

Elevidys In Duchenne Muscular Dystrophy: A Review on Efficacy, Limitations, And Future Directions

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ABSTRACT: Duchenne muscular dystrophy is an inherited condition in which muscle tissues deteriorate over time. DMD follows an X-linked recessive inheritance pattern arising from mutations in the dystrophin-expressing gene, and leads to cardiopulmonary failure, and ultimately death. Conventional interventions such as corticosteroids, do not halt the disease's progression, and provide only symptomatic relief, requiring the need for intervention at molecular level. Therapy involving such genetic corrections and excision is promising to be a revolutionary strategy that aims to correct the condition at root level to provide a potential permanent cure by delivering either functional genes directly to target genes or by gene editing and reframing to silence the mutated pathogenic gene expression. This study examines delandistrogene moxeparvovec-rokl, brand name Elevidys, the first approved genetic treatment by U.S. Food and Drug Administration to intervene DMD, by evaluating its innovative design, mechanism of action, and clinical outcomes while also addressing its limitations in the form of contraindications and socio-economic concerns and future implications. Elevidys comprises of an engineered vector rAAVrh74 associated with adeno virus to transmit a transgene microdystrophin to the muscle tissue in a one-time single intravenous dose. This approach restores the sarcolemma's structural integrity, which is compromised by the absence of native dystrophin and this has shown promising results in clinical trials, including functional motor improvement in ambulatory patients. Despite this potential to restore dystrophin expression, the therapy faces challenges including immune responses. Recent reports of acute liver damage leading to mortality in non-ambulatory patients has put the post-marketing on hold by FDA in certain populations. This review contrasts Elevidys with other gene therapy strategies like gene excision and exon-skipping, highlighting its clinical novelty. This review evaluates Elevidys as a breakthrough in precision medicine for DMD despite imperfections as it lays a foundation in shaping next-generation therapies.

KEYWORDS: Duchenne Muscular Dystrophy, Elevidys, delandistrogene moxeparvovec-rokl, Gene Therapy, Microdystrophin, Adeno-associated virus, rAAVrh74, CRISPR-Cas, Exon-skipping

INTRODUCTION

Gene therapy is a revolutionary tactic to treat rare genetic disorders by addressing the genetic disorder at molecular levels rather than simple symptom management. The conventional drugs require lifelong administration but gene therapy delivers functional gene directly into the target cells, enabling permanent curable outcomes. The recent clinical successes, such as those in spinal muscular atrophy and inherited retinal diseases have shown the target-specific delivery ability of adeno associated virus vectors for in vivo delivery of transgenes with transformative power. These approaches, despite being promising show challenges in the form of limited vector carrying capacity, immune responses to viral vectors, and dose-dependent toxicities, which have encouraged the development of engineered capsids, split-gene systems and non-viral nanoparticles to expand the therapeutic efficacy. Other in vitro strategies involving hematopoietic stem cells are also under interest for correcting metabolic and neuromuscular disorders with great precision. The regulatory

approvals in the last five years have emphasized both scientific progress and the translation of laboratory discoveries of gene therapy into real clinical options to treat rare genetic disorders making gene therapy as a milestone in modern medicine. Gene therapy offers symptomatic relief and promises a potential for permanent cure unlike traditional drugs that provide only symptomatic relief while at the same time present adverse effects (1-4).

One such genetic disorder is Duchenne muscular dystrophy, chronic and one of the most common X-linked neuro-muscular disorders, where approximately 1 boy among 3500-5000 live male infants globally is affected. The technological advancements in diagnosis have improved case detection, but in low- and middle-income countries, due to limited genetic testing infrastructure. The disease has remained underestimated due to poor and limited diagnosis. Clinically, DMD has been characterized by progressive muscle degeneration, loss of ability to walk by adolescence, cardiopulmonary complications and mortality. The socio-economic challenges

for families especially from low- and middle-income countries pose exceptional burden as they face high medical costs, ventilatory care and newer advanced treatments. Click or tap here to enter text.. DMD is not only a devastating medical condition but also a major challenge for the society, requiring an urgency of development of sustainable therapeutic options like gene therapy to present an affordable option for symptomatic relief and long-term cure.

The use of corticosteroids for respiratory support, cardiac care, orthopedics and physiotherapy in the management of DMD may mitigate symptoms but do not promise halting of disease progression. Steroids like prednisone and deflazacort slow muscle degeneration but present significant side effects over prolonged use. Therefore, there is a need to find the genetic causes and find a cure at molecular level which is meaningful and provides durable clinical improvement. The emerging molecular therapies offer a potential cure by providing options including exon-skipping agents that enable altered but functional dystrophin expression, microdystrophin gene replacement using rAAVrh74 vectors, Clustered regularly interspaced short palindromic repeats based gene excision and silencing, utrophin upregulation, and cell-based therapies. The U.S. Food and

Drug Administration has recently approved Givinostat, a non-steroidal drug and oral histone deacetylase inhibitor, and Elevidys, an rAAVrh74-mediated microdystrophin gene therapy, promise an intervention in disease modification. Click or tap here to enter text.. However, these approaches have faced challenges such as limited mutation applicability, immune responses to viral vectors and uncertain long-term efficacy. With advancements, regeneration of muscle and dystrophin restoration may help achieve best clinical outcomes for patients with DMD.

