Itvisma expands the frontiers of gene replacement therapy for spinal muscular atrophy

The Innovation Medicine News Team*
*Correspondence: medicine@the-innovation.org
Received: July 14, 2026; Accepted: July 16, 2026; Published Online: July 17, 2026; https://doi.org/10.59717/j.xinn-med.2026.100243

Citation: The Innovation Medicine News Team (2026). Itvisma expands the frontiers of gene replacement therapy for spinal muscular atrophy. *The Innovation Medicine* **4**:100243.

The European Commission has granted marketing authorization for Itvisma (onasemnogene abeparvovec), developed by Novartis, for the treatment of patients aged two years and older with 5q spinal muscular atrophy (SMA) caused by bi-allelic mutations in the SMN1 gene. The approval, granted in July 2026, extends a therapeutic strategy previously confined to infants into adolescents and adults. The decision marks a significant expansion of precision medicine for inherited neurological disorders and underscores how rapidly the field of genetic medicine continues to evolve.

SMA is an autosomal recessive disorder caused primarily by loss-of-function mutations or deletions in the *SMN1* gene, which encodes the survival motor neuron (SMN) protein. This protein is essential for maintaining spinal motor neurons, and insufficient SMN production leads to progressive motor neuron degeneration, muscle weakness, impaired mobility, respiratory complications, and, in severe cases, premature death.[1] The global birth incidence of the disease is approximately 1 in 10,000 live births, with regional estimates ranging from about 1 in 6,000 to 1 in 16,000.

Disease severity is influenced in part by the copy number and activity of the paralogous gene *SMN2*. Although *SMN2* can produce functional SMN protein, most of its transcripts are abnormally spliced and exclude exon 7, yielding only limited amounts of protein. This mechanism underlies the two dominant therapeutic strategies pursued in SMA: boosting *SMN2*-derived protein production, and directly replacing the defective *SMN1* gene (Figure 1).

DELIVERING A FUNCTIONAL GENE TO MOTOR NEURONS

Itvisma follows the second strategy, using an engineered adeno-associated virus (AAV9) vector to deliver a functional copy of the *SMN1* gene directly into motor neurons. AAV vectors are among the most widely used gene-delivery platforms because of their favorable safety profile, efficient gene transfer, and capacity for long-term expression in non-dividing cells such as neurons.[2]

