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ORIGINAL RESEARCH

Effectiveness of Nusinersen in Adolescents and Adults with Spinal Muscular Atrophy: Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Nusinersen clinical trials have limited data on adolescents and adults with 5q-associated spinal muscular atrophy (SMA). We conducted a systematic literature review (SLR) and meta-analysis to assess effectiveness of nusinersen in adolescents and adults with SMA in clinical practice.

Methods: Our search included papers published 12/23/2016 through 07/01/2022 with ≥ 5 individuals ≥ 13 years of age and with ≥ 6 months' data on ≥ 1 selected motor function outcomes [Hammersmith Functional Motor Scale–Expanded (HFMSE), Revised Upper Limb Module (RULM), and Six-Minute Walk Test (6MWT)]. For meta-analysis, effect sizes were pooled using random-effects models. To understand treatment effects by disease severity, subgroup meta-analysis by SMA type and ambulatory status was conducted.

Results: Fourteen publications including 539 patients followed up to 24 months met inclusion criteria for the SLR. Patients were age 13–72 years and most (99%) had SMA Type II or III. Modest improvement or stability in motor function was consistently observed at the group level. Significant mean increases from baseline were observed in HFMSE [2.3 points (95% CI 1.3–3.3)] with 32.1% (21.7–44.6) of patients demonstrating a clinically meaningful increase (≥ 3 points) at 18 months. Significant increases in RULM were consistently found, with a mean increase of 1.1 points (0.7–1.4) and 38.3% (30.3–47.1) showing a clinically meaningful improvement (≥ 2 points) at 14 months. Among ambulatory patients, there was a significant increase in mean 6MWT distance of 25.0 m (8.9–41.2) with 50.9% (33.4–68.2) demonstrating a

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clinically meaningful improvement (≥ 30 m) at 14 months. The increases in HFMSE were greater for less severely affected patients, whereas more severely affected patients showed greater improvement in RULM.
Conclusions: Findings provide consolidated evidence that nusinersen is effective in improving or stabilizing motor function in many adolescents and adults with a broad spectrum of SMA.

PLAIN LANGUAGE SUMMARY

Motor neurons are specialized cells in the brain and spinal cord that control the function of muscles. People with spinal muscular atrophy (SMA) do not make enough survival motor neuron (SMN) protein, which motor neurons need to function. As a result, people with SMA experience decreased muscle function that gets worse over time. Nusinersen is a drug that increases the amount of SMN protein made in the brain and spinal cord. However, most clinical trials of nusinersen have been in infants and children with SMA. Less is known about the effects of nusinersen in teenagers and adults with SMA who may have less severe but still progressive forms of the disease. In this manuscript, we first conducted a thorough review and analysis of research published by investigators who treated teenagers and adults with nusinersen for up to 24 months. We then used an additional analysis, called a meta-analysis, that allowed us to combine the information from several articles, so that we could better understand whether nusinersen helped these patients. We looked at 3 tests that investigators used to see how nusinersen affected patients' motor function. The Hammersmith Functional Motor Scale–Expanded (HFMSE) assesses upper and lower limb motor function; the Revised Upper Limb Module (RULM) evaluates upper limb function; and the Six-Minute Walk Test (6MWT) measures the maximum distance a person can walk in 6 minutes. Our study showed that nusinersen can improve motor function or prevent motor function from getting worse in many teenagers and adults with SMA.

Keywords: Adults; Adolescents; Motor function; Hammersmith Functional Motor Scale–Expanded; Nusinersen; Revised Upper Limb Module; Six-Minute Walk Test; Spinal muscular atrophy

Key Summary Points

Why carry out this study?

Nusinersen clinical trials have limited data on adolescents and adults with 5q-associated spinal muscular atrophy (SMA), and clinicians and decision-makers rely on real-world data to fill this evidence gap.

There are two previously published systematic literature reviews and meta-analyses assessing the effectiveness of nusinersen, one including patients of all ages, the other including patients ≥ 12 years.

Our analysis included comprehensive subgroup analyses based on SMA type and ambulatory status, which were not fully available in the prior two reviews; this information could significantly improve the clinical interpretation and application of study findings, given the considerable heterogeneity in motor function within each SMA type in adolescents and adults.

What was learned from this study?

Based on the most up-to-date literature search, 14 publications including 539 adolescents and adults followed up to 24 months were included in the literature review and meta-analysis, with findings indicating that nusinersen is effective in improving or stabilizing motor function in many adolescents and adults with SMA over a treatment period of up to 24 months.

Selecting a sensitive scale is important when evaluating outcomes in adolescents and adults with SMA. Type III patients, particularly those who are ambulatory, are more likely to demonstrate a benefit on Hammersmith Functional Motor Scale–Expanded, while those who are Type II or non-ambulatory (regardless of type) are more likely to demonstrate a benefit on Revised Upper Limb Module .

INTRODUCTION

5q-associated spinal muscular atrophy (SMA) is a hereditary neuromuscular disease characterized by neurodegeneration, progressive muscle atrophy, and weakness [1]. It is caused by homozygous deletion or mutation of the survival of motor neuron 1 (*SMN1*) gene and subsequent SMN protein deficiency [1], which results in degeneration of motor neurons in the spinal cord and brain stem [2]. Expression of a paralogous gene, *SMN2,* produces a small amount of functional SMN protein but not enough to compensate for loss of *SMN1* [2].

SMA is traditionally classified into five types (0–IV) based on age of symptom onset and highest motor milestone achieved [2, 3]. The phenotype varies within and between SMA types, with individuals exhibiting a range of functional abilities [4]. Type 0 is a rare but severe form of SMA with death occurring within several weeks of birth [1, 3]. Infants with SMA Type I, also referred to as infantile-onset SMA, have symptom onset within the first 6 months of life and are unable to sit without support [2]. Individuals with Type II have symptom onset between 6 and 18 months and can sit independently but not walk [2]. Those with Type III have symptom onset after 18 months of age and can stand and walk independently [2]. Type IV is the mildest and rarest form, with symptoms often developing in early adulthood [2, 3]. Irrespective of the classification, individuals diagnosed with SMA experience progressive loss of motor function throughout their lifetime.

About half of the prevalent SMA patient population consists of adolescents and adults. Among the adolescent and adult population, the vast majority have a later-onset (Type II or III) phenotype [5], while a small proportion comprises surviving progressed Type I patients and those with Type IV [6]. There is substantial heterogeneity in the motor function abilities and ambulatory status of adolescents and adults with SMA [7], especially for those with SMA Type III who show significant variability in losing the ability to walk over time [8]. Contractures and scoliosis are frequent, especially in individuals with SMA Types II and III who are unable to walk [8].

The prospects for care and expected disease trajectories of SMA have been changing since the introduction of disease-modifying therapies (DMTs) [9]. Nusinersen, an antisense oligonucleotide and the first approved DMT for the treatment of SMA across all phenotypes and ages, modulates splicing of *SMN2* pre-messenger RNA to promote production of full-length SMN protein [3]. Clinical trials of nusinersen have demonstrated significant and clinically meaningful improvements in motor function, survival, and other outcomes across a broad range of primarily pediatric populations, including individuals with presymptomatic, infantile-onset, and later-onset SMA [10–18].

With the clinical focus primarily on infants and children most severely affected by SMA, adolescents and adults have been less extensively studied in the nusinersen clinical development program. However, nusinersen has been widely used in clinical practice to treat adolescents and adults with SMA, and data on the effectiveness of nusinersen on motor function have accumulated from real-world practice [19–21]. However, consolidating the findings of these studies is challenging due to clinical heterogeneity as well as differences in methodological approaches across real-world studies. Previously published reviews on this topic did not provide comprehensive analysis by SMA Type and ambulatory status, which is important to understand the treatment effects in adolescents and adults with wide clinical heterogeneity.

