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Duvyzat (Givinostat) in Duchenne Muscular Dystrophy: Mechanisms, Clinical Impact, and Future Directions

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Keywords

Duvyzat, Histone Deacetylase inhibitors, Duchenne Muscular Dystrophy, Muscle Degeneration, Givinostat, FDA Approval.

Abstract

Duchenne Muscular Dystrophy is a chronic, progressive neuromuscular disorder characterized by muscle degeneration and weakness due to mutations in the dystrophin gene. Although there is no cure, emerging therapies such as histone deacetylase inhibitors offer promising avenues to slow disease progression. Duvyzat (givinostat), an orally active histone deacetylase inhibitor, has recently received FDA approval following results from the Phase 3 EPIDYS trial, which demonstrated a statistically significant improvement in motor function. Patients treated with Duvyzat showed a 1.25-second faster performance on the four-stair climb (4SC) test compared to placebo, and a 1.91-point higher north star ambulatory assessment score over 72 weeks. Duvyzat was also associated with reduced muscle fat infiltration on MRI. This review discusses the mechanism of histone deacetylase inhibition, clinical evidence supporting Duvyzat's efficacy, its safety profile, and implications for the future of Duchenne Muscular Dystrophy treatment. Continued research is essential to explore long-term outcomes and synergistic potential with gene-targeted therapies.

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1. Introduction

Duchenne Muscular Dystrophy (DMD) is a severe, X-linked neuromuscular disorder primarily affecting males, with an incidence rate of approximately 1 in 3,500 to 6,000 male births worldwide. The condition is characterized by progressive muscle degeneration due to mutations in the dystrophin gene, which encodes a critical protein responsible for maintaining muscle fiber integrity. Without dystrophin, muscle fibers become vulnerable to damage during contraction and relaxation, leading to muscle weakness, loss of function, and ultimately, premature mortality due to respiratory and cardiac failure [1], [2]. Currently, available treatments for DMD are limited, with corticosteroids being the primary intervention. While they provide temporary improvement in muscle function, they come with significant side effects. In recent years, histone deacetylase (HDAC) inhibitors, such as Duvyzat (givinostat), have emerged as promising alternatives as illustrated in figure 1. Duvyzat works by targeting HDACs, which regulate gene expression and muscle regeneration. Elevated HDAC activity in DMD patients contributes to muscle degeneration and inflammation [3].

By inhibiting HDACs, Duvyzat promotes the expression of beneficial genes, enhancing muscle regeneration and reducing fibrosis and inflammation. The approval of Duvyzat by the FDA was based on the Phase 3 EPIDYS trial, which demonstrated significant improvements in motor function, including a 1.25-second faster time on the four-step climb test and a 1.91-point improvement in the North Star Ambulatory Assessment (NSAA) score. These results highlight the potential of Duvyzat to slow disease progression and improve patient quality of life. This review explores the mechanisms underlying HDAC inhibition, the clinical evidence supporting the efficacy of Duvyzat, and the implications of its approval for future DMD therapies [4]. DUVYZAT (givinostat) is a histone deacetylase inhibitor approved for the treatment of Duchenne muscular dystrophy (DMD) in individuals aged 6 years and older. This medication is needed because it is the first nonsteroidal anti-inflammatory drug (NSAID) approved for DMD and applicable to all disease variants. The FDA approval of Duvyzat was based on the findings from the placebo-controlled Phase 3 EPIDYS study, which achieves its primary

endpoint, demonstrating that patients administered Duvyzat experienced a significant improvement in the duration required to complete the four-step stair climbing test, an assessment of motor function in DMD patients. Participants receiving Duvyzat exhibited reduced muscle fat and more effectiveness on physical fitness tests compared to those taking a placebo [5], [6].

The most frequent adverse effects reported in the trial included diarrhea, abdominal pain, thrombocytopenia, and elevated triglyceride levels. These side effects can be controlled by monitoring and adjusting the dose. DMD is a severe, X-linked neuromuscular disorder marked by progressive muscle degeneration and weakness. This condition results from a mutation in the gene encoding the cytoskeletal protein dystrophin. Dystrophin is a component of the dystrophin-glycoprotein complex which strengthens muscle fibers and protects them from injury during contraction and relaxation [7], [8].

