

Review Article

Gene Therapy Approaches in Spinal Muscular Atrophy: Neurological Outcomes and Safety

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Abstract

Background: Spinal muscular atrophy (SMA) results from biallelic SMN1 loss, with SMN2 copy number modifying severity. Three disease-modifying therapies are approved: the gene-replacement therapy onasemnogene abeparvovec, and two SMN2 splicing modifiers, nusinersen and risdiplam.

Objective: To review pivotal trial, registry and safety literature on gene-replacement therapy for SMA, contextualised against splicing-modifier data.

Methods: Narrative review of phase 1-3 trials, long-term extensions, newborn-screening cohorts, registries and pharmacovigilance reports.

Findings: Onasemnogene abeparvovec produced survival and motor-milestone gains far exceeding natural history in symptomatic infants, with presymptomatic dosing yielding near-normal development in most infants. Nusinersen and risdiplam show comparable presymptomatic benefit. Hepatotoxicity and thrombotic microangiopathy are gene-therapy-specific safety signals requiring structured monitoring. Newborn screening consistently improves outcomes by enabling earlier treatment.

Conclusions: Treatment timing, more than choice of modality, appears to be the dominant determinant of neurological outcome, supporting newborn screening as central to SMA care.

Keywords: Spinal muscular atrophy; Onasemnogene abeparvovec; Nusinersen; Risdiplam; Newborn screening

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Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive motor neuron disease caused by homozygous deletion or mutation of the survival motor neuron 1 (SMN1) gene, producing progressive degeneration of anterior horn cells, muscle weakness, and, in its most severe untreated form, death or permanent ventilation before the age of two years. A paralogous gene, SMN2, produces low levels of functional SMN protein through alternative splicing, and the number of SMN2 copies an individual carries is the

principal genetic modifier of phenotype severity, ranging from the devastating infantile-onset SMA type 1 to milder later-onset SMA types 2, 3 and 4 [1].

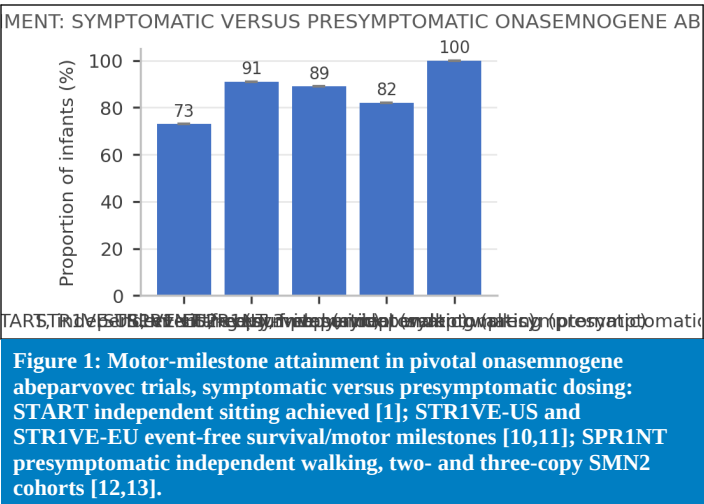
Three disease-modifying therapies have transformed the natural history of this disease within less than a decade. Nusinersen, an intrathecally administered antisense oligonucleotide that promotes SMN2 exon 7 inclusion, was the first approved, following the phase 2 open-label dose-escalation study that established proof of concept [2] and the pivotal sham-controlled ENDEAR and CHERISH trials in infantile- and later-onset disease respectively [3,4]. Risdiplam, an orally administered small-molecule SMN2 splicing modifier, followed, supported by the FIREFISH and SUNFISH programmes [5,6,7]. Onasemnogene abeparvovec, an adeno-associated virus serotype 9 (AAV9) vector delivering a functional SMN1 transgene via a single intravenous infusion, represents a fundamentally different approach: gene replacement rather than splicing modulation, intended as a one-time treatment rather than a chronic regimen [1].

