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NUSINERSEN ADVANCES IN SMA TREATMENT

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ABSTRACT

Spinal muscular atrophy (SMA) is a rare, autosomal recessive neuromuscular disorder caused by mutations or deletions in the SMN1 gene, leading to progressive motor neuron degeneration and muscle weakness. Nusinersen, an antisense oligonucleotide designed to modify SMN2 pre-mRNA splicing and increase functional SMN protein production, represents the first disease-modifying therapy approved for 5q SMA. This review summarizes evidence from pivotal clinical trials, including ENDEAR, CHERISH, EMBRACE, and DEVOTE, as well as real-world data in pediatric and adult populations. Across phenotypes, nusinersen has demonstrated clinically meaningful improvements or stabilization of motor function and increased survival free from permanent ventilation, particularly when initiated early in the disease course. Evidence suggests that treatment response may vary depending on baseline functional status and timing of therapy initiation. Despite proven efficacy, challenges remain, including limited long-term follow-up data, lack of direct head-to-head comparisons with other disease-modifying therapies, and variability in global accessibility due to economic and infrastructural factors. Additionally, manufacturing complexity and high production costs of antisense oligonucleotides influence healthcare system sustainability. Ongoing research focused on dosing optimization, long-term outcomes, and advances in oligonucleotide synthesis technologies may further refine the role of nusinersen within the evolving therapeutic landscape of SMA.

KEYWORDS

Spinal Muscular Atrophy, Nusinersen, Antisense Oligonucleotide, SMN2 Splicing Modulation, Disease-Modifying Therapy

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1. Introduction

Rare diseases pose a substantial medical and societal burden. Although each individual rare condition affects a limited number of patients, their cumulative impact is considerable. In the European Union, a disease is defined as rare when it affects no more than 5 individuals per 10,000 population. Despite this low prevalence threshold, rare diseases collectively affect approximately 1 in 17 individuals in Europe, corresponding to nearly 30 million people.

Many rare diseases are severe, chronic, progressive, and frequently of genetic origin. They are often associated with significant morbidity, reduced life expectancy, and substantial psychosocial and economic consequences for patients and their families. Limited therapeutic options and high development costs further complicate disease management, making rare diseases a major focus of contemporary biomedical research and healthcare policy.

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder and one of the leading genetic causes of infant mortality. The disease results from mutations or deletions in the *SMN1* gene, leading to deficiency of the survival motor neuron (SMN) protein, which is essential for the maintenance and function of alpha motor neurons. The presence of the paralogous *SMN2* gene, which produces only limited amounts of functional SMN protein due to alternative splicing, has provided the molecular basis for the development of targeted therapeutic strategies.

SMA is characterized by degeneration of alpha motor neurons in the anterior horns of the spinal cord, leading to progressive muscle weakness and atrophy. Traditionally, clinical classification has been based on age of onset and the highest achieved motor milestone; however, the introduction of newborn screening programs and disease-modifying therapies has begun to reshape this framework [3].

Advances in RNA biology have led to the development of antisense oligonucleotides (ASOs), which enable post-transcriptional modulation of gene expression. Nusinersen is the first approved ASO-based therapy for the treatment of SMA. Its mechanism of action involves modification of *SMN2* pre-mRNA splicing, resulting in increased production of full-length, functional SMN protein.

The aim of the present study is to review current clinical evidence regarding the efficacy and safety of nusinersen in the treatment of 5q SMA and to discuss selected technological and systemic challenges related to its manufacturing and therapeutic accessibility.

2. Materials and methods

A narrative literature review was conducted using the PubMed, Scopus, and ClinicalTrials.gov databases up to January 2026. The following keywords were used in various combinations: “nusinersen”, “spinal muscular atrophy”, “SMA”, “antisense oligonucleotide”, “ENDEAR”, “CHERISH”, “EMBRACE”, and “DEVOTE”. Randomized controlled trials, observational studies, extension studies, and official regulatory documents from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) were included.

Publications not available in English, conference abstracts without full data, and duplicate reports were excluded. Priority was given to phase II and III clinical trials and peer-reviewed full-text articles.

3. Results

3.1. Clinical characteristics and epidemiology of SMA

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by mutations or deletions in the *SMN1* (survival motor neuron 1) gene located on chromosome 5q13. The number of *SMN2* gene copies inversely correlates with disease severity, as increased *SMN2* copy number partially compensates for *SMN1* loss through residual production of functional SMN protein. Deficiency of survival motor neuron (SMN) protein leads to degeneration of α-motor neurons in the anterior horns of the spinal cord, resulting in progressive muscle weakness and atrophy.

