World Journal of Pharmaceutical and Life Sciences

Impact Factor: 8.21 www.wjpls.org Coden USA: WJPLA7

GENE REPLACEMENT THERAPY FOR SPINAL MUSCULAR ATROPHY: AN OVERVIEW OF ONASEMNOGENE ABEPARVOVEC

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DOI: https://doi.org/10.5281/zenodo.23912589

How to cite this Article: *D. Gayathri, K. Mohana Kumari, L. Gayathri (2026). Gene Replacement Therapy For Spinal Muscular Atrophy: An Overview Of Onasemnogene Abeparvovec. World Journal of Pharmaceutical and Life Sciences, 12(11), 249–251.

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Article Received on 05/10/2026 **Article Revised on 25/10/2026** **Article Published on 01/11/2026**

ABSTRACT

Spinal Muscular Atrophy is a rare autosomal recessive disorder marked by progressive degeneration of anterior horn cells in the spinal cord, leading to muscle weakness, hypotonia, and, in severe cases, respiratory failure. The condition arises due to mutations or deletions in the *SMN1* gene, resulting in inadequate production of survival motor neuron (SMN) protein, which is essential for motor neuron maintenance and function. Zolgensma (onasemnogene abeparvovec) is an advanced gene replacement therapy developed to address the underlying genetic defect in SMA. It employs an adeno-associated virus serotype 9 (AAV9) vector to deliver a functional copy of the *SMN1* gene to motor neurons, enabling sustained production of SMN protein following a single intravenous administration. This innovative approach targets the root cause of the disease rather than providing symptomatic relief. Clinical evidence indicates that early intervention with Zolgensma leads to substantial improvements in survival, motor milestone achievement, and overall functional outcomes, particularly in infants treated prior to the onset of significant symptoms. While the therapy demonstrates remarkable efficacy, its use is associated with considerations such as potential hepatotoxicity, immune-mediated responses, and the necessity for close clinical monitoring.

INTRODUCTION

Spinal Muscular Atrophy (SMA) is one of the rare genetic neuromuscular disorders, caused by a mutation in the SMN-1 (survival motor neuron) gene, which results in severe progressive loss of motor neurons in the anterior horn of the spinal cord, ultimately leading to loss of muscular function. SMN-1 & SMN-2 genes produce survival motor neuron (SMN) protein, which is necessary for the maintenance of highly functional motor neurons. Deficiency of this protein leads to degeneration of motor neurons and increased clinical features of the SMA. Most of the protein is produced by the SMN-1 gene, whereas the SMN-2 gene produces a very low quantity of protein, which is low efficiency compared to the SMN-1 gene due to variation in a single nucleotide. Usually, SMA individuals have the SMN-1 gene completely impaired in protein production. The presence of SMN-2 can make the condition milder, as it contributes minimal protein production. Common clinical features of SMA include muscle weakness, hypotonia, atrophy, and respiratory complications. Death occurs as a result of respiratory failure due to weakness of the intercostal and bulbar muscles as it triggers the aspiration. Treatment of SMA was unelucidated till 2015. Managing was based on supportive empirical care. Disease-modifying therapies (DMTs) were introduced. Nusinersin was approved by the FDA and EMA, respectively, in 2016 and 2017 and is an antisense oligonucleotide that acts as a splicing modifier of the SMN-2 gene mRNA. Later, in 2019, Onasemnogene Abeparvovec was approved by the FDA and by the EMA in 2020. It was a gene therapy that replaces the defective SMN-1 gene using the AAV9 vector. It was specifically for infantile SMA one-time gene therapy. Prognosis was significant, as it transformed the management of spinal muscular atrophy by slowing disease progression and improving survival and motor function, with optimal outcomes achieved through early treatment.

CATEGORY

- **Pharmacological category:** Gene Therapy.
- **Therapeutic Category:** Disease-Modifying Therapy for Spinal Muscular Atrophy (SMA).
- **Regulatory/Drug Category:** Advanced Therapy Medicinal Product (ATMP)
  Adeno-virus vector (AAV9)-based gene replacement therapy.
- **Indication-based Category:** Orphan Drug (approved for rare genetic disease).

BRAND NAMES

Onasemnogene abeparvovec is available in only two brands, Zolgensma and Itvisma, globally. The active pharmaceutical ingredient (API) is similar, but both differ in route of administration and targeted age groups—Zolgensma is only provided to infants < 2 years of age, and Itvisma can be given to both infants and older adults.

ROUTE OF ADMINISTRATION

Onasemnogene abeparvovec was administered through two routes, intravenously and intrathecally; it was based on the formulation type and patient age group. Zolgensma is administered through the intravenous route for infants & young children, whereas Itvisma is intrathecally for adults and older patients.

DOSAGE

The recommended dose of Zolgensma is 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight.

