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Pharmacokinetics of therapies approved for spinal muscular atrophy: A narrative review of current evidence

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Abstract

Spinal muscular atrophy is a severe neuromuscular disorder caused by mutations in the survival motor neuron 1 gene, leading to progressive motor neuron degeneration. Over the past decade, disease-modifying therapies targeting the survival motor neuron pathway—nusinersen, onasemnogene abeparvovec, and risdiplam—have significantly transformed the clinical landscape of spinal muscular atrophy. Despite their common therapeutic goal of restoring functional survival motor neuron protein levels, these agents differ markedly in their molecular design, route of administration, pharmacokinetic behavior, and population-specific efficacy. This narrative review provides a comprehensive synthesis of pre- and post-approval pharmacokinetic data from pivotal trials, real-world studies, and population-based modeling. Nusinersen, an intrathecal antisense oligonucleotide, demonstrates prolonged cerebrospinal fluid exposure and slow systemic clearance. Onasemnogene abeparvovec, a single-dose gene therapy, shows sustained survival motor neuron expression mediated by adeno-associated virus 9 vector delivery and episomal persistence in nondividing neurons. Risdiplam, an orally administered survival motor neuron 2 splicing modifier, exhibits systemic bioavailability with reliable central nervous system penetration and predictable

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pharmacokinetics across age groups. Elimination of gene products and oligonucleotides is a multifaceted process involving enzymatic degradation, immune responses, and excretion through the kidneys or liver. We further discussed how interindividual variability, age, survival motor neuron 2 copy number, and immunological factors influence pharmacokinetic–pharmacodynamic relationships. Personalized treatment strategies for spinal muscular atrophy are increasingly being guided by advances in pharmacokinetic modeling. As the field evolves, biomarker-based monitoring and combination therapies are emerging as promising complementary approaches. With growing clinical experience and an expanding body of pharmacokinetic research on targeted therapies, there is strong potential to further refine treatment strategies—ultimately making spinal muscular atrophy care more effective, safer, and more accessible for patients worldwide.

Keywords
Spinal muscular atrophy, pharmacokinetics, disease-modifying therapies, nusinersen, onasemnogene abeparvovec, risdiplam

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Introduction

Spinal muscular atrophy (SMA) was first described independently by Guido Werdnig and Johann Hoffmann in the 1890s. Together, their clinical and pathological observations provided the first characterization of infantile SMA.[1] SMA is a genetic neuromuscular disorder that primarily affects the anterior horn cells of the spinal cord, resulting in progressive loss of motor neurons, muscle weakness, atrophy, and denervation at the neuromuscular junction. Inherited in an autosomal recessive manner, it has an estimated incidence of 8–11 per 100,000 births, making it the most common monogenic cause of infant mortality.[2]

The disease is most frequently caused by homozygous deletions or gene conversions in the survival motor neuron 1 (*SMN1)* gene located on chromosome 5q. In approximately 95% of cases, patients exhibit a homozygous deletion of exon 7 in *SMN1*, while the remaining 5% typically present with a compound heterozygous mutation involving one deleted allele and a point mutation on the other.[3] A nearly identical copy of *SMN1*, termed *SMN2*, is also present in most individuals. However, due to a critical cytosine-to-thymine (C-to-T) transition in exon 7, *SMN2* predominantly produces a truncated, nonfunctional SMN protein. Nevertheless, a small proportion of transcripts include exon 7 and encode functional SMN protein, which partially compensates for *SMN1* deficiency. Importantly, the number of *SMN2* copies is inversely correlated with disease severity—fewer copies are associated with earlier onset and more severe phenotypes.[4–6]

Newborn screening for SMA is primarily performed using real-time polymerase chain reaction on dried blood spots to detect homozygous *SMN1* deletions and estimate *SMN2* copy number.[7] Diagnostic criteria are defined by the International SMA Consortium and include clinical signs such as motor regression or delay, hypotonia, proximal muscle weakness, reduced or absent deep tendon reflexes, and molecular confirmation of biallelic pathogenic variants in *SMN1*.[8,9]

SMA is clinically classified into five types (0–IV) based on age at onset and disease severity. This classification captures

the wide phenotypic spectrum of the disease, ranging from prenatal onset with severe hypotonia and respiratory failure (Type 0) to adult-onset forms with mild proximal weakness and preserved ambulation (Type IV). An overview of SMA subtypes, including associated *SMN2* copy numbers, clinical features, and natural history, is presented in Table 1.[9,10] However, with the implementation of newborn screening and earlier diagnosis, the classical natural history is increasingly being altered. Early initiation of disease-modifying therapies (DMTs) has been associated with markedly improved outcomes, as motor neuron degeneration can be mitigated before clinical symptoms manifest.[11]

Overview of therapies for SMA

Historically, the management of SMA was limited to supportive interventions aimed at preserving respiratory function and nutritional status. Although a definitive cure for SMA remains elusive, insights into the molecular genetics of the *SMN* locus—particularly the inverted duplication on chromosome 5q11.1-13.3—have paved the way for DMTs.[12,13]

Before the approval of current SMN-targeted therapies, several compounds were evaluated for their potential to enhance SMN protein expression. These early efforts focused on modifying *SMN2* splicing or enhancing transcriptional activity and included agents such as sodium butyrate, valproic acid, salbutamol, hydroxyurea, and 4-phenylbutyrate. Preclinical and early clinical studies demonstrated variable efficacy in upregulating full-length *SMN* messenger RNA (mRNA) and protein levels.[14–18] High-throughput screening further identified small molecules capable of modulating *SMN2* splicing and improving survival in SMA mouse models.[19] A summary of key preclinical and early clinical studies investigating non-gene-targeted therapeutic strategies for SMA is provided in Table 2.

In recent years, the therapeutic landscape for SMA has markedly evolved with the approval of DMTs such as nusinersen, onasemnogene abeparvovec (OA), and risdiplam, each targeting the underlying genetic defect through distinct mechanisms. These advances have significantly altered prognosis, particularly when treatment is initiated early.[11]

This narrative review aims to discuss the pharmacokinetic (PK) properties of the three approved DMTs for SMA, the ways in which they differ, and the challenges involved in understanding their PK profiles. Although these therapies share a common therapeutic goal, they vary markedly in their biochemical composition, routes of administration, and fate within the body. Assessing them side by side offers valuable insight into how distinct pharmacological strategies can achieve clinical efficacy through diverse PK pathways. By comparing these pharmacological approaches, we also explore which PK characteristics may be considered optimal for the treatment of SMA. A comprehensive literature search was conducted in the PubMed databases for studies published from April 2010 to April 2025. The search was performed between 12 and 25 May 2025. The search strategy employed a combination of keywords, including "spinal muscular atrophy," "onasemnogene abeparvovec," "risdiplam," "nusinersen," and "pharmacokinetics." The detailed PubMed search strategy is provided in the **Supplementary Material**.

In addition, a manual search was performed on clinicaltrials.gov and relevant conference proceedings to identify additional eligible studies not captured in the primary database search. Only English-language articles were included. PK parameters such as maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), half-life ($t_{1/2}$), and systemic exposure were summarized

Table 1. Natural history of SMA subtypes prior to DMTs: age of onset, motor function, and clinical features.

SMA type	*SMN2* copy number	Age of onset	Highest motor function achieved	Key clinical features	Natural history
Type 0	1	In utero	None	Widespread motor and sensory neuron loss, congenital contractures, high incidence of cardiac defects	Perinatal death
Type I	2	0–6 months	Never sit	Neonatal hypotonia, poor feeding, respiratory insufficiency, inability to roll or sit unassisted	50% die by 12 months, 90% by 24 months without invasive ventilation
Type II	3	6–18 months	Sit, never stand or walk	Able to sit independently but never stand; progressive weakness of respiratory muscles	Life expectancy of 30–50 years depending on respiratory function
Type III	3–5	After 18 months (IIIa: <3 years; IIIb: >3 years)	Stand and walk independently, though may lose ambulation later	Proximal weakness, especially in lower limbs; variable loss of ambulation; respiratory involvement uncommon	Near-normal life expectancy
Type IV	3–5	Second or third decade	Walk unassisted	Slowly progressive proximal weakness, lower limb predominance, minimal respiratory involvement	Normal lifespan

The table summarizes the relationship between *SMN2* copy number, age at onset, maximal motor function attained, and key clinical features among the SMA subtypes prior to the availability of DMTs.
SMA: spinal muscular atrophy; SMN: survival motor neuron; DMT: disease-modifying therapy.