The estimated incidence of 5q SMA ranges between 1 in 6,000 and 1 in 10,000 live births, with a carrier frequency of approximately 1 in 40–50 individuals. Disease severity correlates with age of onset. In untreated patients with SMA type I, median survival is approximately 7 months, and mortality before 18 months of age reaches up to 95%, with respiratory complications being the leading cause of death.

Clinical classification of SMA is based on age at onset and the highest motor milestone achieved (Table 1).

Table 1. Clinical classification of SMA.

SMA Type	Age at Onset	Motor Milestones Achieved	Clinical Severity / Key Features	Expected Survival (Untreated)
Type 0	Prenatal (decreased fetal movements)	None	Severe hypotonia and weakness at birth, respiratory failure	Few days
Type I (Werdnig–Hoffmann disease)	< 6 months	Never able to sit independently	Severe generalized weakness, hypotonia, feeding difficulties, respiratory insufficiency	Median survival ~7 months; mortality up to 95% by 18 months
Type IA	0–2 weeks	No head control	Profound hypotonia, severe respiratory failure, feeding difficulties	Very short survival
Type IB	~3 months	No head control	Severe weakness, bell-shaped chest, paradoxical breathing	Severe, early respiratory failure
Type IC	3–6 months	Head control achieved; never able to sit	Severe weakness but slightly milder than IA/IB	Severe, requires ventilatory support
Type II (Dubowitz disease)	< 18 months	Able to sit; never able to walk independently	Intermediate severity, progressive weakness, loss of ambulation	Survival into adolescence/adulthood (with respiratory complications)
Type III (Kugelberg–Welander disease)	> 18 months (childhood/adolescence)	Able to stand and walk independently	Mild-to-moderate proximal weakness; may lose ambulation over time	Normal or near-normal life expectancy
Type IV (Adult-onset SMA)	Adulthood	Independent ambulation maintained	Mild proximal weakness, slow progression	Normal life expectancy

3.2 Role of the SMN2 gene

In addition to *SMN1*, humans possess a paralogous gene, *SMN2*, which differs by a critical nucleotide substitution affecting splicing. As a result, approximately 90% of *SMN2* transcripts exclude exon 7, producing truncated, unstable protein. Approximately 10% of transcripts contain exon 7 and generate functional full-length SMN protein. All patients with SMA retain at least one copy of *SMN2*, and disease severity is associated with the number of *SMN2* gene copies.

3.3 Mechanism of action and administration of nusinersen

Nusinersen is an antisense oligonucleotide (ASO) designed to modify splicing of *SMN2* pre-mRNA. It binds to the intronic splicing silencer N1 (ISS-N1) located in intron 7 of *SMN2* pre-mRNA. This interaction displaces splicing repressors and promotes inclusion of exon 7 into the mature mRNA transcript, resulting in increased production of full-length SMN protein.

Nusinersen is administered intrathecally via injection into the cerebrospinal fluid, allowing direct distribution to motor neurons within the spinal cord. The drug is approved for use regardless of patient age or clinical subtype of SMA

3.4 Manufacturing process of nusinersen

Nusinersen is produced using solid-phase oligonucleotide synthesis, in which nucleotides are sequentially added in a defined order. Following synthesis, the process includes chemical group deprotection, oxidation, and multi-step purification. These procedures are performed to stabilize the final product and to remove truncated sequences, by-products, and impurities that could affect safety, efficacy, or immunogenicity of the therapy.

3.5 ENDEAR trial

ENDEAR was a randomized, double-blind, sham-controlled phase III trial including infants aged ≤7 months with genetically confirmed 5q SMA type I. Eligibility criteria required homozygous deletion or mutation of the *SMN1* gene and the presence of two copies of *SMN2*. Clinical symptoms had to occur at ≤6 months of age, without permanent ventilatory support at screening. Participants were randomized in a 2:1 ratio to receive intrathecal nusinersen or a sham procedure.

In the prespecified interim analysis, a motor milestone response was observed in 41% of infants receiving nusinersen compared with 0% in the control group. Following these results, the study was terminated early.

In the final analysis, 51% of infants in the nusinersen group achieved a motor milestone response, whereas none in the control group met this endpoint. Among treated patients, 22% achieved head control, 10% were able to roll over, 8% achieved independent sitting, and 1% were able to stand. None of these milestones were achieved in the control group.

Event-free survival was significantly higher in the nusinersen group. At the time of final analysis, 39% of treated infants and 68% of control patients had died or required permanent ventilation. The risk of death or permanent ventilation was reduced by 47% in the treatment group compared with controls.