The objective of the current study is to provide a comprehensive assessment of the effectiveness of nusinersen on motor function in adolescents and adults with SMA through a systematic literature review (SLR) and meta-analysis of published studies. The SLR aimed to review all available evidence to date on motor function outcomes in adolescent and adult patients with SMA treated with nusinersen. The meta-analysis aimed to consolidate the quantitative findings of publications while accounting for the heterogeneity in patient characteristics and methodological approaches across different publications.

METHODS

This SLR and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [22] (supplementary appendix). The SLR was not prospectively registered in a protocol registry.

Systematic Literature Search

A SLR was conducted to identify published clinical and observational studies reporting the efficacy and effectiveness of nusinersen on motor function outcomes in adolescents and adults with SMA. A prespecified search strategy was used to capture all relevant studies published in peer-reviewed journals from December 23, 2016 (US Food and Drug Administration approval date of nusinersen) to July 1, 2022 in Embase, MEDLINE, and PubMed (see supplementary appendix Tables S1–S3 for search strategy in each database).

Publications were screened according to the prespecified criteria describing the population, intervention, comparator, outcomes, and study types (PICOS; supplementary appendix Table S4). In summary, studies were included if they had ≥ 5 patients with SMA initiating nusinersen at age ≥ 13 years. Broad search terms for age were used to capture studies that included individuals beyond the age eligibility criteria of the phase 3 CHERISH clinical trial (2–12 years of age at screening) [15] and to account for the varying definitions of adolescents and adulthood across different countries. To allow for evaluation of clinical outcomes after the loading dose phase of nusinersen, a minimum of 6 months' follow-up data on ≥ 1 of the following motor function outcome measures were required: Hammersmith Functional Motor Scale–Expanded (HFMSE), Revised Upper Limb Module (RULM), and Six-Minute Walk Test (6MWT). These three validated outcome measures are frequently used in clinical practice for the assessment of motor function in adolescents and adults with SMA; consequently, they commonly appear in the literature [23] and are the focus of this SLR and meta-analysis. The HFMSE consists of 33 items assessing the upper and lower limb motor function in patients with later-onset SMA (range, 0–66) [24]. The RULM consists of 19 items evaluating the upper limb function and reflecting functional abilities across ambulatory and non-ambulatory patients (range, 0–37) [25]. In both assessments, higher scores indicate a better motor function. The 6MWT evaluates exercise capability in ambulatory patients and measures the maximum distance a person can walk in 6 minutes [26]. Both clinical and observational studies with or without comparator groups were screened for inclusion in the SLR. Case reports or case series with < 5 patients were excluded. Clinically meaningful response was defined as a change of ≥ 3 points for HFMSE, ≥ 2 points for RULM, and ≥ 30 m for 6MWT, based on the thresholds commonly reported in the literature [26–28].

Two independent reviewers performed the Level 1 (title and abstract) and Level 2 (full text) screening according to the PICOS criteria, and any discrepancies were adjudicated. All exclusion reasons were recorded for Level 2 screening.

Two independent abstractors extracted study information from the publications included in the SLR, including study setting and design, baseline demographic and clinical characteristics, and motor function outcomes on HFMSE, RULM, and 6MWT during the follow-up period. The risk of bias in the studies included in the SLR was systematically assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, given that all identified studies used a non-randomized, observational

design [29]. Studies were evaluated with respect to seven domains: confounding, selection bias, measurement of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results.

Meta-Analysis

Each publication meeting inclusion criteria for the SLR was further evaluated for inclusion in the meta-analysis. Studies were included in the meta-analysis if they (1) reported mean changes in HFMSE, RULM, and 6MWT scores from baseline, defined as nusinersen initiation to specific timepoints (e.g., 6, 10, 14, or 18 months from baseline) and associated standard deviations (SDs), or (2) provided individual patient data to permit calculation of these parameters.

Effect sizes were pooled across publications using random-effects models with the inverse variance method. Pooled estimates and their 95% confidence intervals (CIs) were obtained for (1) mean difference in motor function scores from baseline to 6, 10, 14, and 18 months of follow-up, and (2) percentage of patients with a clinically meaningful response during the same period. Percentages were pooled using logit transformation and normal approximation for CIs. Heterogeneity between publications (i.e., the level of consistency between study findings) was examined using the I^2 statistic, which measures the proportion of the total variance that can be explained by between-study variance [30]. The I^2 statistic is not sensitive to the number of studies included in a meta-analysis and has been used extensively in medical research. An I^2 of 25%, 50%, and 75% represents low, moderate, and high heterogeneity, respectively [30]. An I^2 of 0 indicates that the included studies are homogeneous, and that the observed variance is attributable to sampling error. For studies that did not report the SD of changes from baseline, SDs required for meta-analysis were calculated from the reported CIs and p values using t distribution and standard normal distribution when possible. For studies that reported individual patient data in the published figures, data points for meta-analysis were extracted using DigitizeIt software, version 2.5.3.

Subgroup Analysis and Meta-Regression

To account for clinical heterogeneity in the adolescent and adult SMA patient population and to examine the consistency of the evidence across the broad range of patients with SMA, subgroup meta-analysis by SMA Type (II or III) and by ambulatory status was conducted whenever available. For meta-analysis outcomes with statistically significant heterogeneity, meta-regression with mixed-effects model was conducted using the study-level baseline characteristic of mean age, mean baseline motor function score, and percentage of ambulatory patients to understand the potential source of heterogeneity. The R statistical software (v.3.5.2; R Foundation for Statistical Computing, Vienna, Austria) was used to perform meta-analysis.

Ethical Approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Systematic Literature Review

Database searching yielded 846 peer-reviewed publications after removing duplicates (Fig. 1). Of the 92 publications that underwent full text review, 78 were excluded from the SLR, including 28 that did not report outcomes of interest and 20 with reporting outcomes that were not specific to patients aged ≥ 13 years (i.e., which aggregated the results of adolescents/adults with those of younger patients < 13 years of age).

Eleven publications were based on data from individual centers that contributed to multicenter publications [20, 21, 31]. Eight of these publications [32–39], which mainly focused on evaluating outcomes other than motor function (e.g., patient-reported outcomes, biomarker