The approval of Elevidys by FDA has revolutionized the treatment for DMD. The FDA accelerated approved the delandistrogene moxeparvovec-rokl marketed and distributed as Elevidys, making it the first clinically accepted therapeutic. The FDA approved and validated the use of Elevidys in infants who are aged 4 or older and have developed DMD after a success in clinical trials in June 2024. This placed Elevidys as a therapy capable of addressing dystrophin deficiency by the use of an engineered microdystrophin gene using rAAVrh74 vectors for its delivery. Elevidys aims at providing one-time treatment with durable dystrophin expression unlike corticosteroids or exon-skipping therapy. The Elevidys therapy, however, is limited

to a specific age and status of ambulation and at the same time, its long-term efficiency and adverse event status is still under investigation including recent serious reports of hepato-toxicity in non-ambulatory patients. Despite this, Elevidys is the first systemic microdystrophin gene therapy to address DMD that transmits a synthetic microdystrophin gene to the target-cells to replace missing dystrophin function, unlike CRISPR-based therapy or exon skipping that partially truncates or silences the mutated gene (5-9).

PATHOPHYSIOLOGY OF DUCHENNE MUSCULAR DYSTROPHY

DMD caused by either frameshift or point mutations in the dystrophin gene, located on chromosome Xp21 is an X-linked recessive genetic disorder. This means the young boys are affected, while females stay as carriers and are typically asymptomatic. The dystrophin gene is one of the largest in the whole human genome. Its length spans in 79 exons and roughly 2.5 megabases, making it vulnerable to various events of gene mutation. The common pathogenic variants include large deletions, duplications, and small mutations constituting approximately 20-27% cases globally. Studies from Delhi revealed that deletions caused 79.5% mutations, 1.3% cases were due to duplications, and 19.2%

of the cases were due to point or small mutations with majority of them stacked in distal “hotspot” exons. The recent analysis also revealed deep intronic variants and abnormal splicing events of mRNA highlighting the need for changing diagnostic approaches beyond exon screening. The deficiency of dystrophin protein compromises the structural integrity of muscle fibers causing instability of sarcolemma, muscular degeneration and regeneration cycles, and gradually the functional muscle tissue replacement with fat and fibrosis.

DMD is caused due to the deficiency of dystrophin protein of the sarcolemma due to which the muscle fiber membrane becomes mechanically unstable and prone to damage during normal contraction of muscle. Dystrophin, forms a complex with glycoprotein on sarcolemma to form dystrophin and glycoprotein complex, which aids in transmission of the stressful forces from cytoskeleton of the sarcolemma to extracellular space, protecting muscle fibers against mechanical stress. Without this spread out of stressful forces, the contraction-induced stress leads to tears in sarcolemma, calcium influx, and activation of proteolytic enzymes, causing necrosis of muscle-fiber. Even though initial cycles of myofiber degeneration collide with satellite-cell mediated regeneration, the

repair process ends quickly, particularly as the stem cells that produce new myofibers have the same genetic defect, reducing the regenerative potential. This net result leads to progressive muscle fiber loss, with replacement by adipose tissue followed by fibrosis leading to a functional decline. This mixture of events involving dystrophin deficiency, membrane fragility, repeated damage and failed regeneration followed by fibrotic remodeling constitutes the central pathophysiology of DMD leading to ambulation in infants. Figure 1 depicts the schematic representation on pathophysiology of DMD (10-12).

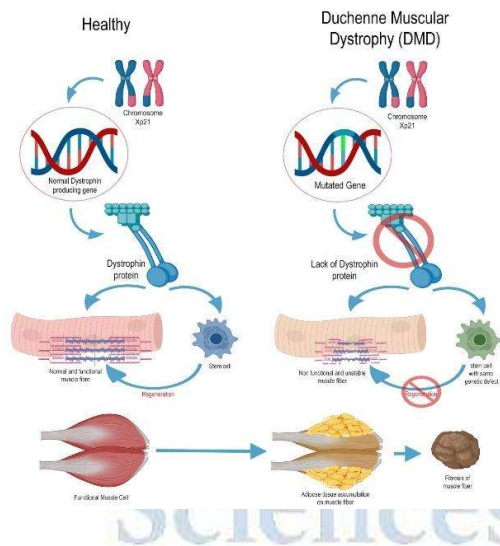


Figure 1. Schematic representation of pathophysiology of DMD

The clinical manifestations of DMD typically begins in early childhood, where boys show developmental delays, frequent falls, waddling gait, difficulty climbing stairs between ages 2-5. As the muscular

degeneration progresses, the loss of independent ambulation or inability to walk independently occurs. This leads to a requirement of a wheelchair by age 10-15 despite steroid treatment. As the muscle weakness progresses, the heart is also affected leading to dilated cardiomyopathy, in adolescence and early adulthood. The respiratory muscles, particularly the intercostal muscles also weaken gradually and this results in respiratory insufficiency. The patient requires non-invasive ventilation or else develop respiratory failure, one of the most leading causes of mortality. Thus, an absence of interventions to deal with DMD causes motor decline, leading to ambulatory loss followed by cardiopulmonary decline leading to mortality.