This review synthesises the pivotal trial, long-term extension, newborn-screening and pharmacovigilance literature on gene-replacement therapy for SMA, situating it against the splicing-modifier evidence base, with particular attention to how treatment timing and SMN2 copy number shape neurological outcome, and to the hepatotoxicity and thrombotic microangiopathy safety signals that distinguish AAV9 gene therapy from its comparators.

Onasemnogene Abeparvovec: Mechanism and Pivotal Trials

Onasemnogene abeparvovec delivers a self-complementary AAV9 vector carrying a codon-optimised SMN1 cDNA under a constitutive promoter. AAV9's capacity to cross the blood-brain barrier after systemic administration allows transduction of

spinal motor neurons following a single intravenous infusion, in contrast to the repeated intrathecal or oral dosing required by the splicing modifiers [1].



The phase 1 START trial treated 15 infants with SMA type 1 and two SMN2 copies, most already symptomatic at enrolment. All 15 achieved event-free survival substantially beyond the historical median of roughly eight months, and a majority achieved motor milestones — independent sitting, and in several cases standing or walking — essentially never observed in the natural history of untreated SMA1 [1]. Respiratory and nutritional outcomes tracked similarly favourably against a contemporaneous natural-history cohort [8]. A five-year extension of the START cohort found durable retention of milestones without evidence of late functional decline, alongside continued long-term safety surveillance [9].

Confirmatory phase 3 trials extended these findings to larger, multicentre populations. STRIVE-US enrolled symptomatic infants with SMA type 1 and one or two SMN2 copies, again demonstrating event-free survival and motor-milestone achievement well above historical benchmarks [10], a result replicated in the European STRIVE-EU cohort with a broader range of baseline disease severity [11]. Across this trial programme, the

consistent signal is that gene replacement, delivered even after symptom onset, meaningfully alters a disease trajectory that is otherwise near-uniformly fatal or severely disabling in its infantile form.

Outcomes by Treatment Age and SMN2 Copy Number

The single most consistent theme across the gene-therapy and splicing-modifier literature alike is that neurological benefit is maximised, and can approach normalisation of motor development, when treatment precedes irreversible motor neuron loss rather than following symptom onset.

The Phase III SPR1NT trial administered onasemnogene abeparvovec to presymptomatic infants, identified through newborn screening or family history, before six weeks of age. Among infants with two SMN2 copies — a genotype otherwise predictive of SMA type 1 — most achieved independent sitting, standing and walking within, or close to, normal developmental windows, an outcome essentially unprecedented for this genotype [12]. A parallel cohort with three SMN2 copies, predictive of a milder SMA type 2/3 trajectory, showed comparably strong results, with the large majority of infants walking independently at the primary endpoint [13].

Table 1: Pivotal trials of disease-modifying therapy for spinal muscular atrophy by treatment timing and SMN2 copy number [1,10,11,12,13,14,15,5,6,7].				
Trial	Agent	Population	Timing	Key outcome
START	Onasemnogene abeparvovec	SMA1, 2 SMN2 copies	Symptomatic	Event-free survival, independent sitting in most
STRIVE-US/EU	Onasemnogene abeparvovec	SMA1, 1-2 SMN2 copies	Symptomatic	Event-free survival above historical benchmark
SPR1NT (2-copy)	Onasemnogene abeparvovec	At-risk for SMA1	Presymptomatic	Independent sitting/standing/walking in most
SPR1NT (3-copy)	Onasemnogene abeparvovec	At-risk for SMA2/3	Presymptomatic	Independent walking in large majority

Trial	Agent	Population	Timing	Key outcome
NURTURE	Nusinersen	At-risk, 2-3 SMN2 copies	Presymptomatic	All walking, none ventilated at 5-year follow-up
FIREFISH	Risdiplam	SMA1	Symptomatic	Sitting achieved; walking in a subset
SUNFISH part 2	Risdiplam	SMA2/non-ambulant SMA3	Symptomatic	Motor function score improved vs placebo

This presymptomatic-treatment advantage is not unique to gene replacement. The NURTURE study of presymptomatic nusinersen reported that essentially all treated children achieved independent walking and none required permanent ventilation at extended follow-up, a finding sustained through five years [14,15]. Similarly, FIREFISH demonstrated that risdiplam produced sitting and, in a subset, walking ability in infants with SMA type 1, with outcomes reported both against natural history and, in the extended analysis, against historical comparator cohorts [5,6]. SUNFISH part 2 showed comparable functional gains with risdiplam in the less severe, later-onset type 2/3 population [7]. Taken together, the cross-modality convergence on early, particularly presymptomatic, treatment as the dominant driver of outcome is one of the most robust conclusions the SMA trial literature currently supports, and it holds regardless of whether the mechanism is gene replacement or splicing modification.