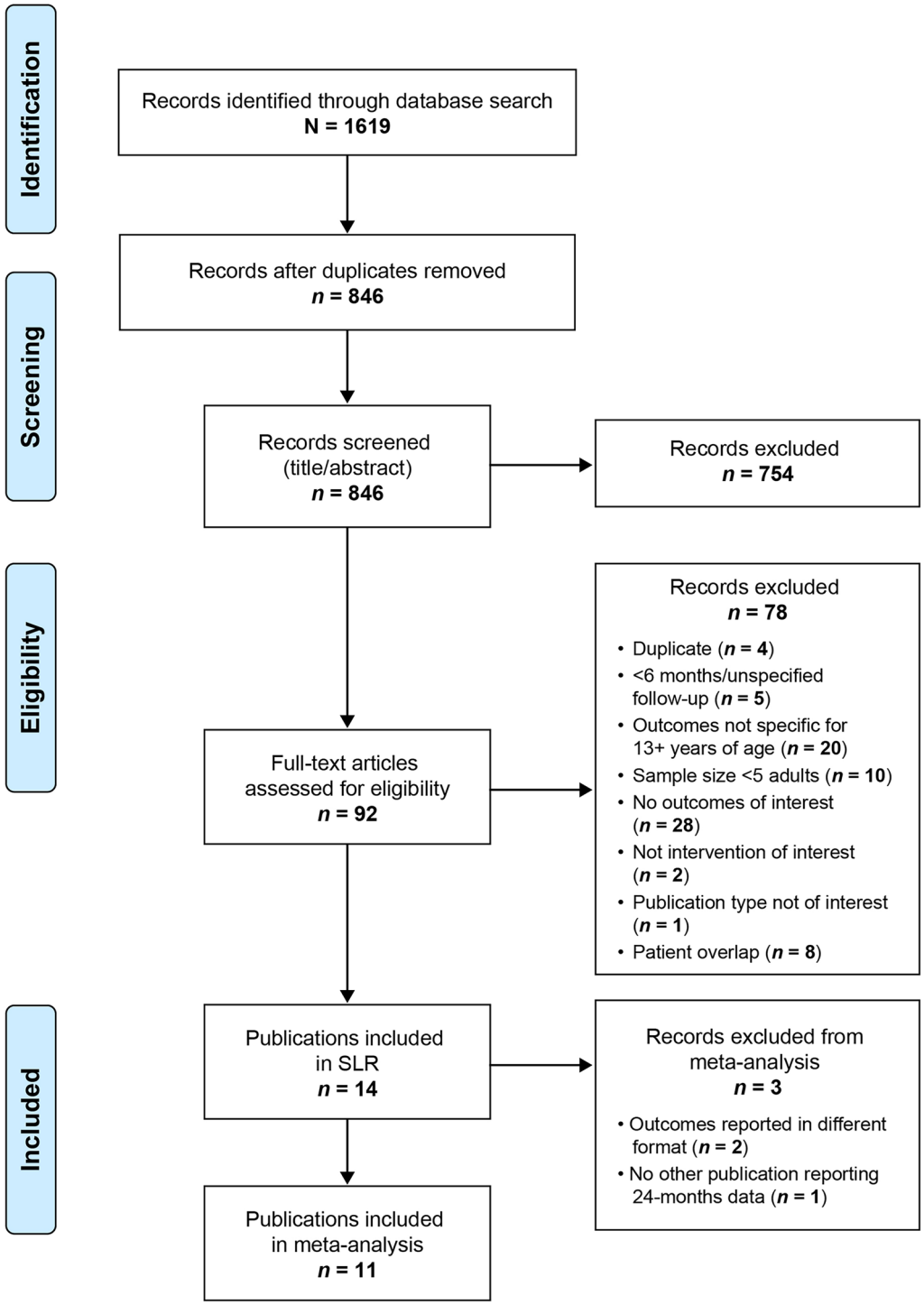

Fig. 1 PRISMA diagram

profiles), were excluded from the SLR to ensure that patients in each study were from independent samples (i.e., eight publications were excluded due to patient overlap; Fig. 1). Three of these publications were retained in the SLR for complete assessment of long-term effectiveness [40–42]; they reported longer follow-up data at 18 and 24 months, which were not available in the larger multicenter publications (up to 14 months) [20, 21, 31]. Only the 18-month and 24-month outcomes were extracted from these three publications, to avoid patient overlap in the analysis.

A summary of the 14 studies that met the eligibility criteria of the SLR is provided in Table 1. All 14 studies included in the SLR were observational studies examining the changes in motor function score after nusinersen treatment. No clinical studies that meet the eligibility criteria were identified. The 539 patients included in these publications ranged in age from 13 to 72 years at baseline; mean and median ages in each study ranged from the late 20s to the early 40s. As expected, most patients (99%) were diagnosed with SMA Types II and III. Approximately 40% of patients were ambulatory.

Data are reported for motor function outcomes up to 24 months of treatment (Table 2). The overall risk of bias was considered moderate in most studies, based on the ROBINS-I tool (supplemental appendix Fig. S1) [29], indicating that the studies provide sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial. Patients being lost to follow-up and treatment discontinuation were uncommon in the 10 studies that reported such data.

HFMSE

Most studies reported average improvements ranging from 0.11 to 5 points following 6–24 months from nusinersen initiation (Table 2). Of note, the 2 largest studies included in the SLR [20, 21] showed a statistically significant improvement in HFMSE score, at each timepoint up to 14 months, with Hagenacker et al. [20] reporting a mean change of 3.12 points (95% CI 2.06–4.19; n = 57) after 14 months of treatment, and Maggi et al. [21] reporting a mean change of 2.69 points (SD 2.92; n = 51; $p < 0.01$) after 14 months of treatment. Two studies with 18-month follow-up reported mean differences of 2.33 (SD 4.09; $p < 0.0001$) and 2.17 points ($p = 0.04$) at 18 months from baseline [40, 41]. One study reported mean differences of 0.7 points (SD 1.1; Type II) and 0.8 points (SD 4.4; Type III) after 24 months of treatment [42].

RULM

Most studies reported stability or improvement from baseline in RULM scores over time (Table 2). The two largest studies similarly reported significant improvement in RULM scores at each timepoint up to 14 months, with Hagenacker et al. reporting a mean change of 1.09 points (95% CI 0.62–1.55; n = 58) and Maggi et al. reporting a mean change of 0.94 points (SD 2.13; n = 49) ($p < 0.01$) after 14 months of treatment [20, 21]. In a study reporting 24-month changes from baseline, the mean differences were 1.3 points (SD 2.3) for SMA Type II patients and – 0.2 points (SD 2.1) for Type III patients.

6MWT

In general, the percentage of ambulatory patients was lower than the percentage of non-ambulatory patients in the real-world cohorts (Table 1). Stability or improvements were generally reported in all studies, ranging from annualized change of 3.29 m to a mean change of 46.0 m after 14 months of treatment (Table 2). The two largest studies included in the SLR reported significant improvements on the 6MWT from baseline following initiation of nusinersen treatment [20, 21].

Meta-analysis

After detailed assessment, a total of 11 publications including 433 adolescents and adults were retained for the meta-analysis [20, 21, 31, 40, 41, 43–48]. Two publications in the SLR were excluded from the meta-analysis because mean difference scores and their SDs at specific timepoints could not be obtained from the published

Table 1 Summary of studies included in systematic literature review and meta-analysis

Author(s)	Year	Study design	Country	SMA type	Sample included in SLR/meta-analysis (*n*)	Mean (range) age, years	Ambulatory, %	Maximum assessment period from baseline	Inclusion in meta-analysis
Hagenacker et al. [20]	2020	Prospective observational multicenter	Germany	I, II, III, IV	124	36 (16–65)	37	14 months	Yes
Maggi et al. [21]	2020	Retrospective observational multicenter	Italy	II, III	116	34 (18–72)	45	14 months	Yes
De Wel et al. [45]	2021	Prospective/retrospective observational single center	Belgium	III,IV	16	38 (22–66)	44	14 months	Yes
Jochmann et al. [48]	2020	Case series single center	Germany	II, III	6	39 (20–68)	17	10 months	Yes
Veerapandiyan et al. [43]	2020	Retrospective observational single center	US	II, III	6[a]	29 (16–52)	17	10 months	Yes
Yeo et al. [44]	2020	Prospective observational single center	US	III	6	30[b] (25–57)	67	14 months[c]	Yes
Elsheikh et al. [46]	2021	Prospective observational single center	US	II, III	19	40 (21–65)	0	14 months	Yes
Elsheikh et al. [47]	2021	Prospective observational single center	US	III, IV	13	37 (18–59)	100	14 months	Yes
Pera et al. [31][d]	2021	International SMA registry (ISMAR)	US, Italy, UK	III	63	34 (15–68)	41	12 months	Yes
Freigang et al. [40][e]	2021	Retrospective observational multicenter	Germany	II, III	57	36 (18–71)	32	18 months	Yes[f]
Milella et al. [41][g]	2021	Observational single center	Italy	II, III	7	43 (18–72)	23	18 months	Yes[f]
Duong et al. [49]	2021	Prospective observational multicenter	US	II, III	42	34 (18–66)	26	Annualized rate of change	No[h]
Walter et al. [19]	2019	Prospective observational single center	Germany	III	17[i]	35 (18–59)	63	10 months	No[h]
Pane et al. [42][j]	2022	International SMA registry (ISMAR)	Italy	II, III	47	NA (13–68)	NA	24 months	No[k]