The clinical intervention primarily involves the use of corticosteroids and gene therapy including the Elevidys. However, significant therapeutic gaps still remain with recent development of hepato-toxicity in non-ambulatory individuals leading to a hold on marketing of Elevidys. The current clinical interventions are mutation-specific, accessible to ambulatory patients and require repeated administration of dosage or carry severe side effects. Non-ambulatory and older DMD patients have few effective treatment options. The accelerated approvals of novel therapies

like exon-skipping agents show a small increase in dystrophin levels but these changes in dystrophin levels do not provide any clear long-term evidence of improved heart or lung function which are the primary causes of mortality. Another challenge is the cost of the existing therapies limiting global access. These limitations and challenges highlight the need for next-generation treatments that are mutation-agonistic, usable by non-ambulatory individuals, and improves cardiopulmonary function and is also financially accessible.

ALTERNATIVE GENE THERAPY MEASURES FOR DMD

The therapeutic design to intervene DMD involves three essential components: choice of vectors, the nature of therapeutic transgene, and the promotor that drives expression. The research studies find that the vectors engineered from adeno virus are more reliable as they are less pathogenic, have high tropism for muscle tissue, and stable episomal persistence in non-dividing cells. However, rAAVrh74 vector has limited carrying capacity, the full-length dystrophin gene cannot be delivered. Hence, engineered microdystrophin genes which retain the key functional domains are used to fit within the rAAVrh74 vector carrying and packaging capacity. The selection of promoter is also important. Muscle-specific promoters like MHCK7,

CK8 or CK6 are used because they restrict the transgene expression to skeletal and cardiac muscles, hence improve safety and efficacy. The comparative studies have shown that ubiquitous promoters like CMV produce higher expression in certain tissues, muscle-specific promoters provide more targeted and potentially less immunogenic expression in DMD gene therapy. The integration of optimized rAAVrh74 vector with microdystrophin transgenes and muscle-targeted promoters form the backbone of current DMD gene therapy that balances expression, tropism, and immunogenicity to achieve the aim of restoration in dystrophin levels in muscle tissue. Delandistrogene moxeparvovec-rokl delivers a synthetic microdystrophin transgene via a vector rAAVrh74 in a single intra-venous dose, to restore the deficient dystrophin protein in muscle tissue due to the mutation of gene that expresses dystrophin protein. Delandistrogene moxeparvovec-rokl marketed and distributed as Elevidys is approved to treat DMD in 2023 and later expanded to include non-ambulatory patients in 2024. However, in 2025 few non-ambulatory patients developed hepato-toxicity that led to a hold on Elevidys in various countries by FDA. Elevidys is still promising as it is a one-time therapy that systemically delivers a functional microdystrophin transgene to

restore dystrophin levels aiming to permanently cure DMD. The other alternative is Exon skipping of mutated exons which is facilitated by antisense oligonucleotides, modulates pre-mRNA splicing to evade the mutated exons and help in the restoration of dystrophin reading frame. The approved therapies include Eteplirsen, Golodirsen, Vitolarsen and Casimersen. This therapy involving various exon-skipping agents require regular dosing and target-specific mutations. One of the most promising approaches is CRISPR-based gene therapy offers a permanent correction of mutated gene by excising or reframing mutant exons at DNA level, such as duplications, thus restoring expression of dystrophin protein in cardiac muscle tissue and skeletal muscle tissues. The preclinical trials demonstrate feasibility but efficient and safe delivery still remains a major challenge. Antisense Oligonucleotides is yet another promising gene therapy which may more broadly regulate splicing and silence deleterious mRNA transcripts or upregulate compensatory proteins. However, ASO approach is still stuck in preclinical stage but their flexibility and specificity make them promising alternatives to conventional exon-skipping (13-16).

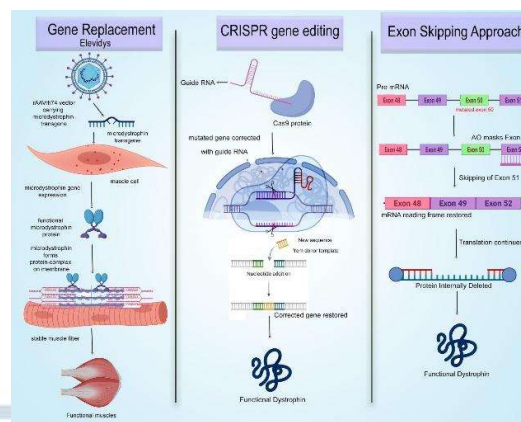


Figure 2. Comparative therapeutic strategies for DMD

ELEVIDYS VS CRISPR-CAS APPROACHES

There are two prominent approaches to intervene DMD - Elevidys and CRISPR-Cas gene editing which emphasize the contrasting mechanisms to restore dystrophin levels to treat DMD via gene therapy. Elevidys-based therapy is clinically accepted to treat DMD. This therapy favours the delivery of a synthetic microdystrophin transgene via the vector rAAVrh74. This microdystrophin is the shortened yet functional form of long conventional gene for dystrophin expression to fit within the packaging capacity of rAAVrh74 vector. This gene is capable of stabilizing muscle fiber membranes and reduce contraction-induced muscle injury. Elevidys thus provides a functional replacement, enabling dystrophin-like activity without correcting the underlying indigenous mutated gene. In

contrast, CRISPR-Cas technology adopts a direct genome-editing approach. Instead of delivering a synthetic gene directly, CRISPR systems modify the endogenous chromosomal locus, typically by excising the exons that disrupt reading frame or by correcting pathogenic mutations. CRISPR aims to restore the functional dystrophin expression through the patient's own gene causing a permanent fix. CRISPR approach relies on precise DNA cleavage and repair pathways within the muscle-cell nuclei while Elevidys approach relies on systemic delivery of a synthetic micro-dystrophic transgene. This contrast has different clinical implications. Elevidys offers an immediate dystrophin expression but long-term durability maybe influenced by rAAVrh74 genome dilution during muscle regeneration and immune responses against viral capsids or microdystrophin protein. CRISPR approaches potentiate lifelong correction but faces challenges during delivery to the muscle tissue, leading to off-target effects and ethical considerations for

germline transmission and it may consequently alter the germline.