Figure 1 illustrates the phases of development of Duvyzat. This condition mostly affects males and symptoms may increase and impair mobility. Ultimately, the cardiac and respiratory muscles are affected, resulting in premature mortality. The review will become the first post-approval synthesis of Duvyzat (Givinostat) in patients with Duchenne Muscular Dystrophy. In contrast to results of previous reviews that analyzed preclinical data or pharmacodynamics as individual entities, this article combines the results of clinical trials, real-world safety reports, develop new case reportage, and post-therapeutic perspectives. Critically assessing the role of Duvyzat in the dynamic treatment field, the aim of the present review is to assist both clinicians and researchers in the effective use of this agent and unmet research opportunities. Approximately 1 in 3500 - 6000 male births globally are affected by DMD [9], [10].

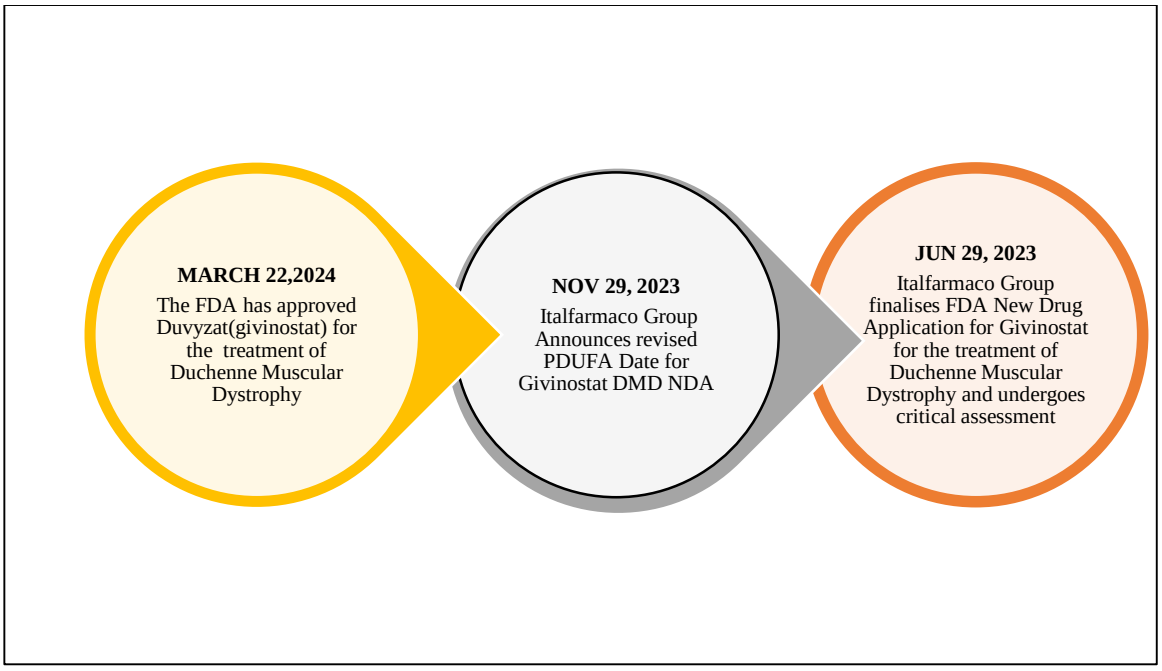

Figure 1: Duvyzat's development timeline.

This timeline illustrates key milestones in the regulatory journey of Duvyzat (givinostat) for Duchenne Muscular Dystrophy. It highlights the FDA application submission, the PDUFA date revision, and final approval granted on March 22, 2024 [11].