Table 1 continued

HFMSE Hammersmith Functional Motor Scale–Expanded, *NA* not available, *SLR* systematic literature review, *SMA* spinal muscular atrophy

[a]Two patients without RULM data at baseline or ≥ 6 months' follow-up were not included

[b]Median

[c]14 months' follow-up data were available from all 6 patients in the study; 3 patients had additional follow-up ranging from 15 to 21 months

[d]Data from patients aged > 15 years obtained from the supplementary information (Table S4) of the publication

[e]HFMSE data at 18 months was available for a subgroup of patients in the study (n = 57). Baseline characteristics of age and ambulatory status were only available from the entire study sample (n = 206)

[f]Included in the meta-analysis of 18-month outcomes only due to potential patient overlap with other multicenter publications

[g]Data from subgroup of 7 patients with 18 months' follow-up data obtained from Fig. 1 of the publication. Baseline characteristics of age and ambulatory status only were available from the entire sample (n = 9)

[h]Mean difference scores and their standard deviations at specific timepoints could not be obtained from published results

[i]Baseline characteristics of the entire sample (n = 19) are reported; 17 patients had ≥ 6 month's data

[j]Data from subgroup of patients aged ≥ 13 years obtained from Table 2 of the publication

[k]No other studies reported 24-month data for pooled analysis

results (i.e., there were differences in reported outcome measures) [19, 49]. One publication was excluded because no other studies reported 24-month data and therefore estimates could not be pooled across studies at that timepoint [42]. In all three publications excluded from the meta-analysis, the authors reported improvements in motor function during 10–24 months of nusinersen treatment [19, 42, 49].

HFMSE

In the overall population of adolescents and adults, statistically significant increases from baseline in HFMSE scores were consistently observed for each timepoint through 18 months of follow-up. Figure 2 summarizes the pooled estimates and the corresponding 95% CIs from each model in the meta-analysis. The mean increase in HFMSE scores was 1.4 points (95% CI 1.0–1.7) at 6 months, 1.9 points (1.1–2.6) at 10 months, 2.0 points (1.0–2.9) at 14 months, and 2.3 points (1.3–3.3) at 18 months in the overall population (Fig. 2a).

The percentage of patients considered to have a clinically meaningful HFMSE response (≥ 3 points) at 6 months was 28.5% (95% CI 23.3–34.4), increasing to 38.2% (32.4–44.4) at 10 months, to 41.3% (31.3–52.1) at 14 months, and to 32.1% (21.7–44.6) at 18 months (Fig. 2b).

The magnitude of the increase from baseline in HFMSE scores was greater among patients with SMA Type III than Type II across all timepoints (Fig. 2a). At 14 months, the mean increase in HFMSE scores was 2.7 points (1.4–4.0) for Type III, and 1.1 points (0.5–1.7) for Type II. Similarly, in the subgroup analysis by ambulatory status, ambulatory patients had greater improvements on the HFMSE scale than non-ambulatory patients (supplementary appendix Fig. S2). Detailed forest plots for HFMSE responses by ambulatory status and for each meta-analysis for the overall population and by SMA subtype are provided in supplementary appendix Figs. S3–S7.

RULM

Statistically significant increases from baseline in RULM scores were consistently observed for

Table 2 Summary of motor function outcomes in studies included in the systematic literature review

Author(s)	Reported outcome estimate	Assessment time	HFMSE	RULM	6MWT
Hagenacker et al. [20]	Mean difference from baseline	6 months	1.73 [CI 1.05, 2.41] ($n = 124$)	0.66 [CI 0.26, 1.05] ($n = 120$)	22.1 [CI 8.7, 35.6] ($n = 47$)
		10 months	2.58 [CI 1.76, 3.39] ($n = 92$)	0.59 [CI 0.15, 1.03] ($n = 90$)	31.1 [CI 15.2, 47.1] ($n = 37$)
		14 months	3.12 [CI 2.06, 4.19] ($n = 57$)	1.09 [CI 0.62, 1.55] ($n = 58$)	46.0 [CI 25.4, 66.6] ($n = 25$)
Maggi et al. [21]	Mean difference from baseline	6 months	1.33 (SD 2.29) ($p < 0.01$) ($n = 116$)	0.37 (SD 1.97) ($p = 0.04$) ($n = 114$)	14.66 (SD 27.57) ($p < 0.01$) ($n = 48$)
		10 months	2.29 (SD 2.75) ($p < 0.01$) ($n = 84$)	0.72 (SD 2.07) ($p < 0.01$) ($n = 80$)	26.45 (SD 34.6) ($p < 0.01$) ($n = 35$)
		14 months	2.69 (SD 2.92) ($p < 0.01$) ($n = 51$)	0.94 (SD 2.13) ($p < 0.01$) ($n = 49$)	23.11 (SD 51.2) ($p = 0.02$) ($n = 24$)
De Wel et al. [45]	Mean difference from baseline	6 months	2.1 ($p = 0.11$) ($n = 16$)	0.9 ($p = 0.10$) ($n = 16$)	16 ($p = 0.06$) ($n = 7$)
		14 months	2.1 ($p = 0.31$) ($n = 16$)	1.06 [CI − 0.79, 2.91] ($n = 16$)	7 [CI − 38.42, 53.27] ($n = 7$)
Jochmann et al. [48]	Mean difference from baseline	10 months	5 (SD: 6.5) ($n = 6$)	7.7 (SD 9.3) ($n = 6$)	Not applicable[a]
Veerapandiyan et al. [43][b]	Mean difference from baseline	6 months	Not reported	2.17 (CI − 0.12, 4.46) ($n = 6$)	Not applicable[a]
		10 months	Not reported	2.8 (CI 0.07, 5.53) ($n = 5$)	Not applicable[a]
Yeo et al. [44]	Mean difference from baseline	14 months	2 (range: 1–5) ($n = 6$)	1.8 (range: 0–3) ($n = 6$)	Not applicable[a]
Elsheikh et al. [46]	Estimated change from baseline	6 months	0.74 [CI − 0.3, 1.78] ($n = 19$)	0.89 [CI − 0.16, 1.95] ($n = 19$)	Not reported
		10 months	0.32 [CI − 0.73, 1.36] ($n = 19$)	0.95 [CI − 0.1, 2.0] ($n = 19$)	Not reported
		14 months	0.11 [CI − 1.11, 1.32] ($n = 12$)	0.27 [CI − 0.96, 1.5] ($n = 12$)	Not reported
Elsheikh et al. [47]	Estimated change from baseline	6 months	2.46 [CI 0.54, 4.39] ($n = 13$)	Not reported	25.27 [CI 8.69, 41.85] ($n = 13$)
		10 months	2.08 [CI 0.15, 4.00] ($n = 13$)	Not reported	19.19 [CI 2.61, 35.77] ($n = 13$)