In clinical trials, the patients treated with Elevidys produced 34-51% of normal microdystrophin levels within three months, and even non-ambulatory patients showed approximately 40% recovery. The Phase III EMBARK clinical trials showed significant improvement in motor abilities in ambulant DMD patients validated through North Star Ambulatory Assessment. CRISPR-Cas editing, in turn typically showed much lower efficiency rates in preclinical models. The data obtained from treated MDX mice showed approximately 1-2% editing efficiency in muscle tissue. Elevidys and CRISPR are complementary to each other. Elevidys is a clinically validated solution with functional benefit while CRISPR technologies remain largely experimental but hold the potential for a permanent cure. Table 1 presents the comparative approaches to treat genetic disorders (17-19).

Table 1. Comparison of Elevidys, CRISPR–Cas and Exon-skipping in Gene Therapy

Feature	Elevidys	CRISPR–Cas approaches	Exon-skipping
Delivery platform	rAAVrh74 vector carrying micro dystrophin transgene	Genome editing at endogenous dystrophin locus	Antisense oligonucleotides inducing exon skipping

		using Cas9/guide RNAs	
Clinical status	FDA-approved, EMBARK phase 3 completed	Preclinical in mdx and humanized models and no systemic human trial yet	FDA accelerated approval but long-term conditional
Dystrophin expression	Approx. 34–51% of normal in EMBARK/ENDEAVOR trials	Preclinical systemic editing: approx. 1–10% muscle fibers expressing dystrophin	Eteplirsen/Golodirsen: <1–2% by WB; fold increases over baseline
Functional outcomes	NSAA improvement in ambulant patients; some functional benefit in non-ambulant	Improved histology and force in preclinical models	Mixed; some slowing of functional decline vs historical controls
Durability / dosing	One-time single dose IV infusion	Potential lifelong correction	Requires repeated dosing
Safety	Immune responses to AAV & microdystrophin	Off-targets, germline risk, editor immunogenicity	Generally well tolerated; renal monitoring required

DESIGN AND MECHANISM OF ACTION OF ELEVIDYS

Elevidys is designed by the use of a vector - rAAVrh74 from adeno virus, aims to deliver recombinant microdystrophin transgene that is designed to intervene and

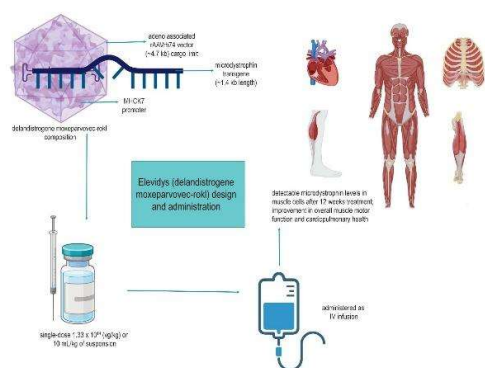
find a curable solution to the genetic disorder DMD. The full-length dystrophin is large while rAAVrh74 vector has a packing limit of only 4.7kb and so, Elevidys uses a synthetic microdystrophin transgene that preserves essential and functional domains of the gene. The rAAVrh74 vector

was chosen for its strong muscular tropism, especially in cardiac muscle and skeletal muscle tissues. This vector also does not activate immune response in the host body compared to its other counterparts, increasing its systemic delivery potential. The transgene expression is controlled by MHCK7 promoter, a creatine kinase 7 and α -myosin heavy-chain enhancer sequence complex, which expresses focusing majorly in the cardiac and skeletal muscle tissue, reducing off-target effects and increasing safety. Thus, delandistrogene moxeparvovec-rokl is a non-replicating therapeutic which is developed using recombinant technology formulated with three key elements: an rAAVrh74 capsid, a cardiac muscle and skeletal muscle tissue promoter MHCK7, along with the recombinant microdystrophin transgene, truncated to have essential functional domains required to produce functional dystrophin to ensure the stability of sarcolemma and muscle integrity (20-23).

Figure 3. Design and administration of Elevidys.

Elevidys is administered as a single IV infusion, with dosing calculated based on the patient's body weight, a patient under 70kg weight is prescribed 1.33×10^{14} vector genomes per kg or 10 mL/kg of suspension and patients above 70kg are prescribed a dose of 9.31×10^{15} vg. Elevidys is administered as a sterile suspension that is free from preservatives and supplied in 10mL single-dose vials that are customized by weight-based dosing. After dosing the vector distributes through systemic circulation, delivering the transgene at target-site. It takes 12 weeks or 3 months for microdystrophin to get distributed in the myofibers of body. The post-treatment screening includes checking for anti-bodies against the vector, count of platelets, proper function of liver and levels of troponin-I. Corticosteroids are also administered after infusion to suppress any immune or inflammatory responses. The Troponin-I monitoring continues every week for a month to check for adverse reactions. Thus, this pharmacology ensures that Elevidys performs as intended.