Table 2. Summary of preclinical and early clinical studies evaluating non-gene-targeted therapeutic strategies for SMA (studies identified from Online Mendelian Inheritance in Man (OMIM)[95]).

Intervention	Mechanism	Model/Population	Outcome
Sodium butyrate[14]	Increased exon 7 inclusion and SMN protein levels	Mouse model (SMA-like) and patient cell lines	Amelioration of SMA symptoms
Valproic acid[15]	Upregulation of full-length *SMN2* mRNA/protein via HTRA2-beta-1	SMA patient fibroblast cultures and rat hippocampal slices	Potential therapeutic via alternative splicing regulation
Valproic acid[20]	Increased SMN mRNA/protein variably in carriers and patients	SMA carriers and patients (n = 30)	Variable response suggests transcription/translation modulation
Phenylbutyrate[16]	Increased *SMN2* transcript and protein levels	Fibroblasts from patients with Type 1–3 SMA	Increased GEMs; potential therapy
Hydroxyurea[17]	Promoted exon 7 inclusion in *SMN2*	Cultured lymphocytes from patients with SMA	Increased full-length SMN expression
Proactive supportive management[21]	Reduced mortality in modern cohort	Questionnaire-based study of 143 patients with SMA	Ventilation, MI-E devices, gastrostomy improved survival
Salbutamol[18]	Increased full-length *SMN2* mRNA and protein	Fibroblasts from patients with Type 1–3 SMA	Rapid increase; increased nuclear gems
Na^+/H^+ exchange inhibitor[22]	Upregulation of exon 7 splicing and SMN protein via SRp20	SMA lymphoid cell lines	pH-mediated splicing regulation
iPSCs from patient with SMA[23]	Modeling SMA-specific motor neuron pathology	iPSCs and derived motor neurons	Disease modeling platform for Type 1 SMA
Small molecules modulating *SMN2* splicing[19]	Selective increase of full-length *SMN2* mRNA	Delta-7 SMA mouse model	Increased SMN, improved function and survival

The table outlines selected interventions investigated prior to or alongside gene-targeted therapies, focusing on pharmacological agents and supportive management approaches aiming to increase SMN expression or improve survival.

SMA: spinal muscular atrophy; SMN: survival motor neuron; HTRA2-beta-1: human transformer 2 beta protein, isoform 1; GEMs: SMN-containing nuclear structures; iPCs: induced pluripotent stem cells; MI-E: mechanical insufflator–exsufflator; mRNA: messenger ribonucleic acid.

narratively, and their clinical relevance was discussed. Given the fundamentally different nature of the three approved therapies, we applied distinct PK terminology where appropriate. For viral vector–based therapy, conventional absorption, distribution, metabolism, and excretion (ADME) categories are less informative; therefore, we consistently used the terms "biodistribution" and "persistence" to better capture its pharmacological behavior. In contrast, for small molecules and antisense oligonucleotides, classical PK descriptors—ADME—were employed. This approach allowed us to reflect the unique properties of each therapeutic class while maintaining conceptual clarity across the review. Although no formal quality assessment tool was applied, priority was given to large, prospective trials with clearly defined methodologies. By synthesizing evidence from pivotal clinical trials, population modeling, and post-approval research, this review emphasizes the key PK findings while also integrating insights from real-world practice and modeling studies. This review was conducted in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines.[24] Ongoing clinical trials are primarily focused on the development of pharmacological strategies that enhance the expression of full-length SMN protein as a therapeutic approach for SMA. Currently, three SMN-targeted therapies have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA): nusinersen (Spinraza®), OA–xioi (Zolgensma®), and risdiplam (Evrysdi®). Each of these therapies employs a distinct mechanism of action and delivery method; however, all of them aim to restore functional SMN protein levels and ameliorate the neuromuscular phenotype. Despite this shared therapeutic goal, these agents differ in terms of PK characteristics, route of administration, target populations, and regulatory approval timelines. Understanding their pharmacological profiles is therefore essential to optimize clinical outcomes and tailor treatment strategies.

Initial PK and pharmacodynamic (PD) findings

Nusinersen

Nusinersen (Spinraza®) is a synthetic antisense oligonucleotide (ASO) consisting of 18 nucleotides with 2′-O-methoxyethyl (2′-MOE) and phosphorothioate backbone modifications. It modulates splicing of *SMN2* pre-mRNA by binding to the intronic splice silencing site 1, leading to exon 7 inclusion through displacement of splicing repressors such as heterogeneous nuclear ribonucleoproteins (hnRNPs), thereby restoring the production of full-length SMN protein.[25] Owing to its large molecular size and polarity, nusinersen is administered intrathecally to ensure central nervous system (CNS) bioavailability. It was the first therapy targeting the underlying genetic mechanism of SMA.

Nusinersen received FDA approval in December 2016 as an orphan drug and was subsequently granted EMA approval in May 2017 for the treatment of 5q-associated SMA, regardless of disease type or patient age. Its efficacy was established by two pivotal studies (ENDEAR and CHERISH), supported by early-phase studies (CS3A and CS1/2). The ENDEAR (CS3B) trial, conducted among symptomatic infants with early-onset SMA ($\leq$6 months), demonstrated significant improvements in event-free survival (EfS) and motor milestone achievement compared with sham control ($p < 0.001$), including a 51% response rate on the Hammersmith Infant Neurological Examination-2 (HINE-2) scale and improved Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores. The CHERISH (CS4) trial, involving patients with later-onset

SMA (median age, 3 years), showed a statistically significant improvement in Hammersmith Functional Motor Scale-Expanded (HFMSE) scores from baseline to month 15 (mean change: +3.9 vs. −1.0; $p < 0.001$).[25,26] These findings were further validated by long-term extension data from the SHINE study and early-phase trials as well as real-world outcomes in pediatric and adult patients.[26,27]

Overview of initial PK/PD studies. Initial PK and PD investigations of nusinersen have characterized its behavior following intrathecal administration, focusing on its ADME. Preclinical studies in rodents and nonhuman primates demonstrated broad CNS distribution and prolonged tissue retention following intracerebroventricular or intrathecal administration, with functional *SMN2* exon 7 inclusion persisting at least 36 weeks postdosing in the spinal cord.[28] First-in-human studies confirmed dose-proportional concentrations in both cerebrospinal fluid (CSF) and plasma, with a terminal CSF half-life ranging from 132 to 177 days.[29] Further clinical investigations confirmed widespread CNS penetration, while population PK modeling using pooled data from five trials revealed a four-compartment model encompassing CSF, CNS, plasma, and systemic tissues. This model estimated a median CSF half-life of 163 days and supported infrequent dosing regimens, consistent with the clinical administration of nusinersen every 4–6 months in pediatric patients.[30,31]

Dosing regimen and bioavailability. Regarding dosing and bioavailability, initial dose-escalation studies evaluated ascending single doses (1–9 mg) and identified 12 mg as the optimal fixed dose for repeated administration.[30,31] Although absolute bioavailability cannot be directly assessed due to the intrathecal route, functional bioavailability is supported by increased SMN protein levels and improved motor function. Age-adjusted simulations initially supported weight-based dosing in infants aged <2 years; however, given the absence of dose-limiting toxicity, a uniform 12-mg regimen was ultimately recommended for all age groups.[31]

Key findings from early-phase trials and PK support for clinical efficacy. Pivotal clinical trials have further established the efficacy of nusinersen across various SMA phenotypes. In the ENDEAR trial involving infants with symptomatic Type 1 SMA, nusinersen significantly improved motor milestone response rates (51% vs. 0%; $p < 0.001$) and prolonged EfS, defined as survival without permanent ventilation. A hazard ratio of 0.37 for mortality further confirmed a substantial survival advantage, particularly among those treated earlier in the disease course.[32] In the CHERISH study, which enrolled children aged 2–12 years with later-onset SMA (mostly Type 2), nusinersen recipients demonstrated a mean gain of +4.0 points in HFMSE scores, whereas children in the sham group experienced a mean decline of −1.9 points ($p < 0.001$). A clinically meaningful improvement (≥3 points) was observed in 57% of treated patients compared with 26% in controls.[33]

Additional data underscore the importance of the timing and anatomical distribution of drug action. Ramos et al. emphasized the importance of temporal distribution of SMN protein, highlighting that the therapeutic efficacy of nusinersen may depend on early initiation and sustained CNS expression. Lower SMN levels in postnatal spinal cords compared with fetal samples highlight the value of early PK/PD optimization in clinical practice. Evidence from presymptomatic cohorts has further reinforced this principle.[34] Longitudinal studies such as NURTURE (presymptomatic infants) and EMBRACE