Table 2 continued

Author(s)	Reported outcome estimate	Assessment time	HFMSE	RULM	6MWT
		14 months	2.6 [CI 0.5, 4.69] (n = 10)	Not reported	15.88 [CI − 2.16, 33.92] (n = 10)
Pera et al. [31][c]	Mean difference from baseline	12 months	1.00 (SD 3.85) (n = 56)	0.16 (SD 2.16) (n = 63)	8.91 (SD 42.08) (n = 23)
Freigang et al. [40]	Mean difference from baseline	18 months	2.33 (SD 4.09) (p < 0.0001) (n = 57)	Not reported	Not reported
Milella et al. [41][d]	Mean difference from baseline	18 months	2.17 (p = 0.04) (n = 6)	2.0 (p = 0.05) (n = 7)	Not applicable[a]
Duong et al. [49]	Average rate of change per year (slope)	Mean (range) follow-up: 12.5 (3–24) months	0.86 (CI − 0.52, 2.24) (n = 31)	0.11 (CI − 0.45, 0.67) (n = 39)	3.29 (CI − 28.04, 34.62) (n = 10)
Walter et al. [19]	Mean scores at each timepoint	Baseline	35.16 (SD 21.14) (n = 19)	32.32 (SD 7.39) (n = 19)	369.50 (SD 126.62) (n = 10)
		180 days	38.59 (SD 20.13) (p = 0.15) (n = 17)	32.76 (SD 7.31) (p = 0.16) (n = 17)	378.83 (SD 147.17) (p < 0.01) (n = 12)
		300 days	39.50 (SD 20.58) (p = 0.20) (n = 12)	33.06 (SD 7.33) (p = 0.05) (n = 16)	377.75 (SD 156.60) (p = 0.01) (n = 12)
Pane et al. [42][e]	Mean difference from baseline	24 months	Type II: 0.7 (SD 1.1) (n = 7) Type III: 0.8 (SD 4.4) (n = 40)	Type II: 1.3 (SD 2.3) (n = 6) Type III: − 0.2 (SD 2.1) (n = 34)	Not reported

6MWT Six-Minute Walk Test, *CI* 95% confidence interval, *HFMSE* Hammersmith Functional Motor Scale–Expanded, *RULM* Revised Upper Limb Module, *SD* standard deviation

[a]6MWT results from these studies were not included in the SLR, as the number of ambulatory patients was < 5

[b]Mean differences and confidence intervals were obtained from individual patient-level data reported in the publication

[c]Data from the supplementary information of the publication were collapsed across the 15–19 and ≥ 20 years age groups using weighted averages. 12-month outcomes reported in the publication were included in the 10-month meta-analysis

[d]Mean differences were obtained from individual patient-level data reported in the publication using DigitizeIt software. *P* values were reported by the authors

[e]For SMA Type III patients, HFMSE analyses data were collapsed across the 15–19 and ≥ 20 years age groups using weighted averages

each timepoint (Fig. 3a). In the overall population, the mean increase in RULM scores was 0.9 points (95% CI 0.4–1.4) at 6 months, 0.8 points (0.3–1.2) at 10 months, and 1.1 points (0.7–1.4) at 14 months.

The percentage of patients considered to have a clinically meaningful RULM response (≥ 2 points) at 6, 10, and 14 months was 26.4% (18.8–35.7), 33.9% (23.0–46.8), and 38.3% (30.3–47.1), respectively (Fig. 3b).

In contrast to the pattern observed for HFMSE, the magnitude of increase in RULM scores was greater for patients with SMA Type II than Type III (Fig. 3a). At 14 months, the mean increase in RULM scores was 1.6 points (0.9–2.3) for Type II and 0.9 points (0.5–1.3) for Type III. Non-ambulatory patients also had a greater increase on the RULM scale than ambulatory patients (supplementary appendix Fig. S8). Detailed forest plots for RULM response by ambulatory status and for each meta-analysis for the overall population and by SMA subtype are provided in supplementary appendix Figs. S9–S13.

6MWT

Among ambulatory patients, the mean difference in 6MWT and the percentage of patients with clinically meaningful 6MWT response (≥ 30 m) significantly increased through 14 months of follow-up. At 14 months, the mean

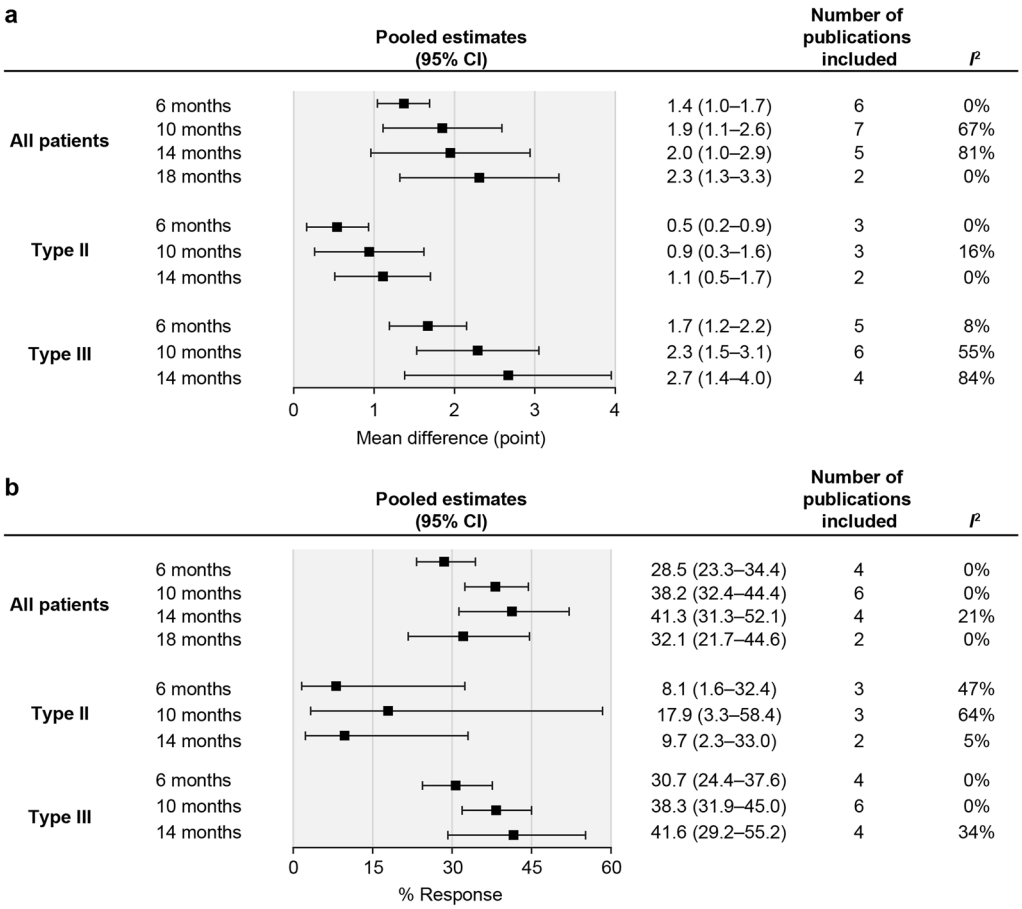

Fig. 2 Summary of meta-analysis for HFMSE. **a** Mean HFMSE differences from baseline. **b** Percentage of patients with clinically meaningful HFMSE response (≥ 3 points). The *black dot* and *error bars* represent the pooled estimate and the corresponding 95% CI, respectively, from each model in the meta-analysis. *CI* confidence interval, *HFMSE* Hammersmith Functional Motor Scale–Expanded

difference from baseline was 25.0 m (95% CI 8.9–41.2; Fig. 4a) and the percentage of patients with clinically meaningful 6MWT response was 50.9% (33.4–68.2; Fig. 4b). Detailed forest plots for each meta-analysis are provided in supplementary appendix Figs. S14 and S15.