Elevidys after administration, leads to systemic delivery that enables the rAAVrh74 vector to move through bloodstream and reach skeletal, cardiac and diaphragm tissue. After delivery to the



target site, the rAAVrh74 capsid helps in transduction of synthetic microdystrophin gene into muscle cells as rAAVrh74 vector has strong tropism for muscle fibers thereby reducing reach out at off-target sites. This specificity enhances the uptake and transgene expression. After reaching inside the muscle fiber, the viral vector uncoats and releases a single stranded DNA strand encoding the microdystrophin transgene which is controlled by the promoter MHCK7 that is active only in skeletal, cardiac and diaphragm tissue. After the successful entry of viral vector genome into the myofiber cell, persists at the episomal area, outside the main-chromosomal area of the host cell without integrating into the host DNA which reduces the risk of mutagenesis. These transduced muscle fibers then begin to express the microdystrophin protein which is transmitted to sarcolemma, the plasma membrane of muscle fiber (24).

The clinical data shows that up to 81.2% of fibers started expressing the protein with full intensity as confirmed by Western blot. Once integrated into the glycoprotein they form a complex of DGC, thus enabling the microdystrophin to restore the stability of sarcolemma from mechanical stress thereby reducing membrane damage. This leads to a reduction in creatine kinase levels in the serum, and muscle function improvement.

The EMBARK clinical trials and NSAA suggest such functional improvement in both ambulatory and non-ambulatory individuals marking sustained effects for at least one year in clinical studies. The preclinical data has verified these findings and suggested that the systemic delivery of microdystrophin transgene system showed functional recovery and improved normalization of the histology of muscle fiber, and increased muscle force without toxicity. Therefore, this clarity in mechanism of action of Elevidys led to its approval by FDA to support an increase in dystrophin expression. However, few contraindications as reported in 2025 have put the marketing and distribution of Elevidys on hold and under conditional distribution in many countries. Elevidys comprises an engineered microdystrophin transgene that is a truncated functional version of dystrophin into a size that is compatible with rAAVrh74 vector delivery, specifically that actin-binding region at N-terminal site, spectrin-like repeats, and a domain rich in cysteine for the formation and interaction of dystrophin-associated protein complex to enhance muscle membrane stability. The preclinical comparisons in MDX mouse model showed that microdystrophin driven by MHCK7 promoter, normalized the muscle morphology in treated animal. Other studies indicate that spectrin-like repeat

regions showed that the R1-R3 construct showed highest affinity for lipid binding showing its role in anchoring the protein into the sarcolemma of muscle fiber. The clinical studies involving muscle biopsy revealed that microdystrophin transgene system administration in human trials demonstrated effective microdystrophin protein deposition within target-sites. Table 2 further summarizes an overall reduction in physical, functional as well as biological biomarkers post-treatment (25).

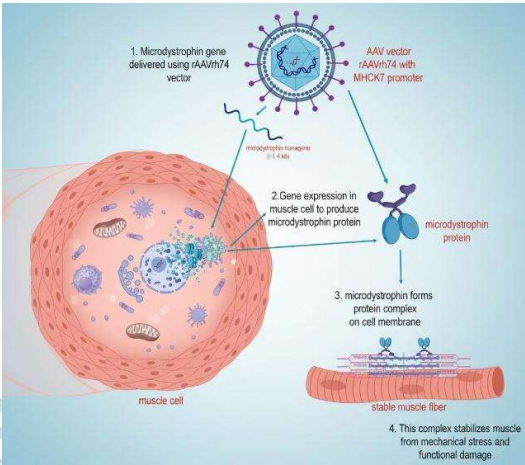


Figure 4. Mechanism of Action of Elevidys-based therapy

Table2. Changes in Physical, Functional and Biological Biomarkers after treatment

Biomarker / Task	Change Reported After Elevidys
Creatine kinase levels	Reduction post-therapy
Troponin-I	Weekly monitoring required
10-meter walk/run	Improvement
Rise-time	Improvement in EMBARK trials

INNOVATIVE APPROACH OF GENE REPLACEMENT

Elevidys-based gene therapy involving the delivery of a synthetic truncated functional transgene using a viral capsid and a promoter that is target-specific has revolutionized gene therapy by delivering a single one-time dose that is capable of benefiting most of the genotypes globally. It is a highly novel and unique technology which holds the capability to correct the

genetic disorder with a single dosing through systemic delivery via IV unlike exon-skipping agents which must be administered repeatedly. The human-trials showed approximately 80% muscle fibers expressing microdystrophin with normal intensity to secure normal muscular morphology and function. This combination of broad applicability to all genotypes, long-term efficacy and complete structural restoration

of muscle fiber makes Elevidys a revolutionary therapy aiming for a permanent cure. Elevidys, unlike other gene therapies, aims to deliver a functional synthetic truncated transgene directly using a vector while other gene therapies like CRISPR-Cas, exon-skipping and other therapies aim to either delete or silence the pathogenic mutated gene strands, and this makes Elevidys innovative. The other therapies have also remained in late preclinical stage while Elevidys is the first clinically validated therapeutic that is in its post-marketing stage, aims to cure DMD despite showing a few adverse effects that can be resolved through close monitoring.