2. Methodology

Based on search criteria implemented in the PubMed, Scopus, and Google Scholar databases, a literature search was carried out in the period 2020- 2025. The keywords used were Duvyzat-, Givinostat-, Duchenne Muscular Dystrophy, HDAC inhibitors, and clinical trials. Medical papers were chosen according to their applicability to clinical efficacy, the mechanism of action, safety data, and the future prospects of duvyzat. Peer-reviewed articles, the outcome of clinical trials, and high-impact reviews were given preference. Only case reports and animal studies were included when they included novel mechanistically informative or translational relevance [12], [13].

3. Mechanism of Action

Duvyzat (givinostat) functions as a histone deacetylase (HDAC) inhibitor, targeting HDAC enzymes that regulate chromatin structure and gene expression. In Duchenne Muscular Dystrophy (DMD), HDAC activity is elevated, leading to suppression of key genes responsible for muscle regeneration and repair. By inhibiting HDACs, Duvyzat promotes epigenetic reprogramming, leading to enhanced satellite cell activation and muscle regeneration [14]. This reactivation of myogenic pathways helps to counteract muscle degeneration, fostering new myofiber formation and improving muscle tone. Furthermore, Duvyzat's inhibition of HDACs reduces inflammatory cytokine production and limits immune cell infiltration, addressing chronic inflammation that exacerbates muscle damage in DMD [15]. Preclinical

studies, including those using the mdx mouse model, have shown that Duvyzat significantly reduces fibrosis and muscle fat infiltration while improving muscle function and endurance. These effects suggest that Duvyzat not only mitigates disease progression but also promotes muscle repair through the restoration of normal gene expression patterns, highlighting its potential as a therapeutic option for DMD [16].

Duvyzat treats DMD by blocking histone deacetylases (HDACs), enzymes that block gene translation by altering the three-dimensional conformation of DNA inside cells. Elevated HDAC activity in DMD patients may inhibit muscle degeneration and inflammation. Duvyzat could slow down the progression of DMD disease, enhance muscle tone, and diminish muscle necrosis by suppressing HDACs. The pathogenesis of Duchenne muscular dystrophy (DMD) is shown in Figure 2 [17], [18].

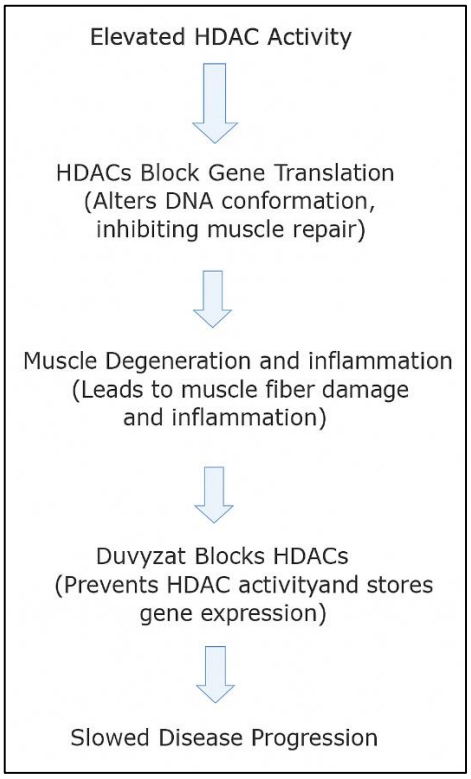

Figure 2: Pathogenesis of DMD.

diagram illustrates the pathogenic role of elevated HDAC activity in DMD and how Duvyzat intervenes. By blocking HDACs, Duvyzat restores gene expression, reducing muscle degeneration and inflammation to slow disease progression [19].