Heterogeneity Between Studies and Meta-regression

Results across studies were largely consistent, with low to moderate heterogeneity in most analyses. In the analysis of the overall population, statistically significant heterogeneity was only observed for mean changes in HFMSE scores at 10 and 14 months (I^2 = 67% and 81%, respectively) and RULM score at 6 months (I^2 = 66%). No significant heterogeneity was observed for percentage of patients with clinically meaningful response analysis. In the meta-regression analysis of HFMSE, mean age at baseline, mean HFMSE score at baseline, or percentage of ambulatory patients in each study did not explain the heterogeneity for mean difference outcome at 10 months (supplementary appendix Fig. S16). In contrast, higher RULM score and percentage of ambulatory patients at baseline was associated with lower mean differences in RULM at 6 months (supplementary appendix Fig. S17).

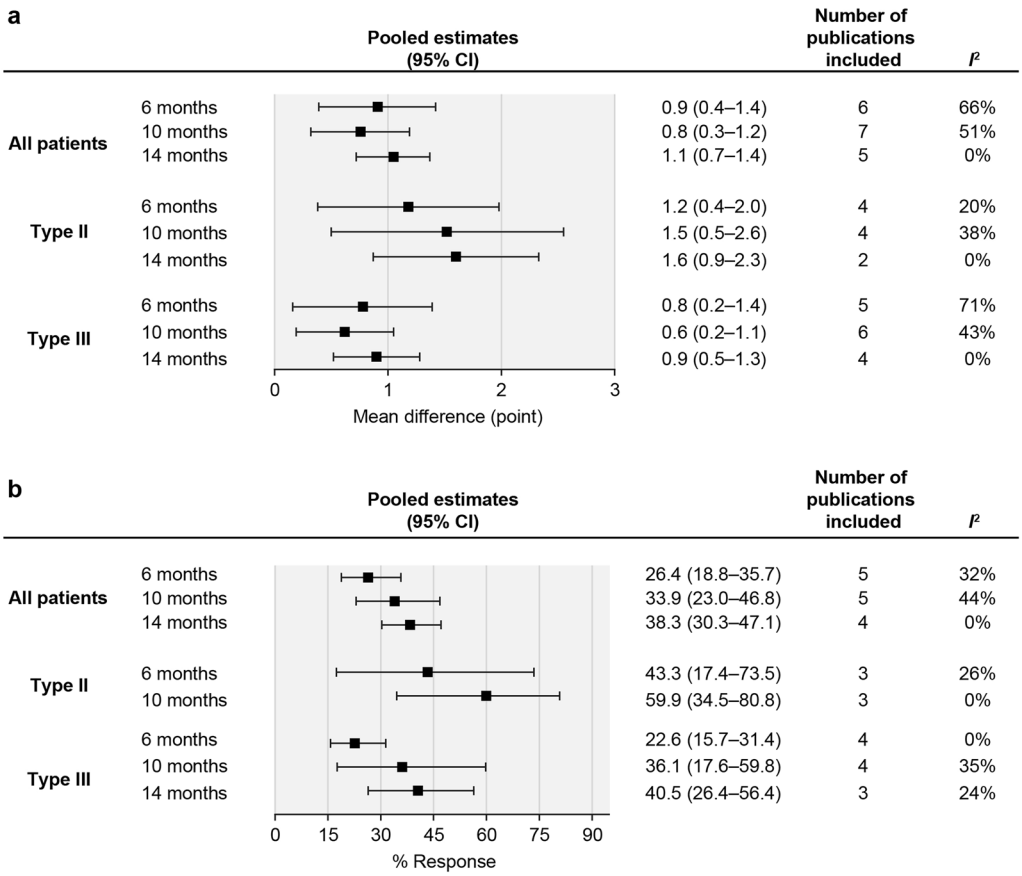

Fig. 3 Summary of meta-analysis for RULM. **a** Mean RULM difference from baseline. **b** Percentage of patients with clinically meaningful RULM response (≥ 2 points). The *black dot* and *error bars* represent the pooled estimate and the corresponding 95% CIs, respectively, from each model in the meta-analysis. Meta-analysis for clinically meaningful RULM response at 14 months in Type II patients was not conducted; only one publication [21] reported such outcome. *CI* confidence interval, *RULM* Revised Upper Limb Module

DISCUSSION

This SLR and meta-analysis provides consolidated evidence from real-world cohorts that nusinersen is effective in improving or stabilizing motor function in many adolescents and adults with SMA up to 24 months after treatment initiation. Modest improvement or stability in motor function ability was consistently observed over time among many nusinersen-treated patients on the key motor function outcomes of the HFMSE, RULM, and 6MWT.

In contrast, published studies evaluating natural disease progression using these assessment scales show a decline in motor function over time in patients with SMA, if left untreated [27, 50–61]. As predicting disease progression over a short period can be challenging for individual patients, some untreated patients may report stability or even clinically meaningful improvement within a shorter timeframe [61]. However, the findings of the natural history studies consistently indicate that, at a group level, motor functions of adolescents and adults with SMA progressively decline over time. Natural history data show overall mean declines in HFMSE scores for adolescents and adults with SMA Types II or III, ranging from 0.26 to 0.7 points over 12 months [50, 54, 62]. For RULM, data collected from untreated patients aged ≥ 15 years with SMA Types II or III showed mean decreases of 0.6 points over 12 months [27]. A study that assessed untreated patients with SMA Type III at 12 months reported declines in 6MWT distance of 20.8 m in individuals aged 11–19 years and 9.7 m in adults [53]. Such declines in untreated patients have the potential to impact activities of daily living and suggest that improvement or even stability in motor function ability following treatment with nusinersen may provide important clinical benefit.

Our findings of nusinersen effectiveness in many adolescents and adults with a broad spectrum of SMA build on the findings from two previously published reviews and meta-analyses [58, 63]. In a comprehensive literature review and meta-analysis of real-world data on motor function in patients with SMA Types II and III [58], Coratti and colleagues analyzed data from nusinersen-treated pediatric and adult patients based on a literature search conducted in January 2021. They found treatment to have a beneficial outcome on motor function, as measured by pooled mean changes from baseline over time for HFMSE, RULM, and 6MWT [58].