THERAPEUTIC EVALUATION AND CLINICAL TRIALS

The early Phase I/II SRP-9001, a non-randomized clinical trial showed significant microdystrophin expression in muscle biopsies and safety making a foundation for larger efficacy studies. In placebo-controlled EMBARK Phase III trials, NSAA showed improvement at 52 weeks but did not reach any statistical significance. Other measures like rise-time

and a continuous walk for 10 meters or run showed some improvement confirming some biological activity and improvement. This long-term efficacy and safety data from an extension for three years showed sustained expression of transgene and stable motor function over time in many male infants. Many participants also showed functional improvements. In ENDEAVOR, the boys gained NSAA points as they improved six-minute walk distances by 20-40 meters, and achieved faster execution of motor tasks, showing functional motor improvement. These results also support the studies on MDX mice where systemic microdystrophin improved muscle fiber morphology and mechanical strength. Therefore, clinical case studies on both MDX mice and humans suggest therapeutic efficacy by demonstrating functional motor improvement although there is a need for standardized biomarkers and long-term assessment . As shown in Figure 5, microdystrophin expression is found to be the highest in ambulatory individuals after 12-week treatment (26).

Table3. Functional Outcomes in Elevidys Clinical Trials

Trial / Assessment	Outcome Measure	Reported Result
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EMBARC	NSAA score	Improvement, but not statistically significant at 52 weeks
ENDEAVOR	NSAA points & 6-minute walk	Gain of 20-40 meters and faster motor tasks
Long-term	Motor function	Stable motor function over 3 years

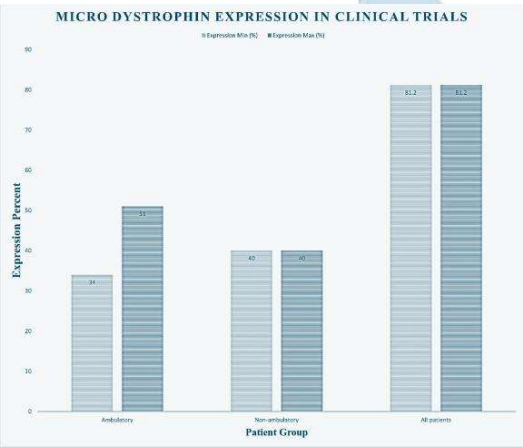


Figure 5. Expression of Microdystrophin in Clinical Trials post-treatment.

BIOCOMPATIBILITY, CONTRAINDICATIONS AND TOXICOLOGICAL PROFILING

The clinicians observed transient elevation in the enzymes in liver like Aspartate aminotransferase, Gamma-glutamyl transferase , Alanine aminotransferase , and Glutamate dehydrogenase indicating acute hepatic stress in approximately 40% of trial volunteers, but these were generally manageable with supportive careClick or

tap here to enter text.. The Elevidys-gene therapy also showed other contraindications like myocarditis-like symptoms validated by troponin-I level elevation in some patients making it a regulatory compulsion by FDA to monitor cardiac activity before infusion and weekly for one month after infusion to eradicate any risks involving cardiac inflammation. Many cases of infusion-related to hypersensitivity reactions, including fever, vomiting, and nausea occurring after hours of administration were also reported but could be controlled by slowing or pausing the infusion to provide symptomatic relief. In non-ambulatory individuals, acute liver failure has been reported after Elevidys administration, leading to suspension of the dosage in these individuals. Many ongoing investigations by health authorities also focus on confirming any underlying immunotoxicity after administration. Table 4 summarizes the different clinical presentations and their management involving Elevidys therapeutic to cure DMD. rAAVrh74 in Elevidys, persist as

episomal concatemers in the host cells without integrating with host DNA which largely mitigates the risk of insertional mutagenesis. However, a very rare and low-frequency integration with the host genome was reported in animal studies increasing concerns about genotoxicity but such concerns have not showed any significant changes in human clinical trials till date, however precautionary measures still have been advised by the regulatory bodies particularly at high doses in hepatic tissues. Recent studies also suggest a long-term study in large animal models, highlighting some rAAVrh74 integrations with clonal expansion in liver cells putting patients at a potential risk with underlying hepatic diseases. Thus, Elevidys trials include long-term monitoring of liver functionality to check for any signs of hepatocellular abnormalities or abnormal cell proliferation resulting in tumor growth. The preclinical studies also validate that systemic delivery of microdystrophin preserved muscle fiber integrity, reducing central nucleation and myofiber degeneration in fibrotic D2.MDX

models, particularly in the diaphragm emphasizing the microdystrophin's capability to protect against damage of membrane due to muscle contraction. This therapy also prevents fibrosis as shown by lower collagen accumulation in treated diaphragms when compared to untreated controls in histological sections. In severe cardiomyopathy DKO mouse model, microdystrophin therapy fully removed the fibrosis of heart along with inflammation and normalized the the percentage of blood pumped by left ventricle, ejection fraction and heart strain measures through 18 months of age, indicating protection against fibrotic remodeling. In other clinical studies, long-lasting outcomes of microdystrophin delivered through rAAVrh74 vector in MDX mice showed supraphysiological expression maintained into adulthood, validating improved muscle strength and indirectly suggesting reduced muscle tissue degeneration and fibrosis over time.

