - Type 1 "sitters" (n = 15) = 2, 3.07 (0, 6) - Type 1 "non-sitters" (n = 31) = 1, 1.23 (0, 6)	NR
					CHOP-INTEND	Med, mean (range) - Type 1 "sitters" (n = 10) = 35.5, 33.7 (22, 40) - Type 1 "non-sitters" (n = 22) = 26.5, 26.9 (6, 38)	Med difference, MD (range), P value Type 1 "sitters" (n = 14) - Mo. 0-2 = 1, 1.36 (0, 5), NR - Mo. 0-6 = 3, 3.07 (0, 9), NR Type 1 "non-sitters" (n = 30) - Mo. 0-2 = 0, 0.8 (-1, 5), NR - Mo. 0-6 = 1, 1.57 (-1, 6), NR NR
Arslan (2023) [61]	2	Nusinersen	6	23	HFMSE	Med (range) = 5 (2, 9)	Med (range) - Mo. 9 = 7 (4, 10) - Mo. 15 = 7.5 (4, 10)
Artemyeva (2022) [63]	1, 2	Onasemnogene abeparvovec	17	12	CHOP-INTEND	Mean (SD) - Mo. 0 (n = 17) = 48.0 (11.8) - Mo. 0 (n = 10) = 50.5 (9.1)	Mean (SD) - Mo. 6 (n = 17) = 55.1 (8.9) - Mo. 12 (n = 10) = 59.9 (3.7)
					HINE-2	Mean (SD) - Mo. 0 (n = 17) = 10.3 (5.4) - Mo. 0 (n = 10) = 10.8 (5.1)	Mean (SD) - Mo. 6 (n = 17) = 13.6 (5.3) - Mo. 12 (n = 10) = 15.2 (4.2)

Table 5. continued

First author (y)	Types of SMA	Gene-based therapy	Sample size*	Duration (mo.)	Measurement	Measuring score		
						Baseline visit	Final visit	Mean difference
Belančić [34] (2023)	1, 2	Nusinersen	21 - Type 1 = 17 - Type 2 = 4	1527 d.	CHOP-INTEND	Mean (SD) Type 1 D. 0 (n = 17) = 9.1 (10.1) Med (range) Type 1 D. 0 (n = 17) = 5 (0, 38)	Mean (SD) Type 1 D. 1527 (n = 3) = 45.3 (13.9)	MD (SD), P value Type 1 D. 0-1527 = 38.0 (NR), NA
						Mean (SD) Type 2 D. 0 (n = 4) = 5.8 (8.0) Med (range) Type 2 D. 0 (n = 4) = 3 (0, 17)	Mean (SD) Type 2 D. 429 (n = 2) = 19.5 (24.7)	MD (SD), P value Type 2 D. 0-429 = 11.0 (NR), NA
Belančić [35] (2024)	1	Risdiplam	6	12	CHOP-INTEND	Mean (SD) = 33.7 (23.7) Med (range) = 31.5 (9, 58)	Mean (SD) - Mo. 6 = 34.3 (23.6) - Mo. 12 = 34.7 (23.3)	MD (SD), P value - Mo. 0-6 = 0.6 (NR), NA - Mo. 0-12 = 1.0 (NR), NA
						Med (range) - All (n = 12) = 41.0 (4, 53) Mean (SD) - Nusinersen-naïve patients (n = 3) = 10.3 (5.7) - Patients who received nusinersen prior to study enrollment (n = 9) = 42.8 (8.9)	Med (range) - All (n = 12) = 52.5 (36, 60) Mean (SD) - Nusinersen-naïve patients (n = 3) = 42.7 (7.0) - Patients who received nusinersen prior to study enrollment (n = 9) = 54.0 (4.1)	Med difference (SD), P value - All (n = 12) = NR (NR), P = 0.004 MD (SD), P value - Nusinersen-naïve patients (n = 3) = 32.4 (NR), NR - Patients who received nusinersen prior to study enrollment (n = 9) = 11.2 (NR), NR
Chacko [26] (2022)	1, 2	Nusinersen	28 - Type 1 = 6 - Type 2 = 12	12	CHOP-INTEND	Med (IQR) - Type 1 (n = 5) = 27.5 (24, 36)	Med (IQR) - Type 1 (n = 5) = 44 (38.5, 55)	NR
Chan [66] (2021)	1	Nusinersen	40	10	RULM	Med (IQR) - Type 1 (n = 1) = 9 - Type 2 (n = 9) = 8.5 (6, 14.5)	Med (IQR) - Type 1 (n = 1) = 10 - Type 2 (n = 9) = 9 (7, 13)	NR
					HFMSE	Med (IQR) - Type 1 = NR - Type 2 (n = 3) = 32 (29, 45)	Med (IQR) - Type 1 = NR - Type 2 (n = 3) = 34 (33, 51)	NR
Chen [27] (2021)	1	Nusinersen	9	26-3	HINE-2	Med (range) (n = 37) = 0.0 (0.0, 4.0)	Med (range) (n = 32) = 4.0 (0.0, 24.0)	Med (range) = 3.0 (0.0, 20.0)
					CHOP-INTEND	Med (range) (n = 23) = 12.0 (0.0, 60.0)	Med (range) (n = 20) = 31.5 (1.0, 64.0)	Med (range) = 8.5 (0.0, 49.0)
Chen [27] (2021)	1	Nusinersen	9	26-3	CHOP-INTEND	Mean (SD; range) = 35.3 (8.6; 25, 49)	Mean (SD; range) = 51.2 (11.2; 33, 62)	NR

Table 5. continued

First author (y)	Types of SMA	Gene-based therapy	Sample size*	Duration (mo.)	Measurement	Measuring score	Final visit	Mean difference
Cho (2023) [50]	1, 2	Nusinersen	124 - Type 1 = 21 - Type 2 = 103	34	HINE-2	Baseline visit Mean (SD) - Type 1 (n = 21) = 1.6 (1.7)	Mean (SD) - Type 1 (n = 7) = 11.4 (8.3)	MD (SD), P value = 9.6 (7.9), NR
					HFMSE	Mean (SD) - Type 2 (n = 103) = 9.6 (11.7)	Mean (SD) - Type 2 (n = 12) = 21.3 (12.0)	MD (SD), P value = 9.2 (4.3), NR
Darras (2019) [23]	2	Nusinersen	11	1, 150 *d.	HFMSE	Mean (SE; range) = 21.3 (2.9; 6, 35)	NR	Mean (SE) = 10.8 (4.3)
Day (2021) [3]	1	Onasemnogene abeparvovec	22	18	CHOP- INTEND	Mean (SD; range) = 32 (9.7; 18, 52) Med (IQR) = 33.5 (24, 38)	NR	MD (SD) - M6 = 14.6 (7.04)
De Holanda Mendonca (2021) [64]	1	Nusinersen	21	24	CHOP- INTEND	Mean (SD; range) = 13.4 (9.8; 2, 33)	NR	MD - M24 = 14
D'Silva (2022) [28]	1, 2	Onasemnogene abeparvovec	9	6	CHOP- INTEND	NR	Mean (range) = 7 (2, 21)	NR
					HFMSE	NR	Mean (range) = 10 (6, 18)	NR
Ergenekon (2022) [60]	1	Nusinersen	52	6	CHOP- INTEND	Med (IQR) = 9.5 (3.0, 23.7)	Med (IQR) = 25 (11, 35)	NR, P < 0.001
Finkel (2021) [8]	1	Nusinersen	20	36.2	CHOP- INTEND	Mean (SD) - 2 SMN2 (n = 13) = 29.7 (10.5)	Mean (SD) - 2 SMN2 (n = 13) = 48.3 (12.7)	MD (SD) - 2 SMN2 (n = 13) = 17.3 (12.2)
					HINE-2	Mean (SD) - 2 SMN2 (n = 13) = 1.46 (0.52)	Mean (SD) - 2 SMN2 (n = 13) = 11.86 (6.18)	MD (SD) - 2 SMN2 (n = 13) = 10.43 (6.05)
Gómez-García de la Banda (2021) [32]	1, 2	Nusinersen	16 - Type 1 = 2 - Type 2 = 14	14	HINE-2	Mean (SD) = 8 (5) Med (range) = 6 (1, 20)	Mean (SD) = 9 (5) Med (range) = 8 (4, 24)	NR, P < 0.001
					MFM Total	Mean (SD) = 34 (17) Med (range) = 38 (4, 60)	Mean (SD) = 43 (17) Med (range) = 44 (5, 76)	NR, P = 0.03
					MFM-20	Mean (SD) (n = 3) = 25 (12) Med (range) (n = 3) = 23 (13, 37)	Mean (SD) (n = 3) = 30 (14) Med (range) (n = 3) = 32 (15, 42)	NR, P = 0.146
					MFM-32	Mean (SD) = 37 (17) Med (range) = 45 (4, 60)	Mean (SD) = 46 (17) Med (range) = 49 (5, 76)	NR, P = 0.11
Gonski (2023) [29]	1, 2	Nusinersen	23 - Type 1 = 8 - Type 2 = 15	2 yr.	WHO	NR	NR	MD (SD), P value - Type 1 (n = 8) = 1.5 (1.4), P = 0.02 - Type 2 (n = 15) = -0.07 (0.70), P = 0.72
					CHOP- INTEND	NR	NR	MD (SD), P value - Type 1 (n = 5) = 17 (9.5), P = 0.02