MECHANISM OF ACTION

Onasemnogene Abeparvovec contains a recombination of the adeno-associated virus-vector (AAV9) adenovirus variant used as a vector for gene delivery, as they are non-pathogenic, non-replicating, and do not trigger any immune reaction. They belonged to the Dependoparvovirus genus and the Parvovirus family. AAV9 has natural tissue-specific tropism towards motor neurons, liver & skeletal muscles. Initially, the AAV9 vector crosses the blood-brain barrier (BBB) through transcytosis by interacting with the endothelial cell surface receptors and enters motor neuronal cells by binding to specific N-linked galactose residues, and the AAV9 internalized via clathrin-mediated endocytosis vector gets enclosed in an endosomal vesicle as its acidified capsid conformational changes trigger the release of the vector. It gets directed towards the nuclear membrane vector entry into the nucleus through the nuclear pore complexes. Capsid uncoating occurs and finally releases the functional gene copy of SMN-1 into the cells. This copy of the gene remains as an episomal gene (a gene that doesn't integrate into the host genome). It rapidly increases the transcribing rate of the gene and promotes the SMN protein production, restores the SMN protein, and reduces the SMA-associated symptoms in the individuals as the SMN protein prevents motor neuronal degeneration and increases survival rates with improved neuromuscular function. After entering the host cell vector directed towards the nucleus, to increase the gene expression, instead of the single-stranded DNA packaging, double-stranded is preferred, as it increases the gene expression. Additionally, using the scAVV ITR promotes the transcribing rate, ultimately raising the desired protein upregulation. Additionally, hybrid CMV promoter and CB enhancer addition cause more efficient sustained SMN protein expression.

PHARMACOKINETICS

Absorption: There is a 90-95% bioavailability of onasemnogene abeparvovec in the case of intravenous route administration and approximately 60-80% intrathecally.

Distribution: It was widely distributed through the hematogenous route; high concentrations were found in the liver, motor neurons, skeletal muscles, and heart due to vector-associated specific tissue tropism.

Metabolism: Onasemnogene abeparvovec is not metabolized as a conventional drug, but the viral capsid proteins get degraded by intracellular proteolytic pathways. The transgene remains as an episomal gene.

Elimination: No renal/biliary occurs; immune-mediated clearance of the viral capsids and loss of episomal genes occur in case of cell turnover.

INDICATIONS

Onasemnogene Abeparvovec, approved for the treatment of Spinal Muscular Atrophy (SMA) in the paediatric population.

CONTRAINDICATIONS

Onasemnogene Abeparvovec Should be avoided in case if individual was previously treated and individuals with active hepatic impairment or any previous history.

CAUTION AND MONITORING

Systemic infections
Acute liver infection, hepatic impairment
Anti-AAV9 Antibodies: Immune consideration
Vaccination Adjustment
Premature neonates
Pre – treatment check ups

Liver function test need to be performed to evaluate normal limits of all parameters and haematological screening advised to check blood cells count especially platelet count. Troponin-I baseline need to be evaluated.

ADVERSE EFFECTS

Due to the specific tissue tropism of the AAV9 vector towards the liver, serum aminotransferase levels get elevated, and it may even progress to acute liver failure. Overloads of the vector in hepatocytes stimulate the immune system, which leads to hepatocellular inflammation. As vectors also have a natural tropism towards cardiac tissue, their entry into cardiomyocytes led to a rise in Troponin-I levels as a result of subclinical myocardial inflammation, but often no significant impairment of the heart has been reported to date. During

infusion of Onasemnogene Abeparvovec, individuals might experience nausea and vomiting due to cytokine release in response to vector load. Thrombocytopenia is encountered as immune-mediated platelet destruction initiated as complement system activation. In some rare cases, thrombocytic microangiopathy (TMA), a severe condition, arises in case of hyperimmune responses against the vector load, which causes endothelial injury and formation of microthrombi in small vessels. Kidneys get affected majorly. The presence of pre-existing neutralizing antibodies against the AAV9 capsid can impede cellular uptake of the vector, promote rapid immune-mediated elimination, heighten the risk of adverse reactions, and preclude repeat administration, ultimately reducing both the therapeutic effectiveness and safety of Zolgensma.

CLINICAL IMPLICATIONS

Onasemnogene abeparvovec has been shown to slow the disease progression, decrease the need for ventilatory support, and markedly improve clinical outcomes. When administered early, especially for presymptomatic infants, this therapy yields substantial gains in survival and motor neuronal functions.

CONCLUSION

In conclusion, **Spinal Muscular Atrophy (SMA)** is a severe, life-limiting condition that has historically relied on supportive and symptomatic management. The introduction of **Zolgensma (onasemnogene abeparvovec)** has transformed the therapeutic landscape by directly targeting the underlying genetic defect through gene replacement. This one-time treatment has demonstrated significant improvements in survival, motor function, and developmental outcomes, especially when administered early in the disease course.

Although challenges such as high treatment cost, potential adverse effects, and the need for careful monitoring remain, the overall clinical benefits of Zolgensma are substantial. It represents a major advancement in precision medicine and highlights the evolving role of gene therapy in the management of genetic disorders.

Ultimately, early diagnosis, timely intervention, and appropriate patient selection are critical to maximizing therapeutic success, making Zolgensma a landmark innovation in improving the prognosis and quality of life of patients with SMA.

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