4. Dosage and Administration

Duvyzat (givinostat) is an oral suspension administered twice daily with food. The suspension should be well mixed, and the drug volume must be measured using the provided oral syringe. The recommended starting dose is based on body weight; 10–20 kg (22–44 lbs): 22.2 mg (2.5 mL) twice daily. 20–60 kg (44–132 lbs): 35.4 mg (4 mL) twice daily. ≥60 kg (132 lbs): 53.2 mg (6 mL) twice daily. The suspension should not be combined with other liquids [20]. Ensure that the bottle is shaken for at least 30 seconds before use.For patients with hepatic impairment (mild to moderate), a dose reduction may be necessary. For those with severe hepatic impairment, the use of Duvyzat should be avoided unless the potential benefits outweigh the risks.For patients with renal impairment, particularly those with severe renal dysfunction (creatinine clearance <30 mL/min), the dose should be carefully adjusted, or treatment should be discontinued if significant

This
adverse effects occur [21], [22].

Regular monitoring of renal function is advised, especially in patients with preexisting kidney conditions.The dosage may need to be adjusted if the patient experiences common side effects such as diarrhea, severe pain, thrombocytopenia (platelet count <150,000/mcL), or elevated triglyceride levels. If such side effects persist, the dose should be reduced, and treatment should be reconsidered based on clinical response [23], [24].

Figure 3 illustrates the composition of DUVYZAT, highlighting both its active and inactive ingredients. The active ingredient is givinostat, which is responsible for the therapeutic effect in Duchenne muscular dystrophy (DMD). The inactive ingredients include creamy flavour, glycerin, non-crystallising sorbitol solution, peach flavour, polysorbate 20, purified water, saccharin sodium, sodium benzoate, sodium hydroxide, tartaric acid, and tragacanth. These excipients serve various roles, such as stabilizing the formulation, enhancing taste, and ensuring proper consistency and solubility, thereby supporting the effective delivery and patient acceptability of the medication [25].

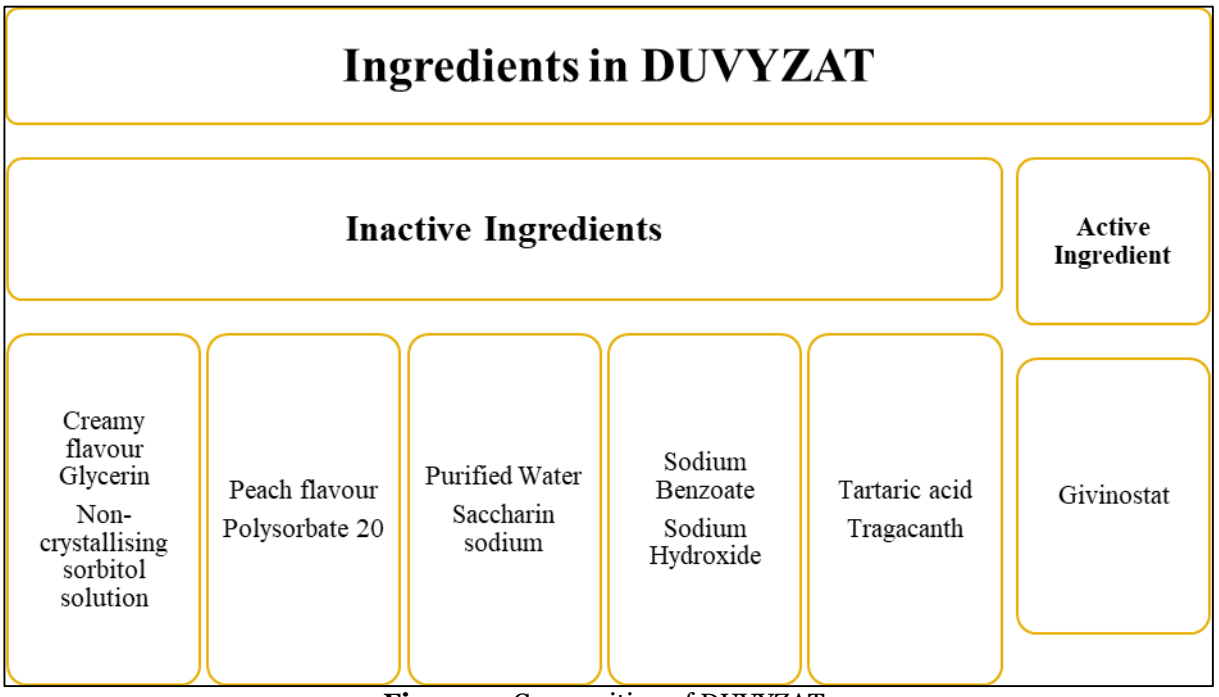

Figure 3: Composition of DUVYZAT.