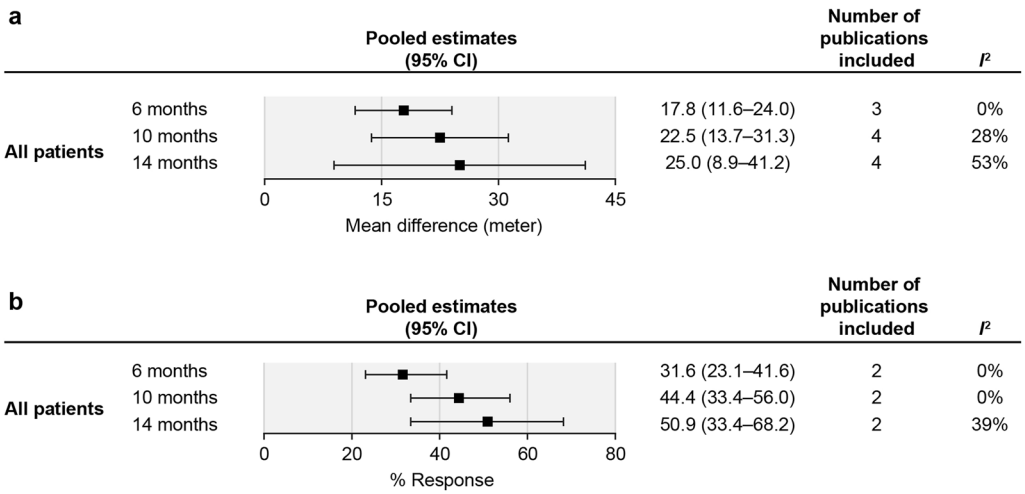

Fig. 4 Summary of meta-analysis for 6MWT. **a** Mean 6MWT differences from baseline. **b** Percentage of patients with clinically meaningful 6MWT response (≥ 30 m). The *black dot* and *error bars* represent the pooled estimate and the corresponding 95% CI, respectively, from each model in the meta-analysis. *6MWT* Six-Minute Walk Test, *CI* confidence interval

Gavriilaki and colleagues carried out a systematic review and meta-analysis of nusinersen-treated patients with SMA aged > 12 years based on a literature search conducted in April 2021 [63]. They also showed significant improvements on HFMSE and RULM following 10 and 14 months' nusinersen treatment, with clinically meaningful changes seen in 43.3% (HFMSE) and 38.9% (RULM) patients after > 6 months' follow-up [63], closely reflecting the percentage of patients in our meta-analysis on the same measures.

Our SLR and meta-analysis add significant value to the field. Meta-analysis of observational studies is particularly challenging due to clinical and methodological heterogeneity across studies [64]. As adults with SMA have wide clinical heterogeneity with respect to their baseline motor function, a single summary measure across the entire population would be inappropriate and difficult to interpret [64]. HFMSE and RULM are also not sensitive to detect changes in the weakest and strongest patients, respectively, due to floor and ceiling effects [65].

Therefore, first, we provided meta-analysis stratified by (1) SMA type and (2) ambulatory status for all endpoints at each timepoint. These comprehensive subgroup analyses, which were not fully available in the two previously published reviews, can significantly improve the usefulness of meta-analysis and help to understand the observed outcomes according to disease severity and type at baseline [64].

Coratti and colleagues included both pediatrics and adults in their subgroup analysis. Analyses that are not specific to adolescents and adults could be difficult to interpret because the patterns of disease progression vary substantially between younger and older patients [66]. Although statistically not significant, the mean increases in HFMSE and RULM were greater in pediatrics than adults [58]. Gavriilaki and colleagues did not provide subgroup analysis by current ambulatory status, which represents the primary source of clinical heterogeneity in adolescents and adults. Considerable heterogeneity in motor function exists within each SMA type in adolescents and adults. This is especially evident in Type III, where there is notable variability in the gradual loss of walking ability over time. As such, it is increasingly recommended to focus on the current functional status rather than the traditional SMA type when evaluating treatment effects in adolescents and adults [67]. In addition, subgroup analysis by SMA type was only provided for Type III and IV patients, but not Type II patients, in the Gavriilaki et al. review.

Our comprehensive subgroup analyses demonstrate that a modest improvement after nusinersen initiation is consistently observed in many adolescents and adults with a broad spectrum of SMA, especially when the most sensitive scales are used for each sub-population (e.g., HFMSE for less severely affected, and RULM for more severely affected). It also provides various summary measures that can be easily interpreted and applied based on the baseline characteristics of the study population.

Second, our analyses included five and six additional publications as compared with the prior two reviews, respectively, based on the most up-to-date literature search in July 2022. These additional publications included longer follow-up data from broader patient populations in US and Europe (n = 143 and 191 patients, respectively). Maximum observation periods included in the prior two reviews were 14 months for the Coratti et al. study and 18 months for the Gavriilaki et al. study (see supplementary appendix Tables S5 and S6 for a comparison of studies included in Coratti et al., Gavriilaki et al., and this meta-analysis).

Third, our study methods also differed from the previously published reviews. In alignment with the guidelines for meta-analysis of observational studies, we employed broad inclusion criteria to identify eligible studies in our systematic review, and subsequently conducted meta-analysis related to study design features (e.g., study design, assessment timepoints, and analytical methods) [64]. This approach limited the high level of methodological heterogeneity observed in the meta-analysis of Coratti and colleagues. The level of statistical heterogeneity was low to moderate for most outcomes in our study, suggesting that findings are consistent across the different publications included in the meta-analysis. Nevertheless, our meta-analysis findings based on strict inclusion criteria also align with

the findings of the Coratti et al. study, suggesting that these findings are not biased by including or excluding certain studies. On the other hand, Gavriilaki and colleagues used standardized mean differences to pool the changes in HFMSE, RULM, and 6MWT. We used the original motor function scales to obtain summary measures that are easily interpretable in clinical practice.

Although the findings regarding the effect of nusinersen on motor function outcomes were largely consistent across different meta-analyses, there were also some differences. Our analysis detected a statistically significant increase in the 6MWT, whereas the study by Gavriilaki and colleagues reported an increasing trend without statistical significance. These findings are likely to differ due to differences in the studies included. Our analysis included two additional publications reporting 6MWT results [31, 47] which became available after Gavriilaki et al. study. Furthermore, their meta-analysis included two publications that did not directly report mean differences and their SDs [19, 45]. To estimate the approximate effect sizes from these publications, Gavriilaki and colleagues made certain conservative analytic assumptions that might have influenced their nonsignificant findings. In contrast, our meta-analysis only included studies from which we could accurately obtain effect sizes based on the published results. Studies without such data were only included in the systematic review for completeness.

We also determined the pooled clinically meaningful response rate for each outcome measure, with the aim of providing useful information to patients and clinicians on which to base expectations for the management of patients with SMA. Our meta-analysis used response thresholds commonly reported in the literature to define a clinically meaningful response for adolescents and adults with SMA [26, 27, 68, 69], because meta-analysis can only be conducted for outcomes that are similarly reported across publications. However, for adolescents and adults with SMA (a disease resulting in progressive motor function decline over time), modest improvement or even long-term stabilization of motor function may be a meaningful clinical outcome with a potential positive impact on daily life. Unlike infants and children, who may experience acute and rapid progression of disease, they are often in the chronic phase of the disease, with slow but constant declines of functions over time [50]. Accordingly, the magnitude of improvements after nusinersen treatment in adolescents and adults may not be as large as that observed in infants and children who are treated in the earlier phase of the disease. The definition of "clinically meaningful response" or "minimal clinically important differences" can vary by age or other patient characteristics. Identifying the proper threshold for each patient population remains a challenge. In addition, it reflects only performance on a single motor scale; patients may respond on one scale and not another, or they may have changes in a particular function that is meaningful to them, but not captured in any of the commonly used scales [70].

Accordingly, in one of the largest studies included in the meta-analysis, the authors proposed the term "overall responder," defined as having achieved a clinically meaningful response in at least one of the HFMSE, RULM, or 6MWT outcomes [21]. In their cohort of predominantly SMA Type III patients, 49% demonstrated a clinically meaningful response on HFMSE, whereas 35% demonstrated a clinically meaningful response on RULM. Overall, 69% were considered "overall responders," showing clinically meaningful response in at least one of the three outcomes. The percentage of overall responders is higher than the percentages reported in each outcome, likely because patients with different baseline motor functions respond to different scales. When sensitive scales are used for each patient population, clinically meaningful improvement may be observed across different SMA types and ambulatory status.