(patients outside pivotal trial eligibility) highlighted the importance of early intervention.[35,36]

OA

OA–xioi (Zolgensma®) is a gene replacement therapy designed to deliver a functional copy of *SMN1* to motor neurons via an adeno-associated virus serotype 9 (AAV9) vector. Once transduced, the gene remains episomal and drives sustained expression of the SMN protein through a cytomegalovirus enhancer/chicken-β-actin hybrid promoter. The AAV9 capsid facilitates crossing of the blood–brain barrier and targets motor neuron populations, directly addressing the genetic root cause of SMA. By introducing this gene into host cells, the therapy enables sustained expression of the full-length SMN protein, directly targeting the genetic root cause of SMA.[37]

This therapy is a single-dose intravenous infusion and represents the first gene therapy approved for the treatment of SMA. It employs AAV9 for its ability to cross the blood–brain barrier and transduce motor neurons following systemic administration. OA received FDA approval as an orphan drug in May 2019 and was granted conditional EMA approval in May 2020, later converted to full authorization in May 2022, based on key clinical trials including START and STR1VE, which demonstrated improved motor milestone achievement, EfS, and sustained efficacy with a single administration.[37–39]

OA–xioi is a single-dose intravenous gene therapy that delivers a functional copy of *SMN1* to motor neurons using an AAV9 vector. Unlike conventional small molecules or oligonucleotide-based drugs, its PK and PD properties are determined by vector biodistribution, transgene expression, and host immune responses, rather than traditional plasma-based parameters such as half-life or clearance.[40]

Vector distribution and biodisposition. Upon intravenous infusion, the AAV9 vector is rapidly distributed systemically and crosses the blood–brain barrier, achieving efficient transduction of motor neurons in the spinal cord. Biodistribution studies in human tissues, including the heart, kidney, and skeletal muscles, demonstrated that vector genome copies are most abundant in the liver, 300–1000-fold higher than that in the CNS; however, therapeutically relevant levels (1.5–2.7 vector genome (vg)/diploid genome) are also detected in spinal motor neurons via laser-capture microdissection, confirming CNS penetration and neuronal uptake. Immunohistochemical analyses confirmed robust SMN protein expression in both motor neurons and glial cells throughout the spinal cord and brain.[40]

SMN protein expression initiates within days post-administration and remains durable due to episomal persistence of the transgene in nondividing neurons. Traditional plasma PK parameters are of limited relevance for recombinant adeno-associated virus (rAAV)–based gene therapies; instead, vector genome copies in tissues and transgene expression levels serve as surrogate PK/PD indicators. Importantly, the presence of pre-existing anti-AAV9 neutralizing antibodies can impair vector transduction and prevent effective gene delivery. As a result, patients are routinely screened for anti-AAV9 seropositivity prior to treatment, as current clinical protocols generally exclude seropositive individuals to ensure efficacy and safety.[41] Shedding of OA predominantly occurs via feces, peaking within the first weeks after infusion and typically resolving within 30 days, as reported in preclinical and regulatory data.[37]

Clinical correlates from early-phase trials. The START trial was the first to demonstrate

the clinical impact of OA in infants with Type 1 SMA. All patients survived beyond 20 months without permanent ventilation, and several achieved developmental milestones such as independent sitting and walking—outcomes rarely observed in untreated populations.[42]

These findings were corroborated in the STR1VE-US and STR1VE-EU studies, where 44% and 59% of the treated infants, respectively, achieved independent sitting. In STR1VE-US, 82% of the treated infants survived without permanent ventilation by 18 months.[43,44] Plasma-based PK data were limited, and there was no clear or consistent increase in either AAV9 or SMN cellular response.[43] In the STR1VE-EU study, 44% of patients achieved independent sitting for at least 10 s by 18 months, and 97% survived without permanent ventilation by 14 months of age, confirming comparable therapeutic efficacy in a European cohort.[44]

Most compellingly, the SPR1NT trial evaluated presymptomatic infants with two or three *SMN2* copies. Early administration of the same dose (1.1×10^{14} vg/kg) resulted in 100% survival and achievement of age-appropriate World Health Organization motor milestones, with 79% of infants with two gene copies standing independently by 18 months of age.[45]

Risdiplam

Risdiplam (Evrysdi®) is an orally administered small molecule designed to treat SMA by modifying the splicing of *SMN2* pre-mRNA. It enhances the inclusion of exon 7, thereby increasing the production of functional, full-length SMN protein systemically, including the CNS. This mechanism directly addresses the pathophysiological deficiency in SMN protein caused by mutations in *SMN1* located on chromosome 5q.[46]

Risdiplam received FDA approval in August 2020 as an orphan drug and EMA approval in March 2021 for the treatment of patients with 5q-associated SMA aged ≥2 months. The clinical efficacy and safety of risdiplam were demonstrated in two pivotal studies. The FIREFISH trial part 2 evaluated symptomatic infants with Type 1 SMA. By month 12, 29.3% of patients achieved the primary endpoint of independent sitting for ≥5 s, rising to 61% by month 24. Importantly, 82.9% of participants were alive without permanent ventilation at 24 months. The SUNFISH trial part 2 assessed nonambulant patients aged 2–25 years with Type 2 or 3 SMA. At month 12, risdiplam-treated patients showed a statistically significant improvement in the 32-item Motor Function Measure (MFM32) and the Revised Upper Limb Module (RULM) scores.[47] These improvements were sustained through 24 months of treatment. Additional data from the RAINBOWFISH trial in presymptomatic infants and JEWELFISH in previously treated patients with SMA further support risdiplam's efficacy across the clinical spectrum of the disease.[48–50]

ADME. Risdiplam is an orally administered small molecule that promotes exon 7 inclusion in *SMN2* pre-mRNA transcripts, thereby enhancing functional SMN protein production. It is the first and only orally administered SMA therapy approved for systemic use, offering broad tissue distribution, including CNS penetration.[46] Preclinical studies in rodents and nonhuman primates confirmed extensive tissue distribution, including the brain, muscle, and visceral organs. CNS penetration is supported by risdiplam's highly passive permeability and minimal interaction with efflux transporters.[51]

In healthy volunteers, risdiplam exhibited linear PK over a dose range of 0.6–18 mg, with a mean terminal half-life of 40–69 h and no significant food effect on systemic exposure.[52] The drug is primarily metabolized by flavin-containing monooxygenases (FMO1 and FMO3) and minimally

by cytochrome P450 (CYP) enzymes, reducing the risk of drug–drug interactions. Excretion occurs predominantly via feces.[46,52] Clinical trials demonstrated dose-proportional exposure and consistent increases in systemic SMN protein levels across patient populations. Risdiplam reached steady-state concentrations within 7–14 days.[53] In the FIREFISH trial (Type 1 SMA), area under the curve (AUC) values ranged from 630 to 2000 ng·h/mL depending on dosage, and this exposure was associated with twofold increases in SMN protein levels within 4 weeks, also supported by the sustained (>12-month) twofold increase reported in SUNFISH Part 1.[54,55]

Dosing schedule and PD. The therapeutic dosing regimen of risdiplam, derived from FIREFISH part 2 and SUNFISH part 2 studies, is 0.25 mg/kg once daily for individuals weighing <20 kg and a fixed 5 mg daily dose for those weighing ≥20 kg. This regimen consistently achieved a more than twofold increase in SMN protein levels within 4 weeks, which was sustained throughout the treatment period. These PD effects were correlated with improvements in motor function and other clinical outcomes across both treatment-naïve and pretreated populations.[49,56,57]

Systemic exposure and clinical outcomes. Systemic exposure to risdiplam varies by age and body weight, with $AUC_{0–24\,h}$ values reaching ~1930 ng·h/mL in infants (1–7 months) and ~2070 ng·h/mL in older patients (2–25 years).[47] Risdiplam's mechanism of action, enhancing exon 7 inclusion in *SMN2* mRNA, results in ≥twofold increases in SMN protein levels within 4 weeks, which is sustained during long-term treatment.[54–56] In FIREFISH part 2, 90% of infants showed EfS at 12 months, and SMN levels increased to a median of 5.87 ng/mL in the high-dose group, correlating with a 44% achievement rate of independent sitting for at least 30 s—milestones rarely observed in untreated SMA.[53,55] In SUNFISH part 2, risdiplam led to a significant improvement in MFM32 scores compared with placebo (+1.55 points; $p = 0.016$), with younger individuals showing functional gains and older participants maintaining stability.[58] The JEWELFISH trial demonstrated preserved PD responses in patients previously treated with other SMA therapies, supporting risdiplam's efficacy across a broad clinical spectrum.[49,50]