Table 5. continued

First author (y)	Types of SMA	Gene-based therapy	Sample size*	Duration (mo.)	Measurement	Measuring score		Mean difference
						Baseline visit	Final visit	
Günther (2024) [69]	2	Nusinersen	67	38	HINE-2	NR	NR	MD (SD), <i>P</i> value - Type 1 (<i>n</i> = 4) = 4.75 (3.59), <i>P</i> = 0.08
					RULM	NR	NR	MD (SD), <i>P</i> value - Type 2 (<i>n</i> = 4) = 3 (7.07), <i>P</i> = 0.46
					HFMSE	NR	NR	MD (SD), <i>P</i> value - Mo. 0–14 (<i>n</i> = 67) = 1.0 (3.1), <i>P</i> = 0.0099 - Mo. 0–26 (<i>n</i> = 44) = -0.5 (3.3), <i>P</i> = 0.3400 - Mo. 0–38 (<i>n</i> = 33) = -0.2 (2.8), <i>P</i> = 0.6704
					RULM	NR	NR	MD (SD), <i>P</i> value - Mo. 0–14 (<i>n</i> = 67) = 1.4 (2.8), <i>P</i> = 0.0001 - Mo. 0–26 (<i>n</i> = 45) = 1.4 (2.6), <i>P</i> = 0.0009 - Mo. 0–38 (<i>n</i> = 32) = 1.1 (2.7), <i>P</i> = 0.0298
Iwayama (2023) [47]	1, 2	Nusinersen	7 - Type 1 = 1 - Type 2 = 6	3–55 yr.	CHOP-INTEND	Mean (range) = 5 (0, 31)	Mean (range) = 21 (0, 39)	MD (range), <i>P</i> value = 5 (0, 26), <i>P</i> = 0.100
					HFMSE	Mean (range) = 0 (0, 3)	Mean (range) = 0 (0, 5)	MD (range), <i>P</i> value = 0 (0, 2), <i>P</i> = 0.346
					RULM	Mean (range) = 1 (0, 20)	Mean (range) = 3 (0, 21)	MD (range), <i>P</i> value = 1 (0, 2), <i>P</i> = 0.089
Kotulska (2022) [43]	1, 2	Nusinersen	170	12	CHOP-INTEND	NR	NR	MD (range), <i>P</i> value = 8.9, <i>P</i> < 0.001
Mendell (2017) [9]	1	Onasemnogene abeparvovec	15 - Low dose = 3 - High dose = 12	24–36	CHOP-INTEND	Mean (range) - Low dose (<i>n</i> = 3) = 16 (6, 27) - High dose (<i>n</i> = 12) = 28 (12, 50)	Mean - Low dose (<i>n</i> = 3) = 24 - High dose (<i>n</i> = 12) = 52.8	MD, <i>P</i> value - Low dose = NR - High dose = - Mo. 1 = 98, <i>P</i> < 0.001 - Mo. 3 = 15.4, <i>P</i> < 0.001
					CHOP-INTEND	Mean (SD; range) (<i>n</i> = 33) = 27.9 (8.3; 14, 55) Med (IQR) (<i>n</i> = 33) = 28 (22, 32)	NR	MD (SD) - Mo. 6 = 13.6 (6.6)
Mercuri (2021) [10]	1	Onasemnogene abeparvovec	33	6	CHOP-INTEND	NR	NR	MD (SD) - Mo. 6 = 13.6 (6.6)
Mirea (2022) [58]	1, 2	1) Nusinersen with physical therapy 2) Nusinersen	20	12	CHOP-INTEND	NR	NR	Mean (range) Mo. 6 1) <i>n</i> = 18; 13.62% (4.17, 21.05) 2) <i>n</i> = 2; 3.45% (3.45, 3.45) Mo. 12 1) <i>n</i> = 18; 33.22% (15.38, 55.56) 2) <i>n</i> = 2; 6.90% (6.90, 6.90)
					HFMSE	NR	NR	Mean (range) Mo. 6 1) <i>n</i> = 16; 5.86% (0, 10.53) 2) <i>n</i> = 10; 2.81% (0, 4.55)

Table 5. continued

First author (y)	Types of SMA	Gene-based therapy	Sample size*	Duration (mo.)	Measurement	Measuring score	
						Baseline visit	Final visit
							Mean difference
							Mo. 12 1) $n = 16$; 10.16% (5.26, 12.96) 2) $n = 10$; 4.35% (0, 7.41)
Modrzejewska (2021) [44]	1	Nusinersen	26	26	CHOP-INTEND	Med (IQR) = 17.50 (6.00, 32.5)	Med (IQR) = 25.50 (12.25, 40.50)
Olsson (2019) [55]	1	Nusinersen	12	*Varied by patient	CHOP-INTEND	NR	NR
Pane (2023) [37]	1	Nusinersen	48	48	CHOP-INTEND	NR	NR
					HINE-2	NR	NR
Pechmann (2018) [41]	1	Nusinersen	61 - ≤ 7 mo. = 17 - > 7 mo. = 44	6	CHOP-INTEND	Mean (SD) Both ages - All SMN2 ($n = 61$) = 22.3 (13.09)	Mean (SD) Both ages - All SMN2 ($n = 17$) = 9 (8)
					HINE-2	Mean (range) - All SMN2 ($n = 61$) = 0.8 (0, 8)	MD (SD) - Both ages = 1.4 (2.1)
Sitas (2024) [36]	2	Risdiplam	15	30	RULM	NR	NR
Strauss (2022) [11]	1	Onasemnogene abeparvovec	14	18	CHOP-INTEND	Mean (SD) = 46.1 (8.8) Med (range) = 49 (28, 57)	MD (SD), P value - Mo. 0–1 = 3.9 (8.3), NR - Mo. 0–3 = 11.2 (8.8), NR - Mo. 0–6 = 14.8 (8.1), NR
Szabo (2020) [46]	1, 2	Nusinersen	34 - Type 1 = 13 - Type 2 = 21	21	CHOP-INTEND	Mean (SD) Type 1 - D. 0 ($n = 7$) = 30 (7.6)	Mean (SD) Type 1 - D. 0–551 = 27.7, NR
					HFMSE	Mean (SD) Type 2 - D. 0 ($n = 15$) = 21.2 (6.5)	Mean, P value Type 2 - D. 0–551 = 5.7, NR
Tokatly Latzer (2023) [53]	2	Onasemnogene abeparvovec	2	23	HFMSE	NR	Mean (SD), P value = 11.0 (42), NR
Tscherter (2022) [56]	1, 2	Nusinersen	33 - Type 1 = 11 - Type 2 = 21	1.9 yr.	CHOP-INTEND	Med (range) - Type 1 ($n = 11$) = 25 (2, 29)	Med (range) - Type 1 = 25 (2, 42)
					HFMSE	Med (range) - Type 2 ($n = 16$) = 5.5 (0, 25)	NR
					RULM	Med (range) - Type 2 ($n = 12$) = 11 (0, 24)	NR