3.6 CHERISH trial

CHERISH was a randomized, double-blind, sham-controlled phase III study conducted in children aged 2–12 years with later-onset 5q SMA (primarily type II). Inclusion criteria required genetically confirmed *SMN1* mutation or deletion, symptom onset after 6 months of age, ability to sit independently, absence of independent walking (defined as walking ≥15 feet unaided), and a baseline Hammersmith Functional Motor Scale–Expanded (HFMSE) score between 10 and 54.

Key exclusion criteria included severe contractures preventing HFMSE assessment, scoliosis with a Cobb angle >40°, need for ventilatory support >6 hours per day, or presence of a feeding tube.

Participants were stratified by age (<6 years vs ≥6 years) and randomized 2:1 to receive intrathecal nusinersen (12 mg) or sham procedure.

After 15 months of treatment, the mean HFMSE score increased by 4.0 points in the nusinersen group, whereas a mean decrease of 1.9 points was observed in the control group. The study was terminated early following demonstration of statistically significant efficacy.

3.7 EMBRACE trial

EMBRACE was a phase II randomized, sham-controlled trial designed to evaluate nusinersen in patients not eligible for ENDEAR or CHERISH. Eligible patients included:

- infants with three copies of *SMN2* and symptom onset ≤6 months,
- patients with two copies of *SMN2* and symptom onset ≤6 months who were older than 7 months at screening,
- patients with two or three copies of *SMN2* with symptom onset between 6 and 18 months of age.

A total of 21 patients were randomized in a 2:1 ratio to receive nusinersen or sham treatment.

No adverse events leading to treatment discontinuation were reported. The most common adverse events were fever, cough, pneumonia, and upper respiratory tract infections. Vomiting was the most frequently reported event associated with lumbar puncture.

Motor function response was observed in 93% of treated participants. Due to the limited sample size, statistical power was restricted.

3.8 Use of nusinersen in adults

Data on nusinersen use in adult patients with SMA are primarily derived from observational and real-world studies. In cohorts consisting predominantly of patients with SMA type III, improvements in motor function assessed by HFMSE were reported following loading doses of nusinersen. Treatment response varied among individuals and appeared to be associated with baseline functional status.

In ambulatory patients, additional outcome measures included the 6-Minute Walk Test (6MWT) and the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R). In patients with SMA type II, treatment was associated with initial improvement followed by stabilization of motor function.

3.9 DEVOTE trial

DEVOTE was a clinical study evaluating higher-dose and accelerated dosing regimens of nusinersen. The study assessed safety, pharmacokinetics, and clinical outcomes.

Part A included a small pediatric cohort and demonstrated acceptable tolerability of higher doses. Reported adverse events were predominantly mild and related to the lumbar puncture procedure. No clinically significant laboratory abnormalities were observed. Cerebrospinal fluid concentrations of nusinersen were consistent with pharmacokinetic model predictions.

Part B included patients with later-onset SMA. Higher-dose nusinersen was associated with numerically greater improvements in motor function assessed by HFMSE and Revised Upper Limb Module (RULM) compared with standard 12 mg dosing and sham-control data from CHERISH.

Part C included a broader age range, including adults previously treated with nusinersen. Transition to the higher-dose regimen was associated with additional improvement or stabilization of motor function assessed using HFMSE, RULM, and Clinical Global Impression of Change (CGI-C). The safety profile remained consistent with previous studies.

4. Discussion

Analysis of available clinical trials, including ENDEAR, CHERISH, EMBRACE, and DEVOTE, indicates that nusinersen is an effective disease-modifying therapy for 5q spinal muscular atrophy (SMA), leading to significant improvements in motor function and increased ventilation-free survival in specific patient populations. The greatest clinical benefit is observed in infants with Type 1 SMA, where treatment is associated with a substantial reduction in the risk of death or permanent ventilation and enables the attainment of motor milestones rarely observed in the natural history of the disease. The efficacy of the therapy has also been confirmed in the late-onset pediatric population (Type 2 SMA), where improvements or stabilization of motor function were observed compared to natural disease progression. Furthermore, results from the EMBRACE study suggest the potential for clinical response in patient groups who did not meet the original inclusion criteria of registration trials, pointing toward a potentially broader application of the therapy.

Observational data from adult populations indicate the possibility of disease stabilization and moderate functional improvement; however, the therapeutic response appears to be contingent upon baseline clinical status and the timing of treatment initiation. These findings underscore the critical importance of early patient identification and the prompt implementation of disease-modifying therapy. Findings from the DEVOTE trial suggest that modifications to the dosing regimen, including the administration of higher doses of nusinersen, may be associated with further improvements in functional parameters while maintaining an acceptable safety profile. Nevertheless, these outcomes require confirmation through studies with longer follow-up periods.