Table 4. Acute Immune reactions and management for Elevidys administration

REGULATORY ASPECTS AND GLOBAL GUIDELINES

Delandistrogene moxeparvovec-rokl therapeutic aims to correct genetic disorders like DMD in patients aged 4 to 5

providing clinical and therapeutic benefit led to its accelerated approval. However, this approval has attracted many critics, who argued that the clinical trial data were insufficient to demonstrate a definitive functional benefitClick or tap here to enter

Reaction Type	Clinical Presentation	Observed Reports	Mitigation Strategy
Liver enzyme levels elevation	Elevated AST, ALT, GGT, GLDH within days post-infusion	40% of patients in trials	Regular liver enzyme monitoring and supportive care
Myocarditis-like symptoms	Elevated troponin-I, tightened chest and discomfort, fatigue	Few cases noted in trials	Weekly cardiac monitoring before infusion and for 1 month after infusion
Infusion-related reactions	Fever, vomiting, nausea, hypersensitivity reactions	Common but mostly mild-to-moderate	Slow infusion rate, pause/stop infusion, symptomatic treatment
Acute liver failure	Jaundice, coagulopathy, encephalopathy, multi-organ failure and Death	Rare, mostly in non-ambulatory patients	Dose suspension in high-risk groups; ongoing safety investigation

years post-approval by FDA in June 2023.The evidences and clinical studies that validated an increase in the expression of microdystrophin in muscle fibres,

text.. For example, NSAA score did not statistically show any significant improvement over placebo. Also, the study’s design and statistical analyses have

be thoroughly questioned. The FDA's reliance on microdystrophin expression has also been under critical debate, while increased levels of this protein are associated with DMD, its direct correlation with clinical outcomes remains uncertain. This raises concerns on appropriateness on regulatory decisions. These questions highlight the need for more clinical evidence and debates over FDA's decision on accelerated approval of Elevidys.

In Europe, Elevidys has been scrutinized and marked by caution. The European Medicines Agency has issued a critical hold on gene therapy citing concerns over its safety profile based on recent contraindications. In contrast, Japan's Ministry of Health, Labour and Welfare has granted an approval that is conditional for the marketing and distribution of Elevidys in May 2025. This approval was based on the trial data from EMBARK phase III which validated long-term functional outcomes. This approval however, is time limited, allowing Elevidys to be marketed for up to seven years provided more data on its safety and efficacy is provided. Many critics also debate between the use of biomarkers and clinical endpoints. It is argued that reliance only on biomarkers may risk the approval of treatment without any proven clinical

benefit and there is a need for balanced evaluation in gene therapy approvals.

CRITICAL LIMITATIONS

delandistrogene moxeparvovec-rokl has shown promising outcomes but faces critical limitations that impact its accessibility and efficacy. The rAAVrh74 vector used in Elevidys can elicit immune responses which may lead to the clearance of microdystrophin transgene modified muscle cells. This immune-mediated elimination might lead to a sustained loss in microdystrophin expression over time reducing the long-term efficacy of the therapy. This may also mean that the sustained expression of the therapeutic protein may not be achievable in all patients. Elevidys delivers a truncated version called microdystrophin, and as this is a modified and engineered version, its therapeutic effect may be limited as it may not provide complete protection against muscle degeneration leading to reduced functional outcomes. The therapy still has shown more favourable outcomes when administered to infants with lesser disease progression. In older patients with more progression however, the potential for functional degeneration is reduced. This age dependency on disease and progression limits the broader applicability of Elevidys across the DMD population. The efficiency of rAAVrh74-mediated delivery can also

vary among different muscles. This variability can also result in uneven expression of microdystrophin affecting overall treatment efficacy (27).

Since the accelerated approval, many cases have reported severe liver injury which was not reported previously in clinical trials or post-marketing. The exact mechanism is not understood fully but the contributing factors might be immune-mediated responses triggered due to rAAVrh74 vector delivering the transgene which may have provoked inflammatory reactions leading to liver damage. Anaphylaxis and other infusion-related reactions have also been reported right after administration. These reactions are also believed to be immune-mediated due to rAAVrh74 vector or other components of the therapy. These reactions can still be managed by close monitoring during or after infusion by following necessary protocol. FDA, however, has instructed to suspend the distribution of Elevidys and the company is now aligned towards enhancing safety protocols, including adjustment to immunosuppressive regimen to completely mitigate these risks and contraindications. Elevidys is also one of the most expensive gene therapies in the world and this high-cost limits accessibility in healthcare systems. Elevidys offers a groundbreaking

approach in treating DMD, but its limitations challenge the global acceptance.

DESPITE FAILURES: WHAT PROMISES DOES ELEVIDYS HOLD?

Despite many challenges and adverse events associated with Elevidys, the therapy still promises a landmark achievement for treating dystrophy of muscles. Elevidys pioneers at providing one-time treatment that delivers microdystrophin via rAAVrh74-vector, restoring dystrophin expression in muscle tissues and curing DMD. The clinical data indicates that Elevidys can achieve microdystrophin expression levels up to 54% of normal in 12 weeks, after treatment with target-specific distribution at the sarcolemma. These findings show the feasibility of high-dose systemic rAAVrh74 delivery establishing long-term safety and systemic distribution although monitoring is essential. The use of the rAAVrh74 vector has opened ways to next-generation systemic delivery systems and has catalyzed capsid engineering to enhance tissue specificity and reduce immunogenicity by improving transduction efficiency, overcoming the limitations of first-generation vectors. Elevidys has also opened pathway to combination therapies such as its integration with exon-skipping drugs like EteplirsenTM or other corticosteroids to add an additive or

synergistic effect to improve functional outcomes for patients with DMD. Elevidys has also provided valuable lessons in patient selection criteria, protocol and regulatory development and close monitoring all of which direct the design of future therapies. Elevidys, despite facing its challenges and limitations, validates systemic gene replacement as a potential therapeutic strategy that promises one-time treatment and also lays foundation in developing more safer next-generation vectors. These promises catalyse the transformation of treatment strategies to cure genetic disorders through precision medicine (28).