Table 5. continued

First author (y)	Types of SMA	Gene-based therapy	Sample size*	Duration (mo.)	Measurement	Measuring score		
						Baseline visit	Final visit	Mean difference
Weiβ (2022) [67]	1, 2	Onasemnogene abeparvovec	56 - Pre-symptomatic = 6 - Type 1 = 45 - Type 2 = 5	6	CHOP-INTEND	Mean (SD; range) - Pre-symptomatic (n = 6) = 47.5 (12.1; 28, 64) - Type 1 (n = 45) = 38.0 (8.9; 16, 61) - Type 2 (n = 5) = 44.0 (11.3; 30, 59) - 2 SMN2 (n = 45) = 38.6 (10.0; 16, 64) - 3 SMN2 (n = 11) = 43.6 (8.2; 30, 59)	Mean (SD; range) - Pre-symptomatic (n = 6) = 62.7 (2.1; 60, 64) - Type 1 (n = 45) = 46.6 (8.3; 22, 64) - Type 2 (n = 5) = 48.0 (11.4; 33, 64) - 2 SMN2 (n = 45) = 48.0 (9.6; 22, 64) - 3 SMN2 (n = 11) = 50.3 (9.0; 33, 64)	Mean (SD; range), P value - Pre-symptomatic = 15.2 (11.9; 0, 36), P < 0.0001 - Type 1 = 8.6 (6.3; -7, 26), P = 0.0162 - Type 2 = 4.0 (1.6; 2, 6), P = 0.5150 SMN2 = 48.0 (9.6; 22, 64), P = 0.24 SMN2 = 6.7 (3.9; 2, 14), NR
Weststrate (2022) [51]	1	Nusinersen	24	1) 6 2) 12 3) 24	CHOP-INTEND	Med = 32	Med 1) = 39 2) = 42 3) = 42	NR
Yang (2023) [62]	1, 2	Nusinersen	28 - Type 1 = 6 - Type 2 = 22	63 d.	p-FOIS longitudinal scores	Med = 3	Med 1) = 1 2) = 2 3) = 2	NR
					CHOP-INTEND	Mean (SD) - Type 1 (n = 6) = 19.5 (11.9)	Mean (SD) - Type 1 (n = 6) = 20.5 (12.1)	MD (SD), P value = NR (NR), P = 0.416
					HINE-2	Mean (SD) - Type 1 (n = 6) = 4.0 (2.9)	Mean (SD) - Type 1 (n = 6) = 4.5 (3.6)	MD (SD), P value = NR (NR), P = 0.416
					RULM	Mean (SD) - Type 2 (n = 20) = 15.8 (8.7)	Mean (SD) - Type 2 (n = 20) = 17.6 (9.3)	MD (SD), P value = NR (NR), P = 0.004
					HFMSE	Mean (SD) - Type 2 (n = 22) = 12.5 (9.8)	Mean (SD) - Type 2 (n = 22) = 15.0 (10.6)	MD (SD), P value = NR (NR), P = 0.000

CHOP-INTEND Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, D. day, HINE-2 Hammersmith Infant Neurological Examination-2, MFm motor function measurement, HFMSE Hammersmith Functional Motor Scale Expanded, MD mean difference, Mo. month, NA not applicable, NR no report, RULM Revised Upper Limb Module, WHO World Health Organization Developmental milestones.

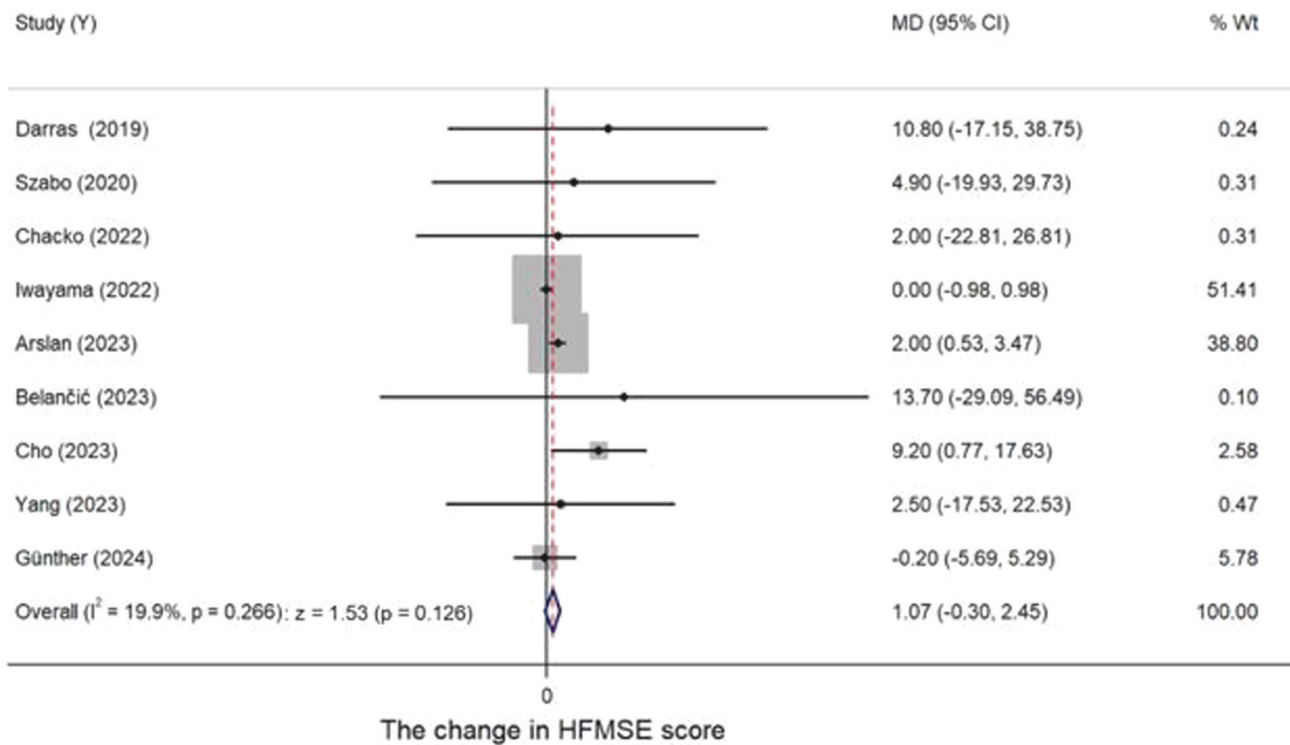


Fig. 5 Forest plot presenting the change in HFMSE score (limited to studies with nusinersen). md mean difference; wt weight.