Sneak peek on post-approval PK studies

Nusinersen

Following regulatory approval, long-term PK evaluation of nusinersen has continued through observational studies and model-based simulations. The approved regimen (12 mg intrathecally every 4 months following four loading doses) has demonstrated consistent CSF exposure. Recent data have explored the potential benefits of higher doses. The relationship between CSF drug levels and clinical outcomes has been demonstrated in previous studies, with higher CSF concentrations associated with greater declines in plasma phosphorylated neurofilament heavy chain (pNF-H) levels and improved CHOP-INTEND scores.[59] The DEVOTE study (Part A) investigated a 28-mg dose, reporting no new safety signals and steady increases in CSF concentrations, reaching median C_{trough} values consistent with population PK model predictions for enhanced efficacy.[60]

Long-term results from clinical trials demonstrated that in children with later-onset SMA, sustained exposure to nusinersen was associated with preserved motor function and improvements in HFMSE and 6-Minute Walk Test scores.[61] In real-world settings, the PANDA study reported steady

increase in CSF levels of nusinersen and no plasma accumulation after multiple doses, accompanied by gains in HINE-2 scores.[62]

Treatment interruptions pose a practical challenge, particularly during long-term therapy. MacCannell et al. (2021) proposed evidence-based strategies for managing delayed or missed doses. Population PK simulations demonstrated that a one-time missed dose during maintenance can be compensated by re-administration followed by a dose at the original interval. For interruptions of $\geq$8 months, MacCannell et al. (2022) showed that depending on the length of treatment interruption, 2–4 reloading doses can restore nusinersen CSF trough concentrations to steady-state levels without exceeding peak exposures observed during the initial loading phase.[63,64]

PK variability of nusinersen is influenced by age, CSF turnover, and spinal anatomy. A semimechanistic model developed by Biliouris et al. predicted pediatric exposure based on allometric scaling from primate data, emphasizing the roles of body size and CSF kinetics.[65] A complementary physiologically based PK (PBPK) model demonstrated heterogeneous ASO distribution along the neuroaxis, suggesting local gradients that limit initial distribution efficiency. Factors such as the slow and pulsatile nature of CSF flow, combined with its low turnover rate, may delay drug access to target tissues in humans.[66]

Real-world immunomodulatory data further suggest PD consequences of nusinersen exposure. Nuzzo et al. showed that nusinersen reduced the levels of inflammatory cytokines, including interleukin (IL)-2, IL-4, IL-7, IL-9, IL-12, IL-17, vascular endothelial growth factor (VEGF), eotaxin, and tumor necrosis factor-alpha (TNF-α), in the CSF of Type 1 SMA patients. Variable changes observed in Types 2 and 3 SMA indicated potential differences in CNS penetration or immunologic sensitivity.[67] Garofalo et al. used CSF RNA sequencing in pediatric patients with SMA and detected differentially expressed cell-free RNAs after 6 months of nusinersen treatment. These RNAs were categorized as disease-specific, treatment-specific, or treatment-dependent, implying dynamic molecular changes linked to drug exposure and laying the groundwork for novel RNA-based PD biomarkers.[68] Similarly, Panicucci et al. reported that nusinersen modulates the CSF proteome in a subtype-specific manner, with glucose metabolism upregulation in Type 1 SMA and complement cascade activation in Type 3 SMA, suggesting distinct biological responses that may serve as PD indicators of treatment efficacy.[69]

OA

Several post-marketing studies have investigated the vector's biodistribution, durability of gene expression, and potential immune responses associated with OA. A detailed human tissue study by Thomsen et al. confirmed widespread vector genome and mRNA biodistribution throughout the CNS and peripheral tissues following intravenous administration. SMN protein levels, which are virtually absent in untreated controls, were restored in the spinal cord, skeletal muscle, and peripheral organs, with the liver harboring the highest vector genome copy numbers.[40] Regarding immunological considerations, Chu and Ng highlighted the risk of cytotoxic T cell responses and anti-AAV9 neutralizing antibodies, both of which may impair rAAV transduction and reduce the durability of transgene expression.[70] Additionally, Muhuri et al. provided a mechanistic overview of how host–immune interactions and hepatocyte turnover could influence the long-term persistence of AAV-mediated transgene expression.[41]

Additionally, comparative data on PD effects across age groups and SMA phenotypes are available from clinical trials.

The SPR1NT trial demonstrated that presymptomatic administration of OA enabled near-normal neuromotor development, emphasizing the critical importance of early intervention and suggesting a strong age-dependent PD response.[45] The STRONG trial investigated intrathecal administration of OA in nonambulatory children with Type 2 SMA, including those ineligible for intravenous dosing due to age or weight. Notably, meaningful improvements in HFMSE scores were observed, particularly in children aged 2–5 years, exceeding gains reported in natural history cohorts.[71]

Long-term follow-up has demonstrated promising results regarding treatment durability. In the 5-year extension of the START trial, Mendell et al. reported that all patients who received the therapeutic dose of OA maintained previously acquired motor milestones, and two achieved new gains, such as standing with assistance, without the use of nusinersen. Notably, none of the patients required permanent ventilation, supporting the long-term clinical durability of a single intravenous administration.[72] These findings are reinforced by the review by McMillan et al., which summarized that long-term benefits—both in survival and motor function—have now been consistently reported in multiple cohorts with follow-up periods exceeding 5 years.[73]

Risdiplam

Following regulatory approval as an orally administered *SMN2* splicing modifier for the treatment of SMA, risdiplam has been extensively studied for its PK across various age groups and previously treated individuals. Reflecting real-world conditions and reporting 24-month outcomes, the JEWELFISH study was conducted among 174 pediatric and adult patients who had previously received other SMA therapies, including nusinersen, OA, or olesoxime. The study evaluated systemic exposure, SMN protein elevation, and motor function outcomes following risdiplam treatment. Increases in SMN protein levels were observed across all age and body weight groups and were sustained through 24 months of treatment. Measures of motor function generally stabilized, suggesting that long-term exposure may contribute to neuromotor benefit.[50]

Advanced modeling studies have focused on enzyme ontogeny affecting risdiplam exposure during childhood. Cleary et al. analyzed over 10,000 plasma concentration data points from 525 individuals aged 2 months to 61 years to model FMO3 enzyme maturation, which was then applied to simulate drug interaction risks in pediatric patients. Their findings indicate that FMO3 activity is higher in children than in adults, potentially impacting systemic exposure to risdiplam.[74] Additionally, a phase I study (NCT03988907) investigated the effect of risdiplam on midazolam, a CYP3A substrate, in healthy adults. Participants received 8 mg of risdiplam once daily for 14 days, and midazolam PK parameters (AUC and C_{max}) were compared before and after co-administration. No clinically significant increase in midazolam exposure was observed.[75] In a complementary PBPK model, CYP3A inhibition data obtained from healthy adults were extrapolated to pediatric patients with SMA. The findings predicted a low likelihood of clinically relevant interactions between risdiplam and CYP3A substrates in children aged $\geq$2 months.[76]

Regarding hepatic function, a dedicated phase I study evaluated PK variability among adults with mild or moderate hepatic impairment following a single 5-mg oral dose of risdiplam. The results showed non-significant changes in the AUC (20% decrease in mild impairment and 8% increase in moderate impairment),

supporting that no dose adjustment is needed in this population.[76]

Post-marketing observational data have provided valuable insights into the long-term effects of risdiplam in adults with SMA. In a Croatian cohort of 31 treatment-naïve adults with Types 2 and 3 SMA, most patients either maintained or showed improvement in motor function based on individualized assessments. Overall, 60% of patients with bulbar dysfunction reported improvements in speech and swallowing, and quality-of-life enhancements were widely observed.[77] In a prospective single-center study, Bjelica et al. found that although gross motor function remained largely stable according to HFMSE scores, over half of the patients demonstrated either stability or clinically meaningful improvement in upper limb function, as measured by the RULM. Treatment satisfaction was generally high.[78] The 24-month extension of the SUNFISH Part 2 study (n = 180) provides strong evidence for the long-term efficacy of risdiplam in patients with Type 2 and nonambulant Type 3 SMA. At 24 months, 32% of participants showed $\geq$3-point improvements and 59% maintained stabilization in MFM32 total scores.[79,80]

These findings in treated cohorts are contradictory to historical data from untreated individuals. The ANCHOVY study, a retrospective review of 60 infants with Type 1 SMA, reported that only 10% of patients were alive without permanent ventilation at 18 months of age, compared with 85% in the risdiplam-treated cohort of FIREFISH Part 2. Furthermore, none of the patients enrolled in ANCHOVY achieved independent sitting or upright head control, underscoring the clinical significance of early and sustained risdiplam treatment in modifying the natural course of the disease.[80] A summary of clinical studies conducted in patients with SMA is provided in Table 3.