Comparative Neurological Outcomes Across Modalities and Combination Therapy

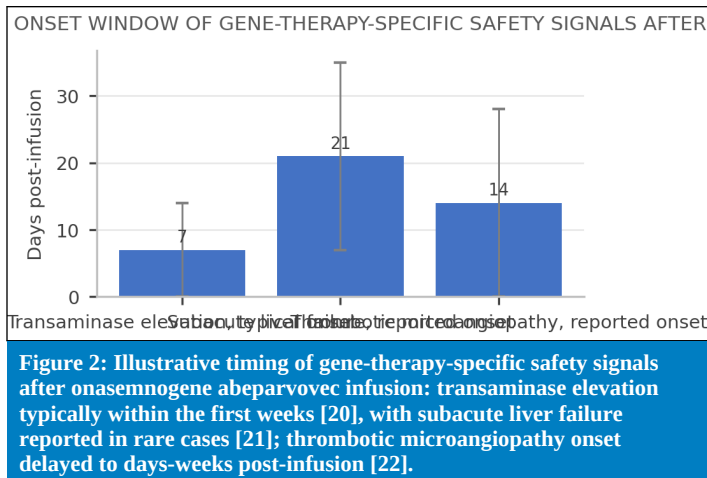
Direct head-to-head randomised comparison of onasemnogene abeparvovec against nusinersen or risdiplam remains absent from the published record; each agent's pivotal evidence rests on single-arm or placebo/sham-controlled designs against natural history or standard care, which complicates formal cross-trial comparison. Real-world registries partially address this gap. The RESTORE registry, capturing gene-therapy outcomes in a broader and more heterogeneous

population than the trials — including older children and a wider range of SMN2 copy numbers — reported effectiveness and safety broadly consistent with the pivotal programme, while also underlining the importance of the hepatotoxicity and thrombotic microangiopathy monitoring described below in routine practice [16]. The SMartCARE platform, established across German-speaking Europe, similarly provides infrastructure for longitudinal, real-life outcome and safety data spanning all three approved therapies, a resource increasingly relied upon given the practical impossibility of large randomised comparative trials in a rare disease already served by multiple approved options [17].

A further open question concerns combination or sequential therapy — for example, initiating a splicing modifier and later adding, or switching to, gene replacement, or maintaining a splicing modifier after gene therapy. The rationale is that SMN2-directed therapy could support motor neurons not adequately transduced by AAV9, particularly outside the central nervous system or in older, larger patients receiving comparatively lower vector doses per kilogram. A critical review of this practice concluded that while case reports and registry signals suggest potential incremental benefit in selected patients, the evidence remains observational, the incremental benefit uncertain, and the additional cost and treatment burden substantial, such that combination therapy cannot yet be recommended as routine practice outside individualised decision-making [18]. A broader synthesis of the three-drug landscape reaches a similar conclusion: the agents differ meaningfully in route, monitoring burden and safety profile, but the comparative-effectiveness evidence base needed to guide first-line selection, let alone combination strategies, is still maturing [19].

Safety: Hepatotoxicity and Thrombotic

Microangiopathy



Two safety signals are sufficiently distinct to AAV9-mediated gene replacement, as opposed to the splicing modifiers, that they warrant dedicated monitoring protocols. Transient elevation of hepatic transaminases occurs in a substantial proportion of treated infants and is now an expected, monitored effect requiring prophylactic and often extended corticosteroid courses; more severe hepatotoxicity, including cases of acute liver injury, has been documented and has prompted revisions to corticosteroid tapering and surveillance schedules [20]. Subacute liver failure, while rare, has been reported, including a fatal case, reinforcing that hepatic monitoring cannot be abbreviated even in infants tolerating the infusion well in the immediate post-dosing period [21].