Collectively, available data indicate that antisense oligonucleotide-based therapies have significantly transformed the SMA therapeutic landscape, while simultaneously highlighting the need for further research into long-term efficacy, dosage optimization, and treatment accessibility across diverse patient populations.

4.1 Manufacturing limitations and cost considerations

Although antisense oligonucleotide therapies have substantially expanded therapeutic options in SMA, their large-scale production remains technologically demanding. Solid-phase synthesis, which constitutes the standard method for manufacturing therapeutic oligonucleotides, is well established and reproducible; however, it presents inherent limitations in scalability. The restricted surface capacity of the solid support and the stepwise nature of nucleotide coupling increase the risk of incomplete reactions and sequence-related impurities, particularly in longer oligonucleotide constructs. These factors may affect batch consistency and overall manufacturing yield.

The production of nusinersen requires highly purified reagents, specialized solvents, and excess coupling agents to ensure adequate reaction efficiency. As each elongation step is associated with incremental loss of yield, cumulative material losses become significant over the full synthesis cycle. Furthermore, purification procedures—necessary to remove truncated sequences, residual solvents, and process-related impurities—may result in substantial reduction of final product yield. Together, these factors contribute to the high manufacturing costs associated with antisense therapies.

4.2 Economic and environmental implications

The technological complexity of oligonucleotide synthesis directly translates into high treatment costs, which may influence healthcare system sustainability and patient access. In addition, current production processes are largely incompatible with circular economy principles. The stringent purity requirements and the use of specialized reagents limit opportunities for solvent recycling or material reuse. As a result, oligonucleotide manufacturing largely follows a linear resource-consumption model, raising concerns regarding long-term environmental impact.

Future optimization of synthesis platforms, process intensification strategies, and greener chemistry approaches may improve manufacturing efficiency, reduce costs, and enhance sustainability without compromising product quality.

4.3 Accessibility and future perspectives

Despite demonstrated clinical efficacy, the widespread implementation of nusinersen therapy is influenced by economic and infrastructural factors. The high cost of treatment may represent a substantial reimbursement challenge in certain healthcare systems, potentially contributing to disparities in patient access. Variability in national funding policies and the organization of rare disease programs further modulate real-world availability of therapy.

At the same time, ongoing advancements in oligonucleotide synthesis technologies, process optimization strategies, and manufacturing scale-up approaches may improve production efficiency over time. Such developments could translate into gradual cost reductions and enhanced sustainability of antisense-based therapeutics.

From a broader perspective, nusinersen represents a paradigm shift in the treatment of genetic neuromuscular disorders by demonstrating the feasibility of RNA-targeted disease-modifying therapy. Continued research is warranted to refine treatment algorithms, optimize dosing strategies, and evaluate long-term clinical outcomes across diverse patient populations.

4.4 Study limitations

Several limitations should be considered when interpreting the available evidence on nusinersen therapy. First, although pivotal trials such as ENDEAR and CHERISH were randomized and controlled, their sample sizes were relatively small due to the rarity of SMA, which may limit statistical power and generalizability to broader patient populations. Second, follow-up durations in registration trials were relatively short, restricting assessment of long-term efficacy, durability of response, and safety outcomes.

In addition, strict inclusion and exclusion criteria applied in clinical trials may not fully reflect real-world patient heterogeneity, particularly in individuals with advanced disease, significant scoliosis, respiratory compromise, or previous surgical interventions. Evidence in adult populations is largely derived from observational studies without randomized control groups, which introduces potential bias and limits causal inference. Finally, the absence of direct head-to-head comparisons between nusinersen and other disease-modifying therapies for SMA makes it difficult to determine relative efficacy and optimal treatment sequencing.

Long-term real-world data and comparative studies are therefore needed to better define the position of nusinersen within the evolving therapeutic landscape of SMA.

5. Conclusions

Nusinersen has demonstrated clinically meaningful efficacy across multiple phenotypes of 5q spinal muscular atrophy, particularly when initiated early in the disease course. Evidence from randomized controlled trials and real-world studies indicates improvement or stabilization of motor function and increased survival free from permanent ventilation in defined patient populations.

Despite its established therapeutic benefit, important challenges remain, including limited long-term data, variability of response in advanced disease stages, high manufacturing complexity, and economic constraints affecting global accessibility. Ongoing optimization of dosing strategies, expansion of real-world evidence, and advancements in oligonucleotide production technologies may further refine the role of nusinersen in SMA management.

Overall, antisense oligonucleotide–based therapies represent a significant advancement in the treatment of genetic neuromuscular disorders and continue to shape the evolving therapeutic landscape of spinal muscular atrophy.

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