Future perspectives regarding the PK of SMA therapies

Emerging research directions

The therapeutic strategy for SMA is progressively shifting toward individualized therapeutic approaches. Patient-specific factors such as age, genotype, body weight, *SMN2* copy number, and CSF turnover significantly influence drug distribution, clearance, and treatment response, necessitating refined population PK models for dose adaptation.[63,66,84] Integration of such models with real-world registry data may further enhance their predictive value and support clinicians in making personalized treatment decisions.[77]

There is growing interest in biomarker-guided approaches for PK/PD monitoring in SMA. Circulating neurofilament light chain and pNF-H have been investigated, with pNF-H validated as a dynamic surrogate marker of motor neuron damage and therapeutic response.[85,86] Emerging CSF biomarkers, including monocyte chemoattractant protein-1 (MCP-1), eotaxin, monocyte chemoattractant protein-1β (MIP-1β), and amyloid-β peptides, have demonstrated potential to reflect CNS drug effects and disease severity and may serve as PD surrogates in future studies.[87,88] Interestingly, a recent study by Şenol et al. evaluated renal and hematological parameters in nusinersen-treated patients and found that urinary creatinine (UCr) levels were associated with improved CHOP-INTEND scores, suggesting that UCr can serve as a surrogate PD marker in patients with Type 1 SMA.[89]

The PK findings for current SMA therapies provide insights that may guide future drug development. Combining oral bioavailability with prolonged neuronal half-life represents a promising yet challenging goal, potentially enhancing patient convenience and therapeutic durability.

Table 3. Summary of key pharmacokinetic characteristics of nusinersen, onasemnogene abeparvovec, and risdiplam.

Study	Route and dosing	Key PK parameters	Notes
Nusinersen			
Rigo F et al., 2014[28]	IT/ICV (rodent, NHP)	CNS exposure >36 weeks; CNS $t^1/_2$: weeks; plasma transient	Preclinical biodistribution
Chiriboga CA et al., 2016[29]	IT, dose-escalation	Plasma peak within hours; CSF measurable up to 29 days; CSF $t^1/_2$: 132–177 days	Plasma <LLOQ by day 7
Finkel RS et al., 2016[30]	IT, multiple doses	Plasma peak ~1 h, decline 24 h; CSF measurable at 15–168 days	Brain concentration >10 μg/g at autopsy
Luu KT et al., 2017[31]	IT, fixed 12 mg	Median CSF $t^1/_2$: 163 days	Supported fixed 12 mg dosing
Finkel RS et al., 2017[32]	IT, age/volume adjusted	PK levels not reported	Trial stopped early (positive results)
Biliouris K et al., 2018[65]	IT, modeling	Model predicted CSF and plasma concentrations; scaled with allometry	Highlighted CSF-to-tissue distribution
Monine M et al., 2021[66]	IT (preclinical, NHP)	CNS peak in 2 days (~4% of dose); liver/kidneys ~88%	PBPK model of ASO distribution
Acsadi G et al., 2021[36]	IT	CSF: 3.9–11.3 ng/mL (Day 15–898); plasma 2.1→ 0.7 ng/mL	No anti-drug antibodies
MacCannell D et al., 2021[63]	IT, pooled 10 trials	C_{trough} ↓ ~10%/month if delayed; est. $t^1/_2$ ~4 months	Supports 4-month dosing interval
MacCannell D et al., 2022[63]	IT	Simulations: 2–4 reloading doses restore CSF trough	Recovery depends on interruption length
Finkel RS et al., 2022[59]	IT, 12 mg vs. higher dose	CSF steady-state: ~5 ng/mL (12 mg), ~12 ng/mL (higher dose)	Based on CS3A and ENDEAR
Finkel RS et al., 2023[60]	IT, 12 mg	Predose CSF steadily ↑ (median 8.7 → 10.2 ng/mL)	
ClinicalTrials.gov results, 2023 (last update)[81]	IT (standard LP vs. ThecaFlex)	C_{max} and $AUC_{0–24\ h}$ under evaluation	Recruiting. Comparative delivery study
ClinicalTrials.gov results, 2024 (last update)[82]	IT	Planned CSF and plasma concentration measurement	Results not posted
Jiang Y et al., 2024[62]	IT, post-marketing	CSF ↑ steadily; no plasma accumulation	

(continued)

Table 3. Continued.

Study	Route and dosing	Key PK parameters	Notes
Onasemnogene abeparvovec			
Mendell JR et al., 2017[42]	IV; weight-based dosing (6.7×10^{13} or 2.0×10^{14}vg/kg)	PK values not numerically reported	Dose-escalation; no plasma/tissue quantification disclosed
Mendell JR et al., 2021[72]	IV; single dose ≤6-month-old infants	Plasma vector genomes: high initial peak, rapid decline	
Thomsen G et al., 2021[40]	IV; autopsy cases from STR1VE trials	Vector DNA and mRNA widely distributed; SMN protein restored in motor neurons	Highest vector copy number in liver; CNS and peripheral biodistribution
ClinicalTrials.gov results, 2025 (last update)[83]	IV; 2–12 years	PK profile under investigation	Trial in progress; results pending
Risdiplam			
Poirier A et al., 2018[51]	Oral, preclinical dosing (rodents, monkeys)	Broad tissue distribution; CSF reflected unbound plasma	Dose-dependent SMN increase in brain, muscle, blood
Sturm S et al., 2019[52]	Oral, single ascending dose (healthy adults)	$t^1/_2$: 40–69 h; C_{max} and AUC dose-proportional	Food/itraconazole had minimal effect; low CYP3A metabolism
Day J et al., 2020[55]	Oral, dose-finding PK/PD	–	>Twofold SMN protein increase after 4 weeks. Sustained ≥12 months
ClinicalTrials.gov results, 2020 (last update)[75]	Oral, 5–8 mg QD	Predictable, time dependent accumulation	No clinically relevant CYP3A inhibition
Cleary Y et al., 2021[53]	Oral, 5–8 mg QD	C_{max}: 78.6–113 ng/mL; $AUC_{0-24\ h}$: 1250–1730 ng·h/mL	PBPK valid across pediatrics; negligible DDI risk
Baranello G et al., 2021[54]	Oral, low vs. high dose	AUC: 630 vs. 2000 ng·h/mL	SMN ↑ 2.1–4.5× from baseline
Masson R et al., 2022[57]	Oral, dose-adjusted	–	SMN protein median level of 4.76 ng/mL at 24 months (1.95× ↑ baseline)
Chiriboga C et al., 2022[49]	Oral, daily	–	A rapid and sustained >twofold ↑ in SMN protein levels in the blood

(continued)

Table 3. Continued.

Study	Route and dosing	Key PK parameters	Notes
Mercuri E et al., 2022[56]	Oral, 0.15–5 mg	Median observed AUC: 822 ng·h/mL (0.15 mg/kg). Median estimated AUC 1450 ng·h/mL (0.25 mg/kg), 1610 ng·h/mL (5 mg)	Twofold SMN ↑ sustained over 24 months
Kletzl H et al., 2022[76]	Oral, 5 mg QD; hepatic impairment	Hepatic impairment; Mild: AUC ↓20%; Mod.: AUC ↑8% and C_{max} ↑∼20%	Changes not clinically significant
Cleary Y et al., 2023[74]	Oral, across 525 SMA pts	–	10,205 samples analyzed; modeled FMO3 ontogeny. Children with up to 3× higher FMO3 activity
Chiriboga C et al., 2024[50]	Oral, 0.25 mg/kg	$AUC_{0–24\ h}$: ∼1700 ng·h/mL	SMN protein doubled in the blood after 4 weeks, sustained 24 months
Servais L et al., 2024[48]	Oral, newborn dosing	Target AUC ∼2000 ng·h/mL	Results pending/full text not posted

This table provides a concise comparison of the major PK parameters reported across preclinical and clinical studies for the three approved therapies for SMA. For each study, route and dosing regimen, principal PK findings (e.g. C_{max}, exposure, and half-life), and critical interpretive notes are summarized. Where classical PK parameters were not available (particularly for gene therapy studies), vector genome kinetics are presented instead. Together, these data highlight similarities and differences in disposition across distinct pharmacological modalities.