This diagram presents the composition of Duvyzat, distinguishing between the active ingredient, givinostat, and various inactive ingredients that support formulation, flavor, and stability [26].

Dosage adjustments of Duvyzat may be necessary if a patient experiences diarrhea or severe pain and has a platelet count below 150,000 per microliter of blood in two tests conducted one week apart. Additionally, fasting measurements from two tests may indicate lower triglyceride levels, warranting dose modification. Depending on the patient's weight, if adverse effects persist even after a second dosage adjustment, Duvyzat treatment should be discontinued [27], [28].

5. Pharmacokinetics and Pharmacodynamics

Duvyzat (givinostat) is administered orally in the form of a suspension. After oral administration, givinostat is absorbed into the bloodstream with a bioavailability of approximately 70-80% when taken with food, which enhances absorption. The drug reaches peak plasma concentrations (Tmax) within 1–2 hours of administration [29].

5.1. Metabolism

Givinostat is extensively metabolized in the liver. It is primarily processed by CYP3A4, a major hepatic enzyme involved in the metabolism of various drugs. A portion of givinostat is also conjugated to form inactive metabolites. The hepatic metabolism of givinostat suggests that caution is needed in patients with liver impairment, as dose adjustments may be required to avoid accumulation [30], [31].

5.2. Half-Life

The elimination half-life of givinostat is approximately 6–10 hours, allowing for twice-daily dosing. This relatively short half-life supports the need for regular dosing to maintain therapeutic levels throughout the day [32].

5.3. Excretion

Givinostat and its metabolites are primarily eliminated via the feces, with a minor amount excreted through the urine. Less than 10% of the drug is excreted unchanged in the urine, indicating that renal clearance does not significantly contribute to the drug's overall elimination [33].

5.4. Pharmacodynamic Biomarkers

The biomarker profile for givinostat in the treatment of Duchenne Muscular Dystrophy (DMD) includes histone acetylation levels as an indirect marker of HDAC inhibition. Elevated acetylation at histone sites, particularly in skeletal muscle tissue, indicates that givinostat is modulating gene expression that supports muscle regeneration and reduces inflammation. Additionally, muscle fat infiltration, as assessed via MRI, has been shown to correlate with drug efficacy in reducing disease progression and improving muscle function. Serum creatine kinase (CK) levels, a marker of muscle injury, can also provide insights into the drug's impact on muscle health [34], [35].

By targeting HDAC enzymes, givinostat influences several molecular pathways, including muscle regeneration, inflammation, and fibrosis. These pharmacodynamic effects are closely tied to the clinical outcomes observed in DMD patients, where improvements in functional measures such as stair climbing velocity and motor function assessments (e.g., NSAA) are observed [36].

6. Clinical Safety and Efficacy

The approval of Duvyzat (givinostat) was supported by the results of the Phase 3 EPIDYS trial, a randomized, double-blind, placebo-controlled study involving 179 ambulatory male patients aged 6 years and older with

Duchenne Muscular Dystrophy (DMD). This trial assessed the efficacy of givinostat administered over 18 months. Participants were stabilized on corticosteroid therapy and randomly assigned to receive either givinostat or a placebo [37], [38].

6.1. Primary Endpoint

The primary endpoint of the study was the change in time required to complete the four-step climb (4SC), a commonly used measure of motor function in DMD. The results demonstrated that patients receiving Duvyzat showed a mean improvement of 1.25 seconds in the 4SC test compared to those on placebo, indicating a statistically significant slowing of disease progression [39].