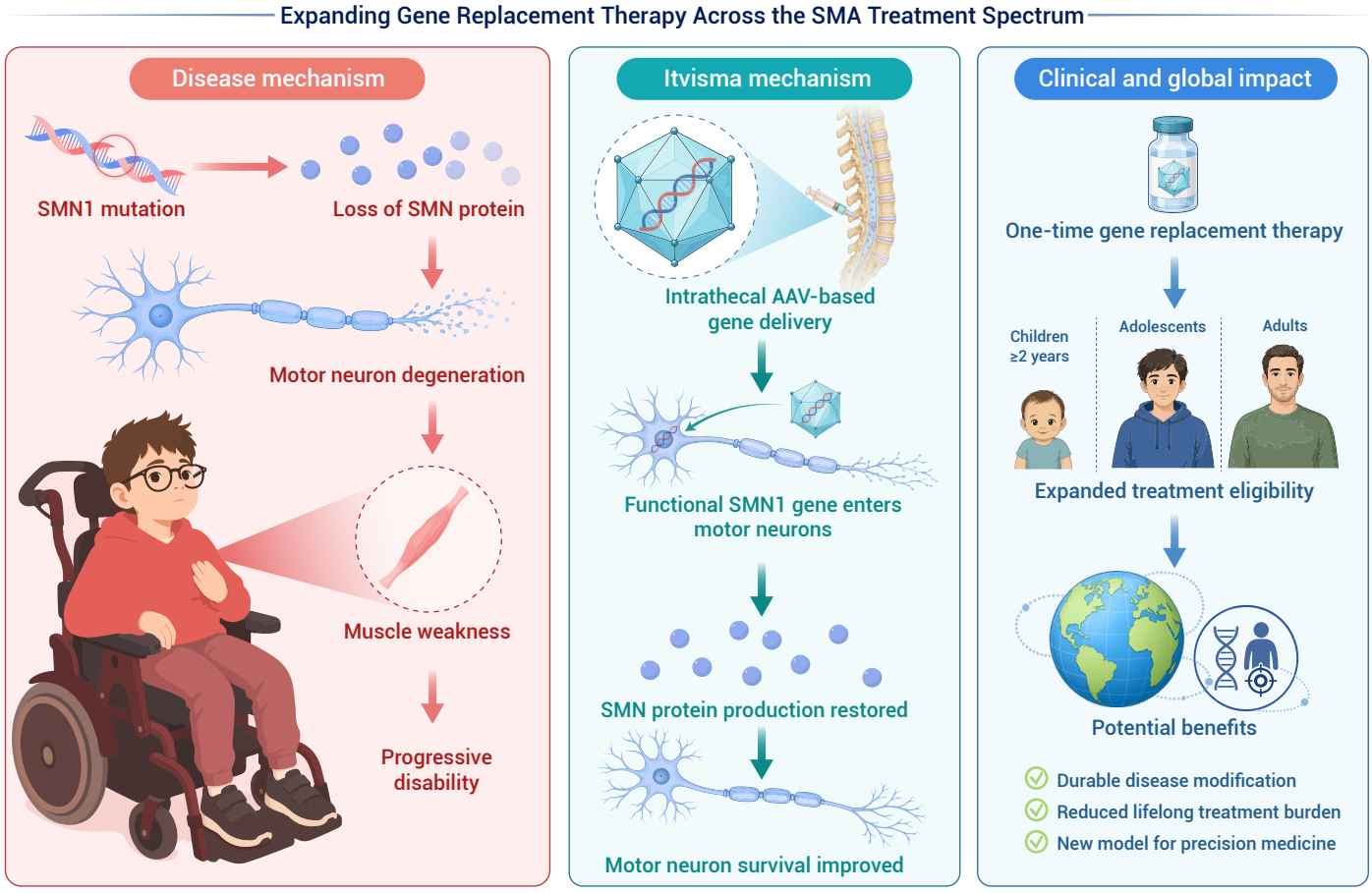

Figure 1. Expanding gene replacement therapy across the SMA treatment spectrum.

Unlike the intravenous administration used for earlier SMA gene-replacement therapy, Itvisma is given as a single intrathecal injection, exposing the central nervous system directly through cerebrospinal fluid. This route is particularly relevant for older and larger patients, since intravenous AAV delivery requires progressively higher viral doses as body weight increases — a limitation that has effectively excluded older children, adolescents, and adults from earlier gene-replacement approaches.

Following administration, the therapeutic *SMN1* gene remains largely

episomal within cells rather than integrating into the host genome. Motor neurons can then produce functional SMN protein, offering the potential for sustained disease modification after a single treatment. By removing the dependence on body weight, intrathecal delivery extends the reach of gene replacement therapy well beyond the early-life treatment window traditionally associated with SMA.

CLINICAL EVIDENCE SUPPORTING APPROVAL

Approval was supported primarily by the Phase III STEER study, which evaluated intrathecal onasemnogene abeparvovec in patients with later-onset SMA, with supportive data from the Phase IIIb STRENGTH study and the Phase I/II STRONG study; results from STEER and STRENGTH have been published in *Nature Medicine*. The trial met its primary endpoint on the Hammersmith Functional Motor Scale–Expanded (HFMSE), a validated measure of motor function in SMA, with treated patients showing a statistically significant, clinically meaningful improvement sustained over roughly 52 weeks.[3]

These results are clinically important because later-onset SMA is characterized by gradual functional decline rather than rapid early deterioration, meaning that preservation or improvement of motor ability represents a meaningful therapeutic outcome. Earlier studies of SMA therapies have consistently shown that earlier intervention produces greater benefit, since genetic medicines can preserve surviving motor neurons but cannot restore those already lost.[4] Newborn screening and early molecular diagnosis therefore remain essential to modern SMA management, and longer-term follow-up will be needed to determine the durability of gene expression and the persistence of clinical benefit.

EXPANDING THE SMA TREATMENT LANDSCAPE

Itvisma adds another option to an increasingly diverse SMA treatment landscape. Current disease-modifying therapies share the common goal of increasing SMN protein availability but differ substantially in mechanism and treatment burden. Biogen's Spinraza (nusinersen) and Roche's Evrysdi (risdiplam) both increase SMN protein production by modifying *SMN2* RNA splicing; Spinraza requires repeated intrathecal dosing throughout life, while Evrysdi is taken orally once daily. Novartis' earlier gene-replacement therapy, Zolgensma (onasemnogene abeparvovec), delivers a functional *SMN1* gene intravenously and has shown substantial benefit, particularly in infants treated before extensive motor neuron loss.[5] Itvisma is the same molecule reformulated for intrathecal delivery, extending gene replacement to patients aged two years and older, including adolescents and adults.

Rather than displacing existing therapies, Itvisma broadens clinicians' options. The choice among therapies will likely depend on age at treatment, disease severity, prior treatment exposure, patient preference, and health-system considerations.

SAFETY PROFILE AND CLINICAL MONITORING

As with other AAV-based gene therapies, Itvisma requires careful safety monitoring before and after administration. Reported adverse effects associated with AAV-mediated gene replacement include elevated liver enzymes, immune-related responses, fever, vomiting, thrombocytopenia, and increased cardiac biomarkers, and patients generally require corticosteroid prophylaxis and laboratory monitoring to reduce the risk of immune-mediated complications.