AUC: area under the curve; CNS: central nervous system; CSF: cerebrospinal fluid; DDI: drug–drug interactions; FMO3: flavin-containing monooxygenases 3; IT: intratechal; IT/ICV: intratechal/intracerebroventricular; LP: lumbar puncture; N/A: not applicable; NHP: nonhuman primates; PBPK: physiologically based pharmacokinetic modeling and simulation; PK: pharmacokinetics; PPK: population pharmacokinetics; QD: once daily; SMA: spinal muscular atrophy; SMN: survival motor neuron protein; LLOQ: lower limit of quantification; ASO: antisense oligonucleotide; CYP3A: cytochrome P450 3A enzyme family; PD: pharmacodynamics.

Achieving this balance may require innovative medicinal chemistry strategies to optimize CNS penetration while maintaining metabolic stability. Novel viral vector designs also hold potential to reduce hepatic sequestration, a known limitation of OA, thereby improving targeted delivery and potentially minimizing off-target effects. Advances in vector engineering, including capsid modifications and tissue-specific promoters, are emerging strategies under investigation to address these challenges. For ASOs, next-generation designs may aim for more uniform CSF distribution to overcome regional variability associated with intrathecal administration. Development of conjugated ASOs or formulation enhancements could further improve CNS tissue penetration and distribution, as demonstrated by recent progress in other neurological ASO therapies.

Biomarker-guided dosing strategies and combination therapies warrant further investigation. Neurofilament light chain has shown promise as a PD biomarker for monitoring treatment response and may inform dose optimization. Combination approaches, such as pairing SMN-enhancing therapies with neuroprotective or muscle-targeted interventions, are currently being evaluated in preclinical and early clinical studies and may provide synergistic benefits. These findings highlight the importance of integrating PK insights with translational research and innovative drug design to advance therapeutic strategies for SMA.

Impact of new therapeutic approaches on PK understanding

Emerging therapeutic approaches, particularly combination strategies, are reshaping the understanding of PK in SMA. For example, combining SMN-enhancing agents, such as nusinersen or risdiplam, with myostatin inhibitors (e.g. apitegromab) has demonstrated synergistic motor benefits in clinical trials but necessitates re-evaluation of exposure–response relationships, tissue distribution kinetics, and intracellular bioavailability, particularly in skeletal muscle and non-neuronal tissues.[9,90] Molecular selectivity and transcriptomic precision are increasingly relevant to the PD impact of combined splice-modulating agents. Ottesen and Singh evaluated off-target transcriptomic effects of splicing modulators, proposing that a combination of low-dose nusinersen with small molecules such as risdiplam could enhance *SMN2* exon 7 inclusion while minimizing transcriptomic disruption. These findings not only support the dose-dependent safety of such approaches but also offer a mechanistic basis for future PK/PD models tailored to combination regimens.[91]

New delivery strategies are introducing additional complexity to the understanding of PK in SMA therapies. For example, administering gene therapy vectors via central venous routes may influence biodistribution and the efficiency of blood–brain barrier penetration.[92,93] As these innovations continue to evolve, there is an increasing need for mechanistic frameworks, including semimechanistic and PBPK models, to accurately simulate drug behavior along the neuroaxis.[66]

Technological advances in PK monitoring

Technological advances are enhancing PK monitoring in SMA therapy. Innovative bioanalytical tools, such as ultrasensitive digital immunoassays (e.g. NULISA) and CSF proteomics, enable detection of subtle molecular effects and PD changes.[94] Simultaneously, digital health solutions, including wearable biosensors and remote motor function monitoring, are being explored as noninvasive assessment tools, although pediatric validation is still ongoing. Furthermore, several neuroinflammatory

cytokines have been shown to be modulated by intrathecal therapies, such as nusinersen, and may serve as longitudinal markers of pharmacological activity within the CNS.[67,87]

Advantages and limitations

This narrative review provided the advantage of examining the PK profiles of the three approved DMTs for SMA in a comparative framework, highlighting their differences and the complexities of characterizing their PK behavior. By discussing therapies that share a common therapeutic goal but differ substantially in biochemical structure, routes of administration, and PK disposition, the review offered insights into how diverse pharmacological strategies achieve clinical efficacy through distinct PK mechanisms. This comparative perspective uniquely facilitated the identification of PK characteristics that may be considered optimal for effective SMA treatment.

A notable disparity exists in the depth of available PK data among the three approved DMTs for SMA, with nusinersen being the most extensively characterized. This imbalance reflects the greater volume of published PK studies on nusinersen compared with risdiplam and OA, which currently have more limited data. This discrepancy is acknowledged as an inherent limitation of the existing literature and constrains direct comparisons among these therapies. It underscores the critical need for further comprehensive PK investigations on risdiplam and OA to better elucidate their profiles and optimize their clinical use.

Conclusions

Summary of key findings

The PK properties of the three currently approved SMA therapies—nusinersen, risdiplam, and OA—have been characterized through clinical trials, post-marketing studies, and model-based simulations. Each therapy exhibits distinct PK attributes influenced by its route of administration and molecular design. Nusinersen demonstrates prolonged CSF exposure following intrathecal dosing; OA provides long-term SMN protein expression after a single intravenous infusion via AAV9-mediated gene transfer; and risdiplam achieves systemic bioavailability with reliable CNS penetration through oral administration.

Across these therapies, PD markers—including neurofilament levels, SMN protein concentrations, and motor function scales—have been associated with drug exposure. Although these relationships are encouraging, interindividual variability remains an important consideration for clinical efficacy and safety. Overall, current evidence highlights the value of integrating PK/PD data to inform treatment selection, guide dosing strategies, and support long-term monitoring in patients with SMA.

Future research

Further research into the PK behavior of SMA therapies may provide opportunities to refine and personalize treatment strategies. Patient-specific factors, including age, disease severity, *SMN2* copy number, and immunological status, influence drug distribution and therapeutic response, warranting the development of adaptive dosing models and individualized monitoring tools. Ongoing and future investigations that integrate biomarkers, advanced modeling techniques, and real-world data are expected to deepen our understanding of treatment dynamics. As novel combination therapies and delivery methods emerge, PK science will remain central—not only in optimizing efficacy and minimizing risk but also in shaping more accessible and sustainable care pathways for individuals living with SMA.

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This article is a narrative review; all data supporting this work are derived from the published literature cited within the manuscript.

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References

1. Iannaccone ST. Spinal muscular atrophy. *Semin Neurol* 1998; 18: 19–26.
2. 38th ENMC International Workshop. Spinal muscular atrophy trial group 10–12 December 1995, Naarden, The Netherlands. *Neuromuscul Disord* 1996; 6: 293–294.
3. Ogino S, Leonard DG, Rennert H, et al. Spinal muscular atrophy genetic testing experience at an academic medical center. *J Mol Diagn* 2002; 4: 53–58.
4. Lefebvre S, Burlet P, Liu Q, et al. Correlation between severity and SMN protein level in spinal muscular atrophy. *Nat Genet* 1997; 16: 265–269.
5. Kolb SJ and Kissel JT. Spinal muscular atrophy. *Neurol Clin* 2015; 33: 831–846.
6. Keinath MC, Prior DE and Prior TW. Spinal muscular atrophy: mutations, testing, and clinical relevance. *Appl Clin Genet* 2021; 14: 11–25.
7. Chien YH, Chiang SC, Weng WC, et al. Presymptomatic diagnosis of spinal muscular atrophy through newborn screening. *J Pediatr* 2017; 190: 124–129.e1.
8. Wang CH, Finkel RS, Bertini ES; Participants of the International Conference on SMA Standard of Care, et al. Participants of the International Conference on SMA Standard of Care. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol* 2007; 22: 1027–1049.
9. Bowerman M, Becker CG, Yáñez-Muñoz RJ; UK SMA Research Consortium, et al. Therapeutic strategies for spinal muscular atrophy: SMN and beyond. *Dis Model Mech* 2017; 10: 943–954.
10. Andrews JA and Shefner JM. Clinical neurophysiology of anterior horn cell disorders. *Handb Clin Neurol* 2019; 161: 317–326.
11. Farrar MA, Carey KA, Paguinto SG, et al. "The whole game is changing and you've got hope": Australian perspectives on treatment decision making in spinal muscular atrophy. *Patient* 2020; 13: 389–400.
12. Darras BT. Spinal muscular atrophies. *Pediatr Clin North Am* 2015; 62: 743–766.
13. Arnold ES and Fischbeck KH. Spinal muscular atrophy. *Handb Clin Neurol* 2018; 148: 591–601.
14. Chang JG, Hsieh-Li HM, Jong YJ, et al. Treatment of spinal muscular atrophy by sodium butyrate. *Proc Natl Acad Sci U S A* 2001; 98: 9808–9813.
15. Brichta L, Hofmann Y, Hahnen E, et al. Valproic acid increases the SMN2 protein level: a well-known drug as a potential therapy for spinal muscular atrophy. *Hum Mol Genet* 2003; 12: 2481–2489.