Thrombotic microangiopathy (TMA) is a second, mechanistically distinct signal, first characterised in a case series describing thrombocytopenia, microangiopathic haemolysis and acute kidney injury emerging days to weeks after infusion, sometimes without preceding warning signs on routine early laboratory testing [22]. Because onset can be delayed relative to the transaminase signal, current practice extends platelet count, haemoglobin and renal function monitoring for several

weeks post-infusion, a substantially longer surveillance window than the splicing modifiers require for their own, mechanistically different safety concerns, such as the coagulation and renal parameters monitored with nusinersen. Registry data from broader real-world populations continue to detect both hepatotoxicity and TMA signals, and are the primary vehicle through which their true incidence and risk factors, including baseline SMN2 copy number and age at treatment, are being characterised outside the constraints of the original trial populations [16].

Newborn Screening Implications

Because treatment timing so strongly predicts neurological outcome across all three agents, newborn screening for SMA has moved rapidly from a research question to an implemented public-health intervention in many jurisdictions. Once screening identifies an at-risk infant, SMN2 copy number typically determines the initial treatment algorithm, since it forecasts phenotype severity in the absence of treatment; consensus recommendations initially addressed infants with one to three copies and were subsequently revised to address the more clinically ambiguous four-copy genotype [23,24].

Programmatic experience supports the trial-level presymptomatic-treatment signal. The German newborn screening pilot reported favourable early clinical outcomes across screened infants over its first two years [25], while the Australian newborn screening cohort found that screening-detected infants achieved substantially better motor outcomes, including a markedly higher proportion walking, than a historical cohort diagnosed clinically after symptom onset [26]. A synthesis of global newborn screening experience concluded that, across differing programme designs and treatment choices, the consistent lesson is that earlier detection, translating into earlier treatment with any of the three approved agents, is the single intervention most reliably associated with

preserved motor function [27]. These findings position newborn screening not as an adjunct to gene therapy but as a precondition for realising its full neurological benefit, and increasingly shape health-system arguments for universal screening implementation.

Table 2: Newborn screening programme experience and resulting treatment-timing recommendations [23,24,25,26,27].		
Source	Setting	Finding/recommendation
Glascok 2018/2020	Consensus algorithm	Treatment choice guided by SMN2 copy number (1-3, later 4)
Vill 2021	Germany, 2-year pilot	Favourable early clinical outcomes in screened infants
Kariyawasam 2023	Australia, cohort study	Screened infants walk more often than clinically diagnosed cohort
Dangouloff 2023	Global synthesis	Earlier detection consistently predicts preserved motor function

Conclusion

The pivotal trial record for onasemnogene abeparvovec — from the phase 1 START cohort through the confirmatory STRIVE trials and the presymptomatic SPRINT programme — establishes gene replacement as a therapy capable of converting a near-uniformly fatal infantile disease into one compatible with age-appropriate motor development, provided treatment occurs early. This benefit is not unique to gene replacement: nusinersen and risdiplam show a comparable presymptomatic-treatment advantage in NURTURE and FIREFISH, indicating that timing, more than modality, is the dominant determinant of neurological outcome currently demonstrable in this literature. Gene therapy carries safety considerations largely distinct from its comparators, principally hepatotoxicity and thrombotic microangiopathy, both of which now warrant structured, extended post-infusion monitoring rather than being treated as transient infusion-related phenomena. Combination and sequential therapy strategies remain plausible but evidentially immature, resting on registry and case-level signals rather than controlled trials. The strongest actionable implication of this body of work is that

newborn screening, by enabling presymptomatic treatment with any approved agent, is likely to be the single largest lever available for improving population-level neurological outcomes in spinal muscular atrophy, and its expansion should be considered alongside, not subordinate to, ongoing debate over which therapy to choose.

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