A key advantage of intrathecal administration is reduced systemic exposure relative to intravenous delivery. Nonetheless, long-term surveillance remains essential, since the durability of gene expression and the possibility of rare, delayed adverse events require extended follow-up. The safety profile must also be weighed against disease severity: for a progressive neurological disease such as SMA, preserving motor function and delaying disability are clinically meaningful outcomes, but these benefits must continue to be balanced against potential treatment risks.

COST, ACCESSIBILITY, AND HEALTHCARE IMPACT

Gene replacement therapies rank among the most significant advances in modern medicine, but their economic impact remains a major challenge. The official European price of Itvisma has not yet been established, as reimbursement is negotiated individually by national healthcare systems. Based on precedents set by other AAV-based gene therapies, including Zolgensma — introduced in the United States with a list price of approximately USD 2.1 million per administration, among the most expensive medicines in the world — the cost of treatment is expected to be substantial.

Although gene therapies require significant upfront investment, health economists argue that their value should also account for potential reductions in lifelong medical care, respiratory support, rehabilitation, and caregiver burden. Future reimbursement models may include outcome-based agreements, installment payments, or risk-sharing arrangements between manufacturers and healthcare systems — approaches likely to become increasingly important as more one-time genetic medicines reach clinical practice.

LIMITATIONS AND FUTURE PERSPECTIVES

Despite its promise, Itvisma faces several unresolved challenges. Gene replacement therapy cannot regenerate motor neurons that have already been lost, so early diagnosis and treatment remain critical to clinical outcomes. Patients treated after substantial neurological damage may see more limited functional recovery. The long-term durability of gene expression remains under investigation — AAV vectors can sustain expression in non-dividing cells such as neurons, but decades of follow-up will be needed to fully characterize persistence and potential limitations.

Manufacturing remains a major bottleneck across the gene therapy field: production of clinical-grade AAV vectors is complex, costly, and difficult to scale, contributing to high treatment costs and constraining global access. Immune responses to AAV vectors remain an ongoing scientific challenge, since pre-existing antibodies or post-treatment immune activation may limit opportunities for repeat administration — an important consideration for diseases requiring lifelong management.

Beyond SMA, Itvisma's development illustrates a broader shift in medicine, from managing the downstream consequences of genetic disease toward correcting its molecular origins. Continued advances in vector engineering, delivery technology, and manufacturing may enable similar strategies for other inherited neurological disorders.

Questions about long-term durability, affordability, and equitable access remain, but the therapy reinforces the potential of gene replacement as a transformative platform for precision medicine. SMA has become a model disease demonstrating how understanding of genetic mechanisms can be translated into targeted therapies that fundamentally alter disease trajectories. As the field matures, the future of genetic medicine will depend not only on correcting disease-causing mutations, but on developing safe, scalable, and economically sustainable strategies that allow patients worldwide to benefit from these innovations.

WEB RESOURCES

European Medicines Agency (EMA). Itvisma (onasemnogene abeparvovec): European Public Assessment Report (EPAR). https://www.ema.europa.eu/. Accessed July 2026

European Commission. European Commission authorisation information for Itvisma. https://ec.europa.eu/. Accessed July 2026

Novartis. Itvisma clinical development and regulatory updates. https://www.novartis.com/. Accessed July 2026

REFERENCES

1. Lefebvre S., Bürglen L., Reboullet S., et al. (1995). Identification and characterization of a spinal muscular atrophy-determining gene. *Cell* **80**:155–165. DOI:10.1016/0092-8674(95)90460-3
2. Wang D., Tai P.W.L. and Gao G. (2019). Adeno-associated virus vector as a platform for gene therapy delivery. *Nat. Rev. Drug Discov.* **18**:358–378. DOI:10.1038/s41573-019-0012-9
3. Proud C.M., Vũ D.C., Wilmshurst J.M., et al. (2025). Intrathecal onasemnogene abeparvovec in treatment-naive patients with spinal muscular atrophy: A phase 3 randomized controlled trial. *Nat. Med.* **32**:481–487. DOI:10.1038/s41591-025-04103-w
4. Finkel R.S., Mercuri E., Darras B.T., et al. (2017). Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N. Engl. J. Med.* **377**:1723–1732. DOI:10.1056/NEJMoa1702752
5. Mendell J.R., Al-Zaidy S., Shell R., et al. (2017). Single-dose gene-replacement therapy for spinal muscular atrophy. *N. Engl. J. Med.* **377**:1713–1722. DOI:10.1056/NEJMoa1706198

DECLARATION OF INTERESTS

The author declares no competing interests.