6.2. Secondary Endpoints

The secondary endpoints included motor function assessments and quality-of-life measures. The North Star Ambulatory Assessment (NSAA) showed that the treated group exhibited an average increase of 1.91 points from baseline to 72 weeks compared to the placebo group, indicating better preservation of motor abilities [40]. Similarly, the cumulative loss-of-function analysis revealed that the number of functional items failed was significantly lower in the Duvyzat group (3.42 items) than in the placebo group (5.56 items), corresponding to a relative risk reduction of 39%. In the time-to-rise test, a change of −3.28 seconds (95% CI: −9.57 to 3.02) suggested some improvement in mobility, although statistical significance was not achieved after multiplicity adjustment. Overall, these findings indicate that Duvyzat may help slow the decline in physical capabilities in ambulatory boys with Duchenne muscular dystrophy (DMD), particularly with regard to stair climbing and overall motor function [41], [42].

6.3. Safety Profile

The safety profile of Duvyzat was generally well-tolerated, with the most common adverse effects being diarrhea, abdominal pain, and thrombocytopenia (low platelet count), while elevated triglyceride levels were also observed in some patients. These side effects were manageable through dose adjustments and regular monitoring. Platelet counts were checked biweekly for the first two months, followed by monthly monitoring for the next three months, and quarterly thereafter. Triglyceride levels were assessed periodically, with dose adjustments made if levels exceeded 300 mg/dL. Long-term monitoring is advised to ensure continued safety, particularly for cardiac health, given the potential risk of QT interval prolongation and electrolyte imbalances [43].

The FDA approved DUVYZAT after a study involving 179 male patients with DMD aged 6 years and older. DUVYZAT was assessed in a randomized, placebo-controlled trial in 179 ambulatory male patients with DMD who were stable after steroid medication. This randomized, double-blind, placebo-controlled trial offers significant evidence to support FDA approval of DUVYZAT in March 2024 [44], [45].

The outcome of the EPIDYS research and its subsequent FDA clearance signifies progress in DMD therapy, particularly since DUVYZAT is the first non-steroidal medication approved for this condition. Ongoing assessment of use in various clinical characteristics and younger age groups. This is an open-label, long-term research of givinostat in all patients with DMD (Duchenne's muscular dystrophy) patients who have previously participated in givinostat trial. Eligibility for the study included ambulatory males aged ≥ 6 years at randomization exhibiting clinical symptoms or signs characteristic of DMD such as proximal muscle weakness, Gowers' maneuver, and elevated serum creatinine kinase levels all of which must have been present at screening. Additionally, a DMD diagnosis must be confirmed through genetic testing [46], [47].

6.4. Current Clinical Study

Boys who completed 18 months of follow-up were invited to participate in an ongoing study (NCT03373968). All participants in this study will also receive Duvyzat. ULYSSES (NCT05933057), will enroll 138 anonymous boys with DMD, ages 9 to 17 years. The primary outcome of ULYSSES is a change in the total score on the Upper Extremity Performance of Upper Limb 2.0 (an instrument that measures upper extremity function). Lung function, vital signs, and side effects will be assessed [48], [49].

7. Case Studies

A comprehensive review of clinical studies and case reports is provided as an in-depth analysis of Duvyzat and HDAC inhibitors' clinical relevance and effectiveness in treating Duchenne Muscular Dystrophy (DMD). The aim is to enhance patient outcomes and contribute to ongoing efforts [50].

7.1. Case Study 1

A study investigated the effects of lipin1 restoration on improving dystrophic phenotype in mice. To clear the role of lipin1 in dystrophic muscle, the researchers administered AAV1-lipin1 via intramuscular injection. The results showed that treatment effectively healed the membrane, inhibited myofiber death, inflammation, and fibrosis, and improved locomotor function in the label as well as isometric and eccentric muscle force production in situ in all animals. This treatment may be a therapeutic target to stabilize the sarcolemma and prevent muscle degeneration and necrosis. Lipin1-mediated sarcolemmal stabilization represents a novel approach to the treatment of DMD [51], [52].