16. Andreassi C, Angelozzi C, Tiziano FD, et al. Phenylbutyrate increases SMN expression in vitro: relevance for treatment of spinal muscular atrophy. *Eur J Hum Genet* 2004; 12: 59–65.
17. Grzeschik SM, Ganta M, Prior TW, et al. Hydroxyurea enhances SMN2 gene expression in spinal muscular atrophy cells. *Ann Neurol* 2005; 58: 194–202.
18. Angelozzi C, Borgo F, Tiziano FD, et al. Salbutamol increases SMN mRNA and protein levels in spinal muscular atrophy cells. *J Med Genet* 2008; 45: 29–31.
19. Naryshkin NA, Weetall M, Dakka A, et al. Motor neuron disease. SMN2 splicing modifiers improve motor function and longevity in mice with spinal muscular atrophy. *Science* 2014; 345: 688–693.
20. Brichta L, Holker I, Haug K, et al. In vivo activation of SMN in spinal muscular atrophy carriers and patients treated with valproate. *Ann Neurol* 2006; 59: 970–975.
21. Oskoui M, Levy G, Garland CJ, et al. The changing natural history of spinal muscular atrophy type 1. *Neurology* 2007; 69: 1931–1936.
22. Yuo CY, Lin HH, Chang YS, et al. 5-(N-ethyl-N-isopropyl)-amiloride enhances SMN2 exon 7 inclusion and protein expression in spinal muscular atrophy cells. *Ann Neurol* 2008; 63: 26–34.
23. Ebert AD, Yu J, Rose FF Jr, et al. Induced pluripotent stem cells from a spinal muscular atrophy patient. *Nature* 2009; 457: 277–280.
24. Baethge C, Goldbeck-Wood S and Mertens S. SANRA—a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev* 2019; 4: 5.
25. Center for drug evaluation and research. Application number: 209531Orig1s000 Clinical pharmacology and biopharmaceutics review(s), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000ClinPharmR.pdf (2016, accessed 18 June 2025).
26. European Medicines Agency. Annex I summary of product characteristics, https://ec.europa.eu/health/documents/community-register/2019/20190823145605/anx_145605_en.pdf (2019, accessed 18 June 2025).
27. National Center for Biotechnology Information. Summary of Safety Data from Long-Term Studies. *Canadian Agency for Drugs and Technologies in Health*, https://www.ncbi.nlm.nih.gov/books/NBK533983/ (2018, accessed 26 May 2025).
28. Rigo F, Chun SJ, Norris DA, et al. Pharmacology of a central nervous system delivered 2′-O-methoxyethyl-modified survival of motor neuron splicing oligonucleotide in mice and nonhuman primates. *J Pharmacol Exp Ther* 2014; 350: 46–55.
29. Chiriboga CA, Swoboda KJ, Darras BT, et al. Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. *Neurology* 2016; 86: 890–897.
30. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet* 2016; 388: 3017–3026.
31. Luu KT, Norris DA, Gunawan R, et al. Population pharmacokinetics of nusinersen in the cerebral spinal fluid and plasma of pediatric patients with spinal muscular atrophy following intrathecal administrations. *J Clin Pharmacol* 2017; 57: 1031–1041.
32. Finkel RS, Mercuri E, Darras BT; ENDEAR Study Group, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med* 2017; 377: 1723–1732.
33. Mercuri E, Darras BT, Chiriboga CA; CHERISH Study Group, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med* 2018; 378: 625–635.
34. Ramos DM, D'Ydewalle C, Gabbeta V, et al. Age-dependent SMN expression in disease-relevant tissue and implications for SMA treatment. *J Clin Invest* 2019; 129: 4817–4831.
35. De Vivo DC, Bertini E, Swoboda KJ; Nurture Study Group, 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: 842–856.

36. Acsadi G, Crawford TO, Müller-Felber W, et al. Safety and efficacy of nusinersen in spinal muscular atrophy: the EMBRACE study. *Muscle and Nerve* 2021; 63: 668–677.
37. U.S. Food and Drug Administration. Byrnes A. Summary Basis for Regulatory Action, https://www.fda.gov/media/127961/download (2019, accessed 27 May 2025).
38. Committee for Medicinal Products for Human Use (CHMP); Committee for Advanced Therapies (CAT). Assessment report. https://www.ema.europa.eu/en/documents/assessment-report/zolgensma-epar-public-assessment-report_en.pdf (2020, accessed 27 May 2025).
39. European Medicines Agency. Annex I summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-product-information_en.pdf (2020, accessed 27 May 2025).
40. Thomsen G, Burghes AHM, Hsieh C, et al. Biodistribution of onasemnogene abeparvovec DNA, mRNA and SMN protein in human tissue. *Nat Med* 2021; 27: 1701–1711.
41. Muhuri M, Levy DI, Schulz M, et al. Durability of transgene expression after rAAV gene therapy. *Mol Ther* 2022; 30: 1364–1380.
42. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med* 2017; 377: 1713–1722.
43. Mercuri E, Muntoni F, Baranello G; Str1ve-eu study group, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy type 1 (STR1VE-EU): an open-label, single-arm, multicentre, phase 3 trial. *Lancet Neurol* 2021; 20: 832–841.
44. Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. *Lancet Neurol* 2021; 20: 284–293.
45. Strauss KA, Farrar MA, Muntoni F, et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. *Nat Med* 2022; 28: 1390–1397.
46. U.S. Food and Drug Administration. Clinical pharmacology review: NDA 213535, Evrysdi (risdiplam), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213535Orig1s000ClinPharmR.pdf (2020, accessed 28 May 2025).
47. European Medicines Agency. Annex I summary of product characteristics, https://www.ema.europa.eu/en/documents/product-information/evrysdi-epar-product-information_en.pdf (2021, accessed 28 May 2025).
48. Servais L, Finkel R, Farrar M, et al. 21O RAINBOWFISH: 2-year efficacy and safety data of risdiplam in infants with presymptomatic spinal muscular atrophy (SMA). *Neuromuscul Disord* 2024; 43: 104441.738.
49. Chiriboga C, Bruno C, Duong T, et al. P.110 JEWELFISH: 24-month safety and pharmacodynamic data in non-treatment-naïve patients with spinal muscular atrophy (SMA). *Neuromuscul Disord* 2022; 32: S88.
50. Chiriboga CA, Bruno C, Duong T; Jewelfish Study Group, et al. JEWELFISH: 24-month results from an open-label study in non-treatment-naïve patients with SMA receiving treatment with risdiplam. *J Neurol* 2024; 271: 4871–4884.
51. Poirier A, Weetall M, Heinig K, et al. Risdiplam distributes and increases SMN protein in both the central nervous system and peripheral organs. *Pharmacol Res Perspect* 2018; 6: e00447.
52. Sturm S, Günther A, Jaber B, et al. A phase 1 healthy male volunteer single escalating dose study of the pharmacokinetics and pharmacodynamics of risdiplam (RG7916, RO7034067), a SMN2 splicing modifier. *Brit J Clinical Pharma* 2019; 85: 181–193.
53. Cleary Y, Gertz M, Grimsey P, et al. Model-based drug-drug interaction extrapolation strategy from adults to children: risdiplam in pediatric patients with spinal muscular atrophy. *Clin Pharmacol Ther* 2021; 110: 1547–1557.
54. Baranello G, Darras BT, Day JW; Fırefish Working Group, et al. Risdiplam in type 1 spinal muscular atrophy. *N Engl J Med* 2021; 384: 915–923.