FUTURE PERSPECTIVES AND RESEARCH GAPS

Elevidys has established a pathway for more innovative therapeutic strategies to enhance the efficacy and accessibility of gene therapies. However, it is important to address key research gaps to understand the full potential for gene therapy in treating DMD or other genetic disorders. The development of neutralizing antibodies to neutralize the immune-response triggered by rAAVrh74 vector poses a significant barrier to repeated dosing. Certain strategies can be developed that can mitigate this immune response by using tolerogenic nanoparticles encapsulating immunosuppressive agents like Rapamycin

for reducing NAb formation and enhancing transgenic expression. Many bispecific antibodies targeting both rAAVrh74 capsid and immune checkpoints can also be explored to suppress immune responses. Many delivery systems like lipid nanoparticles giving a non-viral approach and engineered exosomes, as an alternative over viral vectors can also be used, including reduced immunogenicity and the ability to deliver larger or multiple genetic strands without truncation. Engineered exosomes derived from natural cellular vesicles are being developed for targeted delivery and packaging of longer strands, promising more safer gene delivery. Integration with CRISPR-based genome editing could also enhance therapeutic outcomes by enabling precise correction of genetic mutations in conjugation with gene replacement. Advances in machine learning to identify patient responses to gene therapies is also critical for identifying reliable biomarkers and genomic profiling enabling personalized treatment plants to improve therapeutic outcomes. On-treatment biopsies should be explored to insights to therapy resistance mechanisms. The high cost of gene therapies raises ethical and accessibility concern and strategies to integrate ethical considerations and designing value based therapeutic models are being explored to address and

equitable access to these advanced treatments.

A novel approach gaining attention is in utero gene therapy which involves administering gene therapy to fetuses to correct genetic disorders before birth. This strategy could prevent the onset of many diseases like muscular dystrophy, spinal muscular atrophy and sickle cell anemia. However, ethical and social considerations still remain a challenge. Therefore, addressing these research gaps and considering future perspectives are essential to overcome these limitations and realize full potential in treating genetic disorders (29,29).

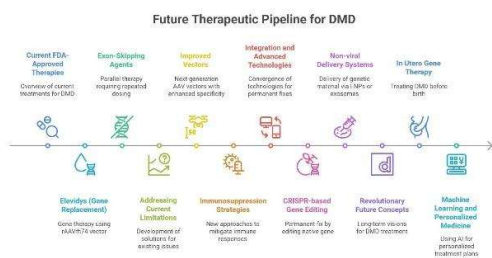


Figure 6. Future perspectives covering existing gaps in Elevidys

CONCLUSION

The studies connected to DMD has led to create a foundation for the development of therapies like Elevidys, making it a pioneer step in systemic transgene delivery for life-threatening genetic disorders. Elevidys addresses directly the root cause of DMD

through delivery of microdystrophin transgene using an rAAVrh74 vector. This has demonstrated motor and functional benefits in both preclinical and clinical settings as the administration is also a single-dose IV infusion. This therapy is accelerated approved by FDA and validates a transformative therapy but also faces certain challenges like immune-responses, hepatotoxicity in non-ambulatory patients, and uncertainty over long term therapeutic efficacy. Elevidys still, has shown effective and sustained expression of the transgene in muscle tissue which is a rare feat as muscle tissues are highly resistant to such therapies making all sorts of muscle dystrophy challenging to cure. Such outcomes reflects a significant shift in the field of precision medicine, promising increased motor function, normalized respiratory output and increased life expectancy in pediatric DMD patients. To address such gaps and critical challenges and debates on its accelerated approval, including non-viral delivery systems like lipid nanoparticles, exosomes, or advanced synthetic polymers with high muscle penetrability may reduce such risks and expand applicability. The other groundbreaking approach could be to directly produce a synthetic nucleoside modified mRNA that encodes for dystrophin and bypasses the integration with host genome which can then be encapsulated by lipid nanoparticles

or advanced polymers. Use of Elevidys thus, represents the closest step towards a permanent and durable cure for DMD and is also a model for case study that lays foundation to design future therapies targeting rare genetic disorders.

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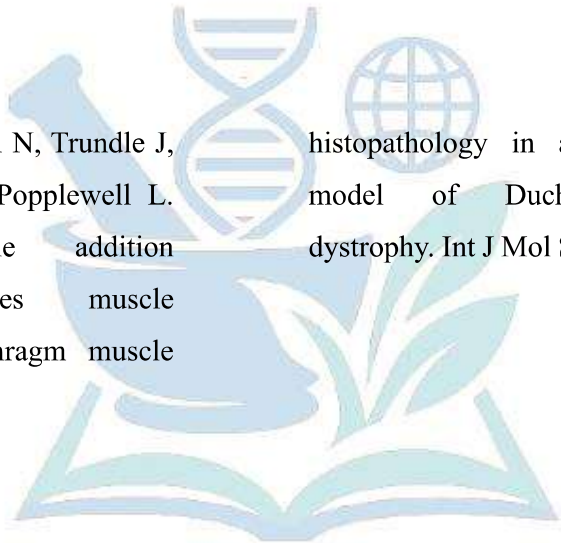
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