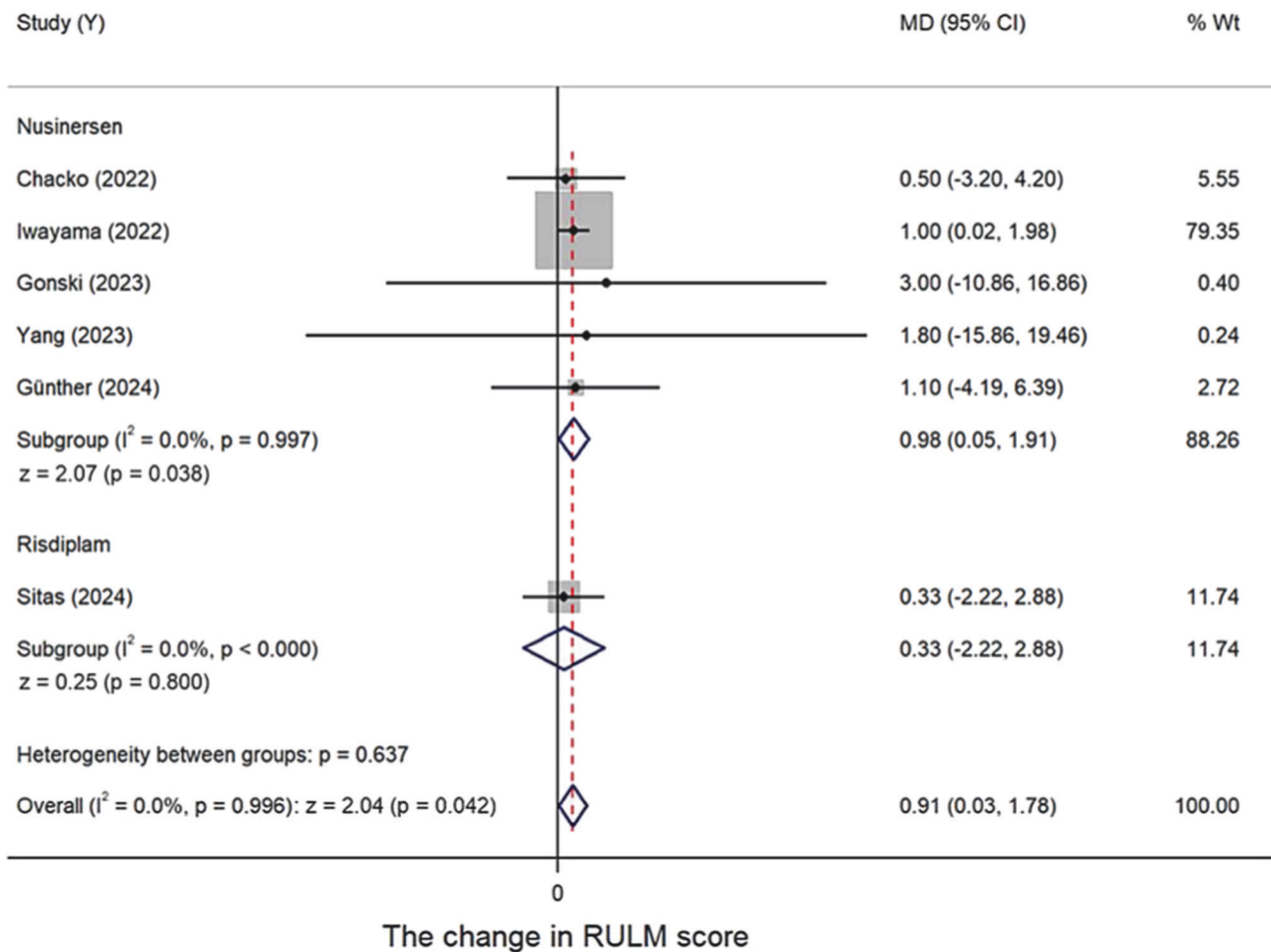


Fig. 6 Forest plot demonstrating the change in RULM score (limited to studies with nusinersen). md mean difference; wt weight.

Table 6. Summary of study outcomes regarding adverse drug reactions.

First author (y)	Types of SMA	Gene-based therapy	Sample size	Duration (mo.)	Details of adverse drug reactions	No. of pts. reported/ Total no. of pts.
Acsadi (2021) [22]	1, 2	Nusinersen	20	14	ADRs possibly related to treatment	2/20 (10%)
Cornell (2024) [52]	1, 2	Risdiplam	92	11	- Gastrointestinal disturbance = 7/92 (7.6%) - Pubertal/menstrual abnormalities = 1/92 (1.1%) - Skin and hair abnormalities = 1/92 (1.1%) - Mood change, memory and concentration difficulties = 1/92 (1.1%)	NR
Crawford (2023) [12]	1	Nusinersen	25	5-7 yr.	- Proteinuria = 1/25 (4%) - Hyperreflexia and tachycardia = 1/25 (4%) - Increased alkaline phosphatase and calcium and protein in urine = 1/25 (4%) - Increased platelet count = 1/25 (4%) - Muscular weakness, weight-bearing difficulty, extensor plantar response, clonus = 1/25 (4%) - Pyrexia, increased ALT, increased AST, increased eosinophil, lymphocyte, and WBC counts = 1/25 (4%) - Rash = 1/25 (4%) - Protein in urine = 1/25 (4%) - Allergic dermatitis = 1/25 (4%) - Headache = 1/25 (4%)	10/25 (40%)
Day (2021) [3]	1	Onasemnogene abeparvovec	22	18	- Hydrocephalus Common = 1/22 (5%) Serious = 1/22 (5%) - Increased alanine aminotransferase Common = 5/23 (23%) Serious = 1/22 (5%) - Increased aspartate aminotransferase Common = 6/22 (27%) Serious = 1/22 (5%) - Increased transaminase (aminotransferase) Common = 1/22 (5%) Serious = 1/22 (5%)	Common = 12/22 (55%) Serious = 3/22 (14%)
D'Silva (2022) [28]	1, 2	Onasemnogene abeparvovec	21	15	- Thrombocytopenia = 7/21 (33%) - Transaminitis = 12/21 (57%) - Vomiting = 21/21 (100%)	21/21 (100%)
Hahn (2022) [42]	1, 2	Risdiplam	111	12	- Gastrointestinal disorders Common = 51/111 (46%) Serious = 5/111 (3.8%) - General disorder and administration site conditions Common = 8/111 (7%) Serious = 1/111 (0.8%) - Infections and infestations Common = 4/111 (3%) Serious = 4/111 (3%) - Injury, poisoning and procedural complications = 11/111 (10%)	111/111 (100%)

Table 6. continued

First author (y)	Types of SMA	Gene-based therapy	Sample size	Duration (mo.)	Details of adverse drug reactions	No. of pts. reported/ Total no. of pts.
					- Nervous system disorders = 10/111 (9%) - Musculoskeletal and connective tissue disorders = 8/111 (7%) - Renal and urinary disorders = 2/111 (2%) - Skin and subcutaneous tissue disorders = 2/111 (2%) - Other (< 5%) = 34/111 (31%)	
Hepkaya (2022) [59]	1, 2	Nusinersen	30	12	Common - Headache (11.5%) - Malaise (4.5%) - Subfebrile fever (7%) - Vomiting (7%)	NR
Kwon (2022) [25]	1, 2	Risdiplam	155	4-8	Common - Constipation = 3/155 (1.9%) - Diarrhea = 3/155 (1.9%) - Dizziness = 2/155 (1.3%) - Headache = 3/155 (1.9%) - Insomnia = 2/155 (1.3%) - Nausea = 2/155 (1.3%) Serious - Constipation = 1/155 (0.6%) - Deep vein thrombosis = 1/155 (0.6%) - Systemic inflammatory response syndrome = 1/155 (0.6%)	Common = 25/155 (16.1%) Serious = 3/155 (1.9%)
Masson (2022) [13]	1	Risdiplam	41	24	- Maculopapular rash = 2/41 (5%) - Skin discolouration = 2/41 (5%) - Constipation = 2/41 (5%) - Increased aspartate aminotransferase = 1/41 (2%) - Increased eosinophilia = 1/41 (2%) - Increased neutropenia = 1/41 (2%) - Upper respiratory tract infection = 1/41 (2%) - Decreased neutrophil count = 1/41 (2%) - Pulmonary hypertension = 1/41 (2%)	7/41 (17%)
Mendell (2017) [9]	1	Onasemnogene abeparvovec	15	24–36	Elevations in aminotransferase levels	All = 4/15 (27%) - Low dose = 1/3 (33%) - High dose = 3/12 (25%)
Mercuri (2021) [10]	1	Onasemnogene abeparvovec	33	14	Common - Constipation = 1 (3%) - Gastro-esophageal reflux disease = 1 (3%) - Hypertension = 1 (3%) - Vomiting = 3 (9%) Common and serious - Abnormal coagulation test Common = 1 (3%) Serious = 1 (3%) Feeding disorder Common	24/33 (73%)