55. Day J, Baranello G, Boespflug-Tanguy O, et al. 263 SUNFISH Part 1: 24-month safety and exploratory outcomes of risdiplam (RG7916) treatment in patients with type 2 or 3 spinal muscular atrophy (SMA). *Neuromuscul Disord* 2020; 30: S123.
56. Mercuri E, Baranello G, Boespflug-Tanguy O; Sunfish Working Group, et al. Risdiplam in types 2 and 3 spinal muscular atrophy: a randomised, placebo-controlled, dose-finding trial followed by 24 months of treatment. *Eur J Neurol* 2023; 30: 1945–1956.
57. Masson R, Mazurkiewicz-Bełdzińska M, Rose K; Fırefish Study Group, 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: 1110–1119.
58. Mercuri E, Deconinck N, Mazzone ES; Sunfish Study Group, et al. Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): a phase 3, double-blind, randomised, placebo-controlled trial. *Lancet Neurol* 2022 ; 21: 42–52.
59. Finkel RS, Ryan MM, Pascual Pascual SI, et al. Scientific rationale for a higher dose of nusinersen. *Ann Clin Transl Neurol* 2022; 9: 819–829.
60. Finkel RS, Day JW, Pascual Pascual SI; Devote Study Group, et al. DEVOTE study exploring higher dose of nusinersen in spinal muscular atrophy: study design and part A results. *J Neuromuscul Dis* 2023; 10: 813–823.
61. Darras BT, Chiriboga CA, Iannaccone ST; ISIS-396443-CS2/ISIS-396443-CS12 Study Groups, et al. Nusinersen in later-onset spinal muscular atrophy: long-term results from the phase 1/2 studies. *Neurology* 2019; 92: e2492–e2506.
62. Jiang Y, Wang Y, Xiong H, et al. A post-marketing surveillance study of nusinersen for spinal muscular atrophy in routine medical practice in China: interim results. *Adv Ther* 2024; 41: 2743–2756.
63. MacCannell D, Berger Z, East L, et al. Population pharmacokinetics-based recommendations for a single delayed or missed dose of nusinersen. *Neuromuscul Disord* 2021; 31: 310–318.
64. MacCannell D, Berger Z, Kirschner J, et al. Restoration of nusinersen levels following treatment interruption in people with spinal muscular atrophy: simulations based on a population pharmacokinetic model. *CNS Drugs* 2022; 36: 181–190.
65. Biliouris K, Gaitonde P, Yin W, et al. A semi-mechanistic population pharmacokinetic model of nusinersen: an antisense oligonucleotide for the treatment of spinal muscular atrophy. *CPT Pharmacometrics Syst Pharmacol* 2018; 7: 581–592.
66. Monine M, Norris D, Wang Y, et al. A physiologically-based pharmacokinetic model to describe antisense oligonucleotide distribution after intrathecal administration. *J Pharmacokinet Pharmacodyn* 2021; 48: 639–654.
67. Nuzzo T, Russo R, Errico F, et al. Nusinersen mitigates neuroinflammation in severe spinal muscular atrophy patients. *Commun Med (Lond)* 2023; 3: 28.
68. Garofalo M, Bonanno S, Marcuzzo S, et al. Preliminary insights into RNA in CSF of pediatric SMA patients after 6 months of nusinersen. *Biol Direct* 2023; 18: 57.
69. Panicucci C, Sahin E, Bartolucci M, et al. Proteomics profiling and machine learning in nusinersen-treated patients with spinal muscular atrophy. *Cell Mol Life Sci* 2024; 81: 393.
70. Chu WS and Ng J. Immunomodulation in administration of rAAV: preclinical and clinical adjuvant pharmacotherapies. *Front Immunol* 2021; 12: 658038.
71. Finkel RS, Darras BT, Mendell JR, et al. Intrathecal onasemnogene abeparvovec for sitting, nonambulatory patients with spinal muscular atrophy: phase I ascending-dose study (STRONG). *J Neuromuscul Dis* 2023; 10: 389–404.
72. Mendell JR, Al-Zaidy SA, Lehman KJ, et al. Five-year extension results of the phase 1 START trial of onasemnogene abeparvovec in spinal muscular atrophy. *JAMA Neurol* 2021; 78: 834–841.
73. McMillan HJ, Proud CM, Farrar MA, et al. Onasemnogene abeparvovec for the

treatment of spinal muscular atrophy. *Expert Opin Biol Ther* 2022; 22: 1075–1090.
74. Cleary Y, Kletzl H, Grimsey P, et al. Estimation of FMO3 ontogeny by mechanistic population pharmacokinetic modelling of risdiplam and its impact on drug-drug interactions in children. *Clin Pharmacokinet* 2023; 62: 891–904.
75. ClinicalTrials.gov. NCT03988907, https://clinicaltrials.gov/study/NCT03988907 (2025, accessed 18 June 2025).
76. Kletzl H, Ajmi H, Antys I, et al. Effect of mild or moderate hepatic impairment on the pharmacokinetics of risdiplam. *Br J Clin Pharmacol* 2022; 88: 3749–3759.
77. Sitas B, Hancevic M, Bilic K, et al. Risdiplam real world data - looking beyond motor neurons and motor function measures. *J Neuromuscul Dis* 2024; 11: 75–84.
78. Bjelica B, Wohnrade C, Cespedes I, et al. Risdiplam therapy in adults with 5q-SMA: observational study on motor function and treatment satisfaction. *BMC Neurol* 2024; 24: 67.
79. Oskoui M, Day JW, Deconinck N; Sunfish Working Group, et al. Two-year efficacy and safety of risdiplam in patients with type 2 or non-ambulant type 3 spinal muscular atrophy (SMA). *J Neurol* 2023; 270: 2547–2549.
80. Cances C, Vlodavets D, Comi GP; Anchovy Working Group, et al. Natural history of type 1 spinal muscular atrophy: a retrospective, global, multicenter study. *Orphanet J Rare Dis* 2022; 17: 300.
81. ClinicalTrials.gov. NCT06555419, https://clinicaltrials.gov/study/NCT06555419 (2025, accessed 18 June 2025).
82. ClinicalTrials.gov. NCT04419233, https://clinicaltrials.gov/study/NCT04419233 (2025, accessed 18 June 2025).
83. ClinicalTrials.gov. NCT06971094, https://clinicaltrials.gov/study/NCT06971094 (2025, accessed 18 June 2025).
84. Fowler S, Brink A, Cleary Y, et al. Addressing today's absorption, distribution, metabolism, and excretion (ADME) challenges in the translation of in vitro ADME characteristics to humans: a case study of the SMN2 mRNA splicing modifier risdiplam. *Drug Metab Dispos* 2022; 50: 65–75.
85. Darras BT, Crawford TO, Finkel RS, et al. Neurofilament as a potential biomarker for spinal muscular atrophy. *Ann Clin Transl Neurol* 2019; 6: 932–944.
86. Musso G, Bello L, Capece G, et al. Neurofilament light chain and profilin-1 dynamics in 30 spinal muscular atrophy type 3 patients treated with nusinersen. *Eur J Neurol* 2024; 31: e16393.
87. Zhang Q, Hong Y, Brusa C, et al. Profiling neuroinflammatory markers and response to nusinersen in paediatric spinal muscular atrophy. *Sci Rep* 2024; 14: 23491.
88. Introna A, Milella G, D'Errico E, et al. Is cerebrospinal fluid amyloid-β42 a promising biomarker of response to nusinersen in adult spinal muscular atrophy patients? *Muscle Nerve* 2021; 63: 905–909.
89. Şenol HB, Yıldız G, Polat Aİ, et al. Safety and efficacy of nusinersen focusing on renal and hematological parameters in spinal muscular atrophy. *Brain Behav* 2025; 15: e70221.
90. Day JW, Howell K, Place A, et al. Advances and limitations for the treatment of spinal muscular atrophy. *BMC Pediatr* 2022; 22: 632.
91. Ottesen EW and Singh RN. Synergistic effect of an antisense oligonucleotide and small molecule on splicing correction of the spinal muscular atrophy gene. *Neurosci Insights* 2024; 19: 26331055241233596.
92. Ravi B, Chan-Cortés MH and Sumner CJ. Gene-targeting therapeutics for neurological disease: lessons learned from spinal muscular atrophy. *Annu Rev Med* 2021; 72: 1–14.
93. Pitarch Castellano I, López Briz E, Ibáñez Albert E, et al. Onasemnogene abeparvovec administration via peripherally inserted central catheter: a case report. *Children (Basel)* 2024; 11: 590.
94. Pant DC and Verma S. Identifying novel response markers for spinal muscular atrophy revealed by targeted proteomics following gene therapy. *Gene Ther* 2025.
95. McKusick VA. Spinal muscular atrophy, type I; SMA1. *Online Mendelian Inheritance in Man, OMIM*, https://omim.org/entry/253300 (1986, accessed 11 May 2025).