7.2. Case Study 2

Researchers investigated the efficacy of long-term treatment of mdx mice, a mouse model of Duchenne muscular dystrophy (DMD) with multiple doses of the HDAC inhibitor givinostat. The results showed that givinostat had a positive effect on functional and histological parameters in the range of 5-10 mg/kg/d, with a decreased effect at a dose of 1 mg/kg/day [53].

Dosage studies suggested that effective treatment with givinostat requires injections of more than 1 mg/kg/d are required for a therapeutic effect of givinostat, suggesting a recommendation of doses 5-10 mg/kg/d in the mdx model. PK/PD analysis determines expected drug exposure. This study also found that givinostat had a 50% effect on histological lesions, which is required for increased efficacy. This study supports the inclusion of givinostat in clinical trials in children with DMD. Future studies will focus on understanding the interactions of givinostat with other therapeutic interventions to optimize the use of combination therapy [54], [55].

7.3. Case Study 3

A study was designed to evaluate the histological effects of Givinostat in boys with DMD aged 7 to 11 years. Twenty boys were given Givinostat for 12 months, and experience muscle biopsy was taken to measure muscle tone and fibrotic tissue. The results showed that Givinostat treatment increased muscle mass in biopsies, reduced tissue size, and reduced tissue necrosis and fat replacement. The sample size of this study is not large enough to draw definitive conclusions, but it does suggest that treatment with Givinostat beyond one year may affect histological disease in ambulant DMD boys [56], [57].

7.4. Case Study 4

Givinostat and steroids were administrated for 15 weeks in DMD rat models and their efficacy was assessed in terms of preservation of strength and functional failure and histological examinations. Givinostat treatment increased maximal normalized strength to levels comparable to those of healthy rats with a dose effect. It also improved muscle mass and endurance outperforming steroids in some tests [58], [59].

7.5. Case Study 5

A phase 3 clinical trial evaluated the safety and efficacy of givinostat, an orally active histone deacetylase inhibitor, in ambulant boys with Duchenne muscular dystrophy (DMD). The study included 179 boys aged 6 years and over who were treated for 18 months. The results showed significant changes in the duration of the 4-step staircase and a positive outcome, supporting the widespread use of MRI biomarkers in clinical trials [60].

7.6. Case Study 6

Studies showed that reprogramming miPSCs into MPC can repair muscle damage and restore dystrophin in diabetic cardiomyopathy (DMD) muscles. Givi-MPC exhibited enhanced growth and migration potential, reduced reactive oxygen species, and restored dystrophin and activated stem cells in Mdx/SCID mice [61].

7.7. Case Study 7

Researchers explore advances in understanding the mechanisms of Duchenne muscular dystrophy (DMD) and in developing treatments to slow the disease. Treatment initially focuses on the genetic abnormalities that cause DMD, such as loss or reduction of dystrophin. Genetic therapies, such as exon skipping and gene editing, hold promise for treating dystrophin disease. Adeno-associated viruses (AAVs) have shown promising results in preclinical and clinical studies. Secondary therapies aim to preserve muscle function and improve quality of life by reducing DMD symptoms and complications. Supportive care targeting calcium dysregulation, histone deacetylase, and redox imbalance is essential for maintaining overall health [62], [63].

7.8. Case Study 8

A recent study shows that targeting microRNA-25 (miR-25) using adeno-associated virus serotype 9 (AAV9) can alleviate cardiac and skeletal muscle dysfunction in a model of Duchenne muscular dystrophy (DMD). Intramuscular injection of a potent miR-25 tough decoy (TuD) improves cardiac function, reduces fibrosis, and improves skeletal muscle function in aged mdx/utrn (+/−) mice. miR-25 inhibition increases SERCA2a expression, improves calcium handling, and reduces TGF-β-mediated fibrotic signaling [64].

7.9. Case Study 9

Myostatin inhibition therapy is promising in treating muscle diseases, but clinical trials have not shown any significant changes in disease. To improve outcomes, patients' physical abilities and activities should be considered, and molecular targets like Mss51 should be targeted. Exercise or a combination of medications that improve motor function may also be helpful [65].