Table 6. continued

First author (y)	Types of SMA	Gene-based therapy	Sample size	Duration (mo.)	Details of adverse drug reactions	No. of pts. reported/ Total no. of pts.
					= 1 (3%) Serious = 1 (3%) Hypernatraemia Common = 1 (3%) Serious = 1 (3%) Hypertransaminasaemia Common = 8 (24%) Serious = 1 (3%) Gastroenteritis Common = 2 (6%) Serious = 1 (3%) Increased alanine aminotransferase Common = 7 (21%) Serious = 1 (3%) Increased aspartate aminotransferase Common = 6 (18%) Serious = 1 (3%) Pyrexia Common = 4 (12%) Serious = 2 (6%) Rhinovirus infection Common = 1 (3%) Serious = 1 (3%) Thrombocytopenia Common = 1 (3%) Serious = 1 (3%) Viral infection Common = 1 (3%) Serious = 1 (3%)	
Strauss (2022) [11]	1	Onasemnogene abeparvovec	14	18	- Increased aspartate aminotransferase = 3 (21%) - Increased alanine aminotransferase = 1 (7%) - Increased gamma-glutamyltransferase = 1 (7%) - Thrombocytopenia = 1 (7%) - Decreased platelet count = 1 (7%) - Increased blood creatine phosphokinase MB = 1 (7%) - Increased blood creatine phosphokinase = 1 (7%) - Increased troponin = 1 (7%)	7/14 (50%)

where it remains stable. Although the vectors have been developed from a nonpathogenic virus, evidence that the vector does not incorporate into host DNA is still lacking [71]. Gene therapies have been used to treat conditions such as Leber congenital amaurosis, HIV, and Alzheimer's disease. [72–74] Onasemnogene abeparvovec was approved by the US Food and Drug Administration in 2019, and it is the only approved medication for the treatment of SMA that works by replacing the SMN1 protein. This unique pharmacological property and its application may be one of the reasons why onasemnogene

abeparvovec demonstrated notable effects compared to the others. While there are still a limited number of studies investigating its effects, further research is warranted to confirm the effects of onasemnogene abeparvovec for SMA treatment. Long-term follow-up studies are crucial.

Unlike onasemnogene abeparvovec, nusinersen and risdiplam target the SMN2 gene. An additional SMN gene copy, also designated SMN2, resides on chromosome 5q13 and encodes the exon 7-skipped protein, which is unstable, mislocalized, and only partially functional [1]. Although the small amount of full-length

SMN protein derived from SMN2 is insufficient to fully compensate for the loss of SMN1, its production is essential for viability in the absence of SMN1. These characteristics define SMN2 as an ideal therapeutic target for the potential treatment of SMA, and the need for medication is lifelong. Nusinersen is an antisense oligonucleotide that binds to a specific sequence in intron 7 of SMN2 pre-mRNA to facilitate the inclusion of exon 7 in the final mRNA transcript, subsequently producing a functional SMN protein.

On the other hand, risdiplam is the first small molecule that works by increasing the inclusion of exon 7 of SMN2 transcripts, allowing the production of full-length SMN protein. According to our findings of the effects of gene-based therapy on patient survival and motor function improvement, risdiplam demonstrated relatively high effects, whereas nusinersen was moderate. Although both increase functional SMN2 transcript levels, their effects are still less than those of onasemnogene abeparvovec, which directly replaces the missing SMN1. Nusinersen was approved by the US Food and Drug Administration in 2016, and risdiplam was approved in 2020. Several studies investigating novel therapies targeting the SMN2 gene are currently underway. These studies emphasize the need for further research to confirm the effects of this type of treatment and to strengthen our findings from the current body of research.

Onasemnogene abeparvovec resulted in the highest number of patient survivals and motor function improvements and reduced the number of patients who needed ventilatory support. However, it showed approximately the same improvement in the CHOP-INTEND score as nusinersen. We believe this is because all the patients treated with onasemnogene abeparvovec had type 1 SMA, while those treated with nusinersen had a combination of types 1 and 2 SMA. Our findings were subject to clinical heterogeneity resulting from disparities in patient groups, and this might be key to nusinersen demonstrating relatively high effects, partly due to the less severe symptoms in patients with type 2 SMA. When we performed a subgroup analysis of the effects of gene-based therapy among patients with only type 1 SMA, onasemnogene abeparvovec improved the score more than nusinersen.

As to risdiplam, the results showed a nonsignificant difference in score changes; however, only a study by Darras et al. [13] was included in our analysis. In addition, the sample size of the study by Darras and colleagues was relatively small ($N = 41$) compared to those of onasemnogene abeparvovec ($N = 55$) and nusinersen ($N = 252$). Thus, definitive conclusions about the effects could not be drawn, suggesting that further large-scale studies are warranted to quantify the effects of risdiplam.

In analyzing Spinal Muscular Atrophy (SMA) treatments such as gene therapy, risdiplam, and nusinersen, the duration of observation after treatment initiation is crucial. Improvements can be observed as early as 1 month, with significant improvement often seen by 6–12 months. All studies include patients observed for more than 6 months, ensuring outcome improvements. However, response times can vary based on clinical trial data, with effectiveness influenced by the age at treatment start and disease severity [4, 10, 75].

Regarding the major serious ADR of onasemnogene abeparvovec, potentially life-threatening liver failure and thrombotic microangiopathy (TMA) associated with the drug are noted. However, these serious ADRs were not found from our systematic review (Table 6). Recent reports and FDA documents highlight that about one-third of patients treated with onasemnogene abeparvovec have experienced liver-related adverse events, including cases of serious liver failure. These events have led to the inclusion of a black box warning for liver toxicity, recommending systemic corticosteroid treatment for affected patients [76]. Additionally, nine patients out of approximately 1,400 treated with onasemnogene abeparvovec have experienced thrombotic

microangiopathy (TMA), a rare but serious condition that can cause low platelet counts and organ damage, and has resulted in death in some cases [76].

Several limitations should be acknowledged. First, in our review, we did not assess the quality of the included studies. Most of these studies are observational and are therefore subject to a high risk of bias, resulting in relatively low quality. While these studies represent the only available evidence regarding SMA treatment, caution should be exercised when interpreting the findings. The bias in these studies could impact their reported outcomes, thereby influencing the pooled estimates of the meta-analysis results.

Second, there were various characteristics of the patients in the included studies that might be associated with the effects of gene-based therapy. These characteristics include the first symptom onset, the baseline numbers of patients with ventilatory support, feeding support, and SMN2 copies, as well as the ages at starting treatment and the last follow-up. Unfortunately, we could not perform a meta-regression analysis of these factors due to the limited number of included studies. This indicates the need for further research to confirm the validity and reliability of the results. Furthermore, it is essential to note that some of the effects of gene-based therapy (onasemnogene abeparvovec and risdiplam) on motor function improvement were derived from a single study, raising concerns about the generalizability of the findings. Therefore, healthcare professionals should consider whether their settings are comparable before implementing gene-based therapy.

The value of this study is highlighted in two ways. First, it provides healthcare professionals and policymakers with current evidence of the effects of gene-based therapy for SMA. Additionally, the study offers insights into each type of gene-based therapy, namely, nusinersen, onasemnogene abeparvovec, and risdiplam. These insights will contribute to the development of future research in the field.

CONCLUSIONS

This review compiles current evidence relating to the effects of gene-based therapy for SMA types 1 and 2, demonstrating benefits to patient survival and motor function improvement. Onasemnogene abeparvovec and risdiplam appear highly effective, while nusinersen exhibits moderate effectiveness. Our findings provide healthcare professionals and policymakers with current evidence of the effects of gene-based therapy for SMA.

DATA AVAILABILITY

All datasets and data article cited in this manuscript were included in the reference list. Share data is available.