The different patterns of response seen in our subgroup analyses based on SMA subtype and ambulatory status illustrate that the HFMSE is a more sensitive measure in less severely affected patients, whereas the RULM is more sensitive in patients who are more severely affected. For example, mean increases in HFMSE and RULM at 14 months were 3.07 and 0.57 points in ambulatory patients, whereas in non-ambulant

patients, mean increases in HFMSE and RULM were 1.73 and 0.95 points during the same period (Figures S2 and S8). A recent study to validate outcome measures in adult patients with SMA showed a floor effect in the weakest patients of < 5 on the HFMSE and < 10 on the RULM scale; the ceiling effect in the stronger patients was > 60 on the HFMSE and > 35 on the RULM [65]. Our observation that a higher RULM score and percentage of ambulatory patients at baseline was associated with lower mean differences in RULM in meta-regression may also reflect the ceiling effect of RULM for less severely affected individuals.

Although most studies focused on reporting the percentage of patients with clinically meaningful improvements, percentages of patients with no changes/stability or decline were also available from eight studies. However, pooled summary measures could not be obtained due to variability in definitions across studies. For example, few studies reported clinically meaningful HFMSE decline using the same 2-point thresholds (i.e., > 2 points decline), whereas some reported the percentage of patients with any negative changes in scores, which may not always be clinically meaningful. Despite the inconsistencies in definitions, the reported findings also support that many patients experience a modest improvement or stability after nusinersen treatment. The reported ranges of no changes/stability were between 23.5% and 53.8% for HFMSE, 33.3% and 87.5% for RULM, and 10% and 63.6% for 6MWT, over a follow-up period ranging from 6 to 21 months. The reported ranges of declines (any or clinically meaningful) were between 0% and 29.4% for HFMSE, 0% and 18.8% for RULM, and 0% and 9.1% for 6MWT.

Our study focused on motor function outcomes, which are the primary outcomes in many clinical trials for later-onset SMA [15, 71]. They are also the most frequently reported standardized outcomes in real-world studies of adolescents and adults. Despite the known limitations of ceiling and floor effects, motor function outcomes are generally suitable for the majority of adolescents and adults with Type II and III SMA, if appropriate scales are used based on patient characteristics (e.g., HFMSE for less severely affected patients and RULM for more severely affected patients). Other outcomes such as pulmonary or bulbar functions were often not consistently defined across studies and were not available in most large multicenter studies. Additionally, many scales and assessments that focus on non-motor outcomes were not validated for SMA, especially in adults. These outcomes may also hold greater significance for a selected group of patients in severe disease stages.

Although pooled summary measures cannot be obtained due to variability in assessment methods across studies, pulmonary function was assessed in seven studies included in the SLR. Most studies reported stability or mild improvement of pulmonary function after nusinersen [19, 21, 45–49], which may be of value, as respiratory infection is a considerable cause of morbidity and mortality in these patients [49].

Disease duration was not systematically assessed in our study, as we focused on adolescents and adults with SMA. Although disease duration is an important predictor of treatment response in children with SMA, current motor function is likely more important to understand the heterogeneity in treatment effects in adolescents and adults [60, 61]. There were also no clear associations between disease duration and treatment effects in studies which reported such outcomes in adolescents and adults [19–21, 48]. In addition, the majority of patients included in our analysis had Type II or Type III SMA and were between 13 and 72 years of age at nusinersen initiation. As SMA symptoms typically start before 18 months of age, a patient's disease duration can be approximated from their age at baseline. Most publications included in our review accordingly reported age at baseline, but not disease duration. We therefore conducted various subgroup analyses and meta-regression by baseline age and motor function to understand the potential differences in treatment effects.

Although the evidence was consolidated from observational studies without a randomized comparator group, three studies included in the SLR compared the findings of patients treated with nusinersen to the natural history of untreated patients [31, 42, 45]. Two studies reported annual or 12-month deterioration of

motor function and muscle strength in untreated patients [31, 45]. The mean HFMSE 12-month changes in the untreated patients were always negative after the age of 7 years [31]. One study compared Type II and III patients treated with nusinersen versus those untreated with respect to HFMSE and RULM at 12 months and 24 months [42]. All comparisons were statistically significant, except for RULM at 24 months in Type III patients. Although not included in the SLR as the publication became available after the search date, another study similarly showed statistically significant improvements in HFMSE and 6MWT in nusinersen-treated patients compared to untreated patients during a mean follow-up of 16 months [61]. Clinically meaningful improvements were more frequent in treated patients in all scales, although the differences were statistically significant only for RULM and other functional scales of Amyotrophic Lateral Sclerosis Functional Scale Revised and Egen Klassifikation 2.

There are several limitations to our study. First, as different studies and varying patient populations contributed to the meta-analyses at each timepoint, the results across different timepoints and outcomes cannot be directly compared. Second, although the protocol of the SLR was not prospectively registered in a publicly available database, a study protocol that includes the PICOS and database search terms were developed prior to conducting the SLR. Third, the maximum duration of follow-up in our study is longer than the previous two reviews. However, longer follow-up data and additional data in more severely affected patients may still be needed. Fourth, stability of motor function observed in some patients may not always be the results of nusinersen treatment, and not all patients may have benefited from nusinersen. Fifth, our SLR and meta-analysis consolidate evidence from observational studies without a randomized comparator group; however, the risk of bias in these publications was assessed using the ROBINS-I tool and was considered moderate for the majority of studies included in the SLR. Sixth, statistically significant heterogeneity observed for HFMSE at 10 months and 14 months could not be explained by the meta-regression analysis. The findings of meta-regression at 14 months were limited due to the small number of studies reporting baseline characteristics of the subgroup of participants in the 14-month analysis and were not included in the results.

CONCLUSIONS

The findings of our SLR and meta-analysis elaborate on those of the two earlier studies [58, 63], and represent the most up-to-date search of the literature (to July 2022). Our analysis includes publications with longer follow-up data and broad SMA populations supporting the effectiveness of nusinersen up to 18 and 24 months after treatment initiation. Consistent findings across these studies based on different methodological approaches for meta-analysis further suggest the effectiveness of nusinersen on motor function in adolescents and adults with SMA. Our study also provides comprehensive subgroup analyses by SMA type and ambulatory status. These analyses can enhance the clinical interpretation and applicability of our meta-analysis for clinicians and decision-makers, helping them understand the observed outcomes in relations to disease severity at baseline. Our comprehensive SLR and meta-analysis indicates that nusinersen is effective in improving or stabilizing motor function in many adolescents and adults with a broad spectrum of SMA over a treatment period of up to 24 months, when the most sensitive scales are used for each patient population.

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Data Availability. Requests for the materials and data supporting this manuscript should be submitted to https://vivli.org/.

Declarations

Conflict of Interest. Tim Hagenacker received grants/research support from Biogen, Novartis, and Roche, and honoraria or consulting fees from Biogen, Novartis, and Roche. Lorenzo Maggi received a grant from Biogen and honoraria for speaking, and consulting fees or compensation for congress participations from Amicus Therapeutics, Biogen, Janssen Pharmaceutics, Roche, and Sanofi Genzyme. Giorgia Coratti has received honoraria for speaking and compensation for congress participation from AveXis, Biogen, BioLogix, Novartis, and Roche. Bora Youn and Angela D. Paradis are employees of Biogen and may hold stock in the company. Stephanie Raynaud is a former employee of Biogen and may have held stock in the company at the time of the study. Eugenio Mercuri has served on advisory boards for SMA studies for AveXis, Biogen, Ionis, Novartis, and Roche; as Principal Investigator for ongoing Biogen/Ionis and Roche clinical trials; and has received funding from Famiglie SMA Italy, Italian Telethon, and SMA Europe.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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