7.10. Case Study10

A study using the zebrafish DMD mutant strain SAPJE as an animal model of Down syndrome (DMD) demonstrated that a library of epigenetic small molecules could be used to correct the embryonic-larval stage of the mutant zebrafish. Using multiple muscle birefringence measurements to assess the effects of small amounts of muscle repair, the researchers identified a library of candidate compounds that could improve skeletal muscle structure in the mutant zebrafish. They identified a specific combination of two HDACi compounds, oxamflatin and salermide, that ameliorated skeletal muscle degeneration in the mutant zebrafish. The combination also increased the level of histone H4 acetylation in zebrafish larvae. This study adds to the growing evidence that epigenetic small molecules may be promising candidates for treating DMD [66], [67].

7.11. Case Study 11

The study found that reprogramming hiPSCs into muscle progenitor cells (MPC) using, a histone deacetylase inhibitor givinostat to treat diabetic retinopathy (DRD) showed improved proliferation and migration ability. These MPCs were shown to strengthen and repair dystrophin, reduce inflammation, and produce new muscle fibers [68].

7.12. Case Study 12

A study proves YSR734, a covalent HDAC inhibitor active against in acute myeloid leukemia and Duchenne muscular dystrophy. It targets HDAC2Cys2742 using a 2-aminobenzanilide Zn2+

chelate and a pentafluorobenzenesulfonamide electrophile. It shows nM potency against HDAC1–3 and sub-μM activity in MV4–11 cells, with limited cytotoxicity against healthy fibroblasts [69].

7.13. Case Study 13

Taldefgrobep alfa is an anti-myostatin protein that blocks myostatin signaling. It has been shown to reduce myostatin and increase muscle mass in animals, including dystrophic mice. Clinical studies in dystrophic muscular dystrophy (DMD) show that taldefgrobep alfa is effective and can increase muscle mass. However, the program was discontinued in 2019 because it did not meet the treatment evaluation criteria [70].

7.14. Case Study 14

A study shows that dystrophic mice deficient in a skeletal muscle-specific HDAC4 gene (mdx; KO mice) exhibit a threefold increase in Histone deacetylase4, which plays a role in depression. Loss of HDAC4 in skeletal muscles leads to increased muscle weakness and degeneration, resulting in muscle dysfunction. Defective repair in muscles and tendons is responsible for the Mdx; KO genotype. Restoring HDAC4 levels in mdx; KO muscles can rescue the Mdx; KO phenotype. Given the role of Trim72mRNA in muscle repair, this study suggests that stimulating HDAC4's cytoplasmic functions may be beneficial in muscular dystrophy treatments [71], [72].

8. Safety and Adverse Effects

Duvyzat (givinostat) has shown a generally manageable safety profile in clinical trials, although some adverse effects were reported. Common side effects observed in the Phase 3 EPIDYS trial included [73].

8.1. Gastrointestinal Effects

Gastrointestinal effects were among the most commonly reported adverse events with Duvyzat treatment. Diarrhea occurred in a significant proportion of patients, making it one of the most frequent side effects. Abdominal pain and vomiting were also noted, particularly during the early stages of therapy, but these events were generally manageable with supportive care and monitoring [74].

8.2. Hematological Effects

Thrombocytopenia (low platelet count) was noted, which may increase the risk of bleeding and bruising. Patients undergoing treatment with Duvyzat should have their blood counts monitored regularly, especially during the first few months of therapy. If thrombocytopenia becomes severe, the dose should be adjusted or treatment may need to be discontinued [75].

8.3. Metabolic Effects

Elevated triglycerides were another commonly observed adverse event associated with Duvyzat, posing a potential risk for cardiovascular complications. To mitigate this, patients are advised to undergo periodic monitoring of triglyceride levels, typically at 1-, 3-, and 6-months following treatment initiation. If triglyceride levels exceed 300 mg/dL, dose adjustments should be implemented to ensure safety and reduce long-term cardiovascular risk [76], [77].

8.4. Cardiac Effects