REFERENCES

1. Lefebvre S, Bürglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell*. 1995;80:155–65. [https://doi.org/10.1016/0092-8674\(95\)90460-3](https://doi.org/10.1016/0092-8674(95)90460-3)
2. Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. *Orphanet J Rare Dis*. 2017;12:124. <https://doi.org/10.1186/s13023-017-0671-8>
3. Day JW, Finkel RS, Chiriboga CA, Connolly AM, Crawford TO, Darras BT, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STRIVE): an open-label, single-arm, multicentre, phase 3 trial. *Lancet Neurol*. 2021;20:284–93. [https://doi.org/10.1016/S1474-4422\(21\)00001-6](https://doi.org/10.1016/S1474-4422(21)00001-6)
4. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med*. 2017;377:1723–32. <https://doi.org/10.1056/NEJMoa1702752>
5. Baranello G, Darras BT, Day JW, Deconinck N, Klein A, Masson R, et al. Risdiplam in type 1 spinal muscular atrophy. *N Engl J Med*. 2021;384:915–23. <https://doi.org/10.1056/NEJMoa2009965>

6. Abbas KS, Eltaras MM, El-Shahat NA, Abdelazeem B, Shaqfeh M, Brašić JR. The safety and efficacy of nusinersen in the treatment of spinal muscular atrophy: a systematic review and meta-analysis of randomized controlled trials. *Med (Kau-nas)*. 2022;58:213. <https://doi.org/10.3390/medicina58020213>
7. Pascual-Morena C, Cervero-Redondo I, Lucerón-Lucas-Torres M, Martínez-García I, Rodríguez-Gutiérrez E, Martínez-Vizcaíno V. Onasemnogene abeparovect in type 1 spinal muscular atrophy: a systematic review and meta-analysis. *Hum Gene Ther*. 2023;34:129–38. <https://doi.org/10.1089/hum.2022.161>
8. Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: final report of a phase 2, open-label, multicentre, dose-escalation study. *Lancet Child Adolesc Health*. 2021;5:491–500. [https://doi.org/10.1016/S2352-4642\(21\)00100-0](https://doi.org/10.1016/S2352-4642(21)00100-0)
9. Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med*. 2017;377:1713–22. <https://doi.org/10.1056/NEJMoa1706198>
10. Mercuri E, Muntoni F, Baranello G, Masson R, Boespflug-Tanguy O, Bruno C, et al. Onasemnogene abeparovect gene therapy for symptomatic infantile-onset spinal muscular atrophy type 1 (STRIVE-EU): an open-label, single-arm, multi-centre, phase 3 trial. *Lancet Neurol*. 2021;20:832–41. [https://doi.org/10.1016/S1474-4422\(21\)00251-9](https://doi.org/10.1016/S1474-4422(21)00251-9)
11. Strauss KA, Farrar MA, Muntoni F, Saito K, Mendell JR, Servais L, et al. Onasemnogene abeparovect for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the Phase III SPRINT trial. *Nat Med*. 2022;28:1381–9. <https://doi.org/10.1038/s41591-022-01866-4>
12. Crawford TO, Swoboda KJ, De Vivo DC, Bertini E, Hwu WL, Finkel RS, et al. Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study. *Muscle Nerve*. 2023;68:157–70. <https://doi.org/10.1002/mus.27853>
13. Masson R, Mazurkiewicz-Beldzińska M, Rose K, Servais L, Xiong H, Zanoteli E, et al. Safety and efficacy of risdiplam in patients with type 1 spinal muscular atrophy (FIREFISH part 2): secondary analyses from an open-label trial. *Lancet Neurol*. 2022;21:1110–9. [https://doi.org/10.1016/S1474-4422\(22\)00339-8](https://doi.org/10.1016/S1474-4422(22)00339-8)
14. De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscul Disord*. 2019;29:842–56. <https://doi.org/10.1016/j.nmd.2019.09.007>
15. Glascock J, Sampson J, Haidet-Phillips A, Connolly A, Darras B, Day J, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. *J Neuromuscul Dis*. 2018;5:145–58. <https://doi.org/10.3233/JND-180304>
16. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg*. 2003;73:712–6. <https://doi.org/10.1046/j.1445-2197.2003.02748.x>
17. Higgins JPT, Savovic J, Page MJ, Hróbjartsson A, Boutron I, et al. A revised tool for assessing risk of bias in randomized trials. In: Chandler J, McKenzie J, Boutron I, Welch V, editors. *Cochrane Methods. Cochrane Database of Systematic Reviews*; 2016. Issue 10 (Suppl 1). <https://doi.org/10.1002/14651858.CD201601>
18. Abbas A, Hassan MA, Shaheen RS, Hussein A, Moawad M, Meshref M, et al. Safety and efficacy of unilateral focused ultrasound pallidotomy on motor complications in Parkinson's disease (PD): a systematic review and meta-analysis. *Neurol Sci*. 2024. <https://doi.org/10.1007/s10072-024-07617-2>
19. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health*. 2014;72:39. <https://doi.org/10.1186/2049-3258-72-39>
20. Higgins JPT, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd Edition. Chichester (UK): John Wiley & Sons, 2019.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–34. <https://doi.org/10.1136/bmj.315.7109.629>
22. Acsadi G, Crawford TO, Müller-Felber W, Shieh PB, Richardson R, Natarajan N, et al. Safety and efficacy of nusinersen in spinal muscular atrophy: The EMBRACE study. *Muscle Nerve*. 2021;63:668–77. <https://doi.org/10.1002/mus.27187>
23. Darras BT, Chiriboga CA, Iannaccone ST, Swoboda KJ, Montes J, Mignon L, et al. Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies. *Neurology*. 2019;92:e2492–e506. <https://doi.org/10.1212/WNL.00000000000007527>
24. Chiriboga CA, Swoboda KJ, Darras BT, Iannaccone ST, Montes J, De Vivo DC, et al. Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. *Neurology*. 2016;86:890–7. <https://doi.org/10.1212/WNL.00000000000002445>
25. Kwon JM, Arya K, Kuntz N, Phan HC, Sieburg C, Swoboda KJ, et al. An expanded access program of risdiplam for patients with Type 1 or 2 spinal muscular atrophy. *Ann Clin Transl Neurol*. 2022;9:810–8. <https://doi.org/10.1002/acn3.51560>
26. Chacko A, Sly PD, Ware RS, Begum N, Deegan S, Thomas N, et al. Effect of nusinersen on respiratory function in paediatric spinal muscular atrophy types 1–3. *Thorax*. 2022;77:40–6. <https://doi.org/10.1136/thoraxjnl-2020-216564>
27. Chen KA, Widger J, Teng A, Fitzgerald DA, D'Silva A, Farrar M. Real-world respiratory and bulbar comorbidities of SMA type 1 children treated with nusinersen: 2-Year single centre Australian experience. *Paediatr Respir Rev*. 2021;39:54–60. <https://doi.org/10.1016/j.prrv.2020.09.002>
28. D'Silva AM, Holland S, Kariyawasam D, Herbert K, Barclay P, Cairns A, et al. Onasemnogene abeparovect in spinal muscular atrophy: an Australian experience of safety and efficacy. *Ann Clin Transl Neurol*. 2022;9:339–50. <https://doi.org/10.1002/acn3.51519>
29. Gonski K, Chuang S, Teng A, Thambipillay G, Farrar MA, Menezes MP, et al. Respiratory and sleep outcomes in children with SMA treated with nusinersen - real world experience. *Neuromuscul Disord*. 2023;33:531–8. <https://doi.org/10.1016/j.nmd.2023.04.007>
30. Aragon-Gawinska K, Seferian AM, Daron A, Gargaun E, Vuillerot C, Cancas C, et al. Nusinersen in patients older than 7 months with spinal muscular atrophy type 1: A cohort study. *Neurology*. 2018;91:e1312–e8. <https://doi.org/10.1212/WNL.00000000000006281>
31. Audic F, Dubois SM, Durigneux J, Barnerias C, Isapof A, Nougues MC, et al. Effect of nusinersen after 3 years of treatment in 57 young children with SMA in terms of SMN2 copy number or type. *Arch Pediatr*. 2024;31:117–23. <https://doi.org/10.1016/j.arcped.2023.10.009>
32. Gómez-García de la Banda M, Amaddeo A, Khirani S, Pruvost S, Barnerias C, Dabaj I, et al. Assessment of respiratory muscles and motor function in children with SMA treated by nusinersen. *Pediatr Pulmonol*. 2021;56:299–306. <https://doi.org/10.1002/ppul.25142>
33. Hully M, Barnerias C, Chabaliere D, Le Guen S, Germa V, Deladriere E, et al. Palliative care in SMA type 1: a prospective multicenter french study based on parents' reports. *Front Pediatr*. 2020;8:4. <https://doi.org/10.3389/fped.2020.00004>
34. Belančić A, Strbad T, Kučan Stiglic M, Vitezić D. Effectiveness of nusinersen in type 1, 2 and 3 spinal muscular atrophy: croatian real-world data. *J Clin Med*. 2023;12:2839. <https://doi.org/10.3390/jcm12082839>
35. Belančić A, Strbad T, Kučan Stiglic M, Vitezić D. Switching from nusinersen to risdiplam: a Croatian real-world experience on effectiveness and safety. *J Pers Med*. 2024;14:244. <https://doi.org/10.3390/jpm14030244>
36. Sitas B, Hancevic M, Bilic K, Bilic H, Bilic E. Risdiplam real world data - looking beyond motor neurons and motor function measures. *J Neuromuscul Dis*. 2024;11:75–84. <https://doi.org/10.3233/JND-230197>
37. Pane M, Coratti G, Sansone VA, Messina S, Catteruccia M, Bruno C, et al. Type I spinal muscular atrophy patients treated with nusinersen: 4-year follow-up of motor, respiratory and bulbar function. *Eur J Neurol*. 2023;30:1755–63. <https://doi.org/10.1111/ene.15768>
38. Sansone VA, Pirola A, Albamonte E, Pane M, Lizio A, D'Amico A, et al. Respiratory needs in patients with type 1 spinal muscular atrophy treated with nusinersen. *J Pediatr*. 2020;219:223–8 e4. <https://doi.org/10.1016/j.jpeds.2019.12.047>
39. Bitetti L, Manna MR, Stella R, Varone A. Motor and neurocognitive profiles of children with symptomatic spinal muscular atrophy type 1 with two copies of SMN2 before and after treatment: a longitudinal observational study. *Front Neurol*. 2024;15:1326528. <https://doi.org/10.3389/fneur.2024.1326528>
40. Favia M, Tarantino D, Cerbo LD, Sabia A, Campopiano R, Pani M. Onasemnogene abeparovect: post-infusion efficacy and safety in patients with spinal muscular atrophy (SMA)-A Fondazione Policlinico Gemelli IRCCS Experience. *Hosp Pharm*. 2024;59:39–46. <https://doi.org/10.1177/00185787231182562>
41. Pechmann A, Langer T, Schorling D, Stein S, Schara U, et al. Evaluation of children with SMA type 1 under treatment with nusinersen within the expanded access program in Germany. *J Neuromuscul Dis*. 2018;5:135–43. <https://doi.org/10.3233/JND-180315>
42. Hahn A, Günther R, Ludolph A, Schwartz O, Trollmann R, Weydt P, et al. Short-term safety results from compassionate use of risdiplam in patients with spinal muscular atrophy in Germany. *Orphanet J Rare Dis*. 2022;17:276. <https://doi.org/10.1186/s13023-022-02420-8>
43. Kotulska K, Chmielewski D, Mazurkiewicz-Beldzińska M, Tomaszek K, Pierzchlewicz K, Rabcenko D, et al. Safety, tolerability, and efficacy of a widely available nusinersen program for Polish children with Spinal Muscular Atrophy. *Eur J Paediatr Neurol*. 2022;39:103–9. <https://doi.org/10.1016/j.ejpn.2022.06.001>
44. Modrzejewska S, Kotulska K, Kopyta I, Grędowska E, Emich-Widera E, Tomaszek K, et al. Nusinersen treatment of Spinal Muscular Atrophy Type 1 - results of expanded access programme in Poland. *Neurol Neurochir Pol*. 2021;55:289–94. <https://doi.org/10.5603/PJNNS.a2021.0020>
45. Łusakowska A, Wójcik A, Frączek A, Aragon-Gawinska K, Potulska-Chromik A, Baranowski P, et al. Long-term nusinersen treatment across a wide spectrum of spinal muscular atrophy severity: a real-world experience. *Orphanet J Rare Dis*. 2023;18:230. <https://doi.org/10.1186/s13023-023-02769-4>

46. Szabo L, Gergely A, Jakus R, Fogarasi A, Grosz Z, Molnár MJ, et al. Efficacy of nusinersen in type 1, 2 and 3 spinal muscular atrophy: Real world data from Hungarian patients. *Eur J Paediatr Neurol*. 2020;27:37–42. <https://doi.org/10.1016/j.ejpn.2020.05.002>
47. Iwayama H, Kawahara K, Takagi M, Numoto S, Azuma Y, Kurahashi H, et al. Long-term efficacy of nusinersen and its evaluation in adolescent and adult patients with spinal muscular atrophy types 1 and 2. *Brain Dev*. 2023;45:110–6. <https://doi.org/10.1016/j.braindev.2022.10.006>
48. Tachibana Y, Sato R, Makioka H, Hoshino M, Jin M. Safety and effectiveness of nusinersen, a treatment for spinal muscular atrophy, in 524 patients: results from an interim analysis of post-marketing surveillance in Japan. *Int J Neurosci*. 2023;1–13. <https://doi.org/10.1080/00207454.2023.2251662>
49. Kim AR, Lee JM, Min YS, Lee H, Kim D, Hwang SK, et al. Clinical experience of nusinersen in a broad spectrum of spinal muscular atrophy: a retrospective study. *Ann Indian Acad Neurol*. 2020;23:796–801. https://doi.org/10.4103/aian.AIAN_524_20
50. Cho J, Lee J, Kim J, Lee H, Kim MJ, Lee YJ, et al. Nusinersen demonstrates effectiveness in treating spinal muscular atrophy: findings from a three-year nationwide study in Korea. *Front Neurol*. 2023;14:1294028. <https://doi.org/10.3389/fneur.2023.1294028>
51. Weststrate H, Stimpson G, Thomas L, Scoto M, Johnson E, Stewart A, et al. Evolution of bulbar function in spinal muscular atrophy type 1 treated with nusinersen. *Dev Med Child Neurol*. 2022;64:907–14. <https://doi.org/10.1111/dmcn.15171>
52. Cornell N, Childs AM, Wraige E, Munot P, Ambegaonkar G, Chow G, et al. Risdiplam in spinal muscular atrophy: safety profile and use through the early access to medicine scheme for the paediatric cohort in Great Britain. *J Neuromuscul Dis*. 2024;11:361–8. <https://doi.org/10.3233/JND-230162>
53. Tokatly Latzer I, Sagi L, Lavi R, Aharoni S, Bistrizter J, Noyman I, et al. Real-life outcome after gene replacement therapy for spinal muscular atrophy: a multi-center experience. *Pediatr Neurol*. 2023;144:60–8. <https://doi.org/10.1016/j.pediatrneurol.2023.04.007>
54. Ali HG, Ibrahim K, Elsaid MF, Mohamed RB, Abeidah MIA, Al Rawwas AO, et al. Gene therapy for spinal muscular atrophy: the Qatari experience. *Gene Ther*. 2021;28:676–80. <https://doi.org/10.1038/s41434-021-00273-7>
55. Olsson B, Alberg L, Cullen NC, Michael E, Wahlgren L, Kroksmark AK, et al. NFL is a marker of treatment response in children with SMA treated with nusinersen. *J Neurol*. 2019;266:2129–36. <https://doi.org/10.1007/s00415-019-09389-8>
56. Tschertner A, Rüsch CT, Baumann D, Enzmann C, Hasselmann O, Jacquier D, et al. Evaluation of real-life outcome data of patients with spinal muscular atrophy treated with nusinersen in Switzerland. *Neuromuscul Disord*. 2022;32:399–409. <https://doi.org/10.1016/j.nmd.2022.02.001>
57. Axente M, Mirea A, Sporea C, Pădure L, Drăgoi CM, Nicolae AC, et al. Clinical and electrophysiological changes in pediatric spinal muscular atrophy after 2 years of nusinersen treatment. *Pharmaceutics*. 2022;14:2074. <https://doi.org/10.3390/pharmaceutics14102074>
58. Mirea A, Leanca MC, Onose G, Sporea C, Padure L, Shelby ES, et al. Physical therapy and nusinersen impact on spinal muscular atrophy rehabilitative outcome. *Front Biosci (Landmark Ed)*. 2022;27:179. <https://doi.org/10.31083/j.fbl2706179>
59. Hepkaya, Kilinc Sakalli E, Ülkersoy AA, İ, Başkan AK, Arslan H, et al. The effects of nusinersen treatment on respiratory status of children with spinal muscular atrophy. *Pediatr Int*. 2022;64:e15310. <https://doi.org/10.1111/ped.15310>
60. Ergenekon AP, Yilmaz Yegit C, Cenk M, Gokdemir Y, Erdem Eralp E, Ozturk G, et al. Respiratory outcome of spinal muscular atrophy type 1 patients treated with nusinersen. *Pediatr Int*. 2022;64:e15175. <https://doi.org/10.1111/ped.15175>
61. Arslan D, Inan B, Kilinc M, Bekircan-Kurt CE, Erdem-Ozdamar S, Tan E. Nusinersen for adults with spinal muscular atrophy. *Neurol Sci*. 2023;44:2393–400. <https://doi.org/10.1007/s10072-023-06698-9>
62. Yang H, Tao Q, Li D, Yang J, Cai Q, Gan J, et al. Assessment of motor function and nutritional status in children with spinal muscular atrophy treated with nusinersen after loading period in Western China: a retrospective study. *BMC Neurol*. 2023;23:35. <https://doi.org/10.1186/s12883-023-03063-3>
63. Artemyeva SB, Papina YO, Shidlovskaya OA, Monakhova AV, Vlodavets DV. Experience of using gene replacement therapy with Zolgensma® (onasemnogene abeparvovec) in real clinical practice in Russia. *Neuromuscul Dis*. 2022;12:29–38. <https://doi.org/10.17650/2222-8721-2022-12-1-29-38>
64. De Holanda Mendonca R, Jorge Polido G, Giro M, Jorge Fontoura Solla D, Conti Reed U, Zanoteli E. Clinical Outcomes in Patients with Spinal Muscular Atrophy Type 1 Treated with Nusinersen. *J Neuromuscul Dis*. 2021;8:217–24. <https://doi.org/10.3233/JND-200533>
65. Osredkar D, Jilková M, Butenko T, Loboda T, Golli T, Fuchsová P, et al. Children and young adults with spinal muscular atrophy treated with nusinersen. *Eur J Paediatr Neurol*. 2021;30:1–8. <https://doi.org/10.1016/j.ejpn.2020.11.004>
66. Chan SH, Chae JH, Chien YH, Ko TS, Lee JH, Lee YJ, et al. Nusinersen in spinal muscular atrophy type 1 from neonates to young adult: 1-year data from three Asia-Pacific regions. *J Neurol Neurosurg Psychiatry*. 2021;92:1244–6. <https://doi.org/10.1136/jnnp-2020-324532>
67. Weiß C, Ziegler A, Becker LL, Johannsen J, Brennenstuhl H, Schreiber G, et al. Gene replacement therapy with onasemnogene abeparvovec in children with spinal muscular atrophy aged 24 months or younger and bodyweight up to 15 kg: an observational cohort study. *Lancet Child Adolesc Health*. 2022;6:17–27. [https://doi.org/10.1016/S2352-4642\(21\)00287-X](https://doi.org/10.1016/S2352-4642(21)00287-X)
68. Aragon-Gawinska K, Daron A, Ulinici A, Vanden Brande L, Seferian A, Gidaro T, et al. Sitting in patients with spinal muscular atrophy type 1 treated with nusinersen. *Dev Med Child Neurol*. 2020;62:310–4. <https://doi.org/10.1111/dmcn.14412>
69. Günther R, Wurster CD, Brakemeier S, Osmanovic A, Schreiber-Katz O, Petri S, et al. Long-term efficacy and safety of nusinersen in adults with 5q spinal muscular atrophy: a prospective European multinational observational study. *Lancet Reg Health Eur*. 2024;39:100862. <https://doi.org/10.1016/j.lanepe.2024.100862>
70. Friedmann T, Roblin R. Gene therapy for human genetic disease? *Science*. 1972;175:949–55. <https://doi.org/10.1126/science.175.4025.949>
71. Choudhury SR, Hudry E, Maguire CA, Sena-Esteves M, Breakefield XO, Grandi P. Viral vectors for therapy of neurologic diseases. *Neuropharmacology*. 2017;120:63–80. <https://doi.org/10.1016/j.neuropharm.2016.02.013>
72. Luxturna. (voretigene neparvovec-rzyl) intraocular suspension for subretinal injection Spark Therapeutics Available at: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=08313a24-e7ce-457a-bb3f-161bc45517ee> Accessed October 7, 2022.
73. Cornu TI, Mussolino C, Muller MC, Wehr C, Kern WV, Cathomen T. HIV gene therapy: an update. *Hum Gene Ther*. 2021;32:52–65. <https://doi.org/10.1089/hum.2020.159>
74. Nilsson P, Iwata N, Muramatsu S, Tjernberg LO, Winblad B, Saido TC. Gene therapy in Alzheimer's disease - potential for disease modification. *J Cell Mol Med*. 2010;14:741–57. <https://doi.org/10.1111/j.1582-4934.2010.01038.x>
75. Lowes LP, Alfano LN, Arnold WD, Shell R, Prior TW, McColly M, et al. Impact of age and motor function in a phase 1/2A study of infants with SMA type 1 receiving single-dose gene replacement therapy. *Pediatr Neurol*. 2019;98:39–45. <https://doi.org/10.1016/j.pediatrneurol.2019.05.005>
76. Novartis AG Zolgensma acute liver failure update [Internet]. c2024 [updated 2022 Aug 11; cited 2024 Aug 10]. Available from: <https://www.novartis.com/news/zolgensma-acute-liver-failure-update>.

ACKNOWLEDGEMENTS

We thank David Park for English Editing, Dr. Pattara Leelahavarong for the suggestion and Cheewasan Apirukphanakhet for study coordination.

AUTHOR CONTRIBUTIONS

BC: Contributed to the design and execution of the study, assessed the quality of the included studies, analyzed the data, discussed the results, drew conclusions, and wrote the manuscript with support from OS. BC also contributed to the final manuscript. OS: Contributed to the design and execution of the study, analyzed the data, discussed the results, and provided support in writing the manuscript. OS also contributed to the final manuscript. TS: Collected the data, assessed the quality of the included studies, and participated in discussions regarding the results. TS also contributed to the final manuscript. PV: Collected the data and participated in discussions regarding the results. PV also contributed to the final manuscript. VY: Collected the data, analyzed the data, discussed the results, and contributed to writing the manuscript. VY also contributed to the final manuscript.

FUNDING

This study was supported by a research grant from the Ratchadaphiseksomphot Endowment Fund of Chulalongkorn University (ReinUni_65_01_33_27) and the Siriraj Research Developmental Fund, Faculty of Medicine, Siriraj Hospital, Mahidol University (R016437001).

COMPETING INTERESTS

OS received research grant from Novartis and Thermo Fisher Scientific. OS received honoraria for lectures and Speaker's Bureau from F. Hoffmann–La Roche and Novartis. OS serves as a board member of the Foundation to Eradicate Neuromuscular Diseases (FEND) and advisory panel for Thai SMA group.

ETHICAL APPROVAL

This systematic review and meta-analysis does not require IRB approval.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41434-024-00503-8>.

Correspondence and requests for materials should be addressed to Varalee Yodsurang or Oranee Sanmaneechai.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

© The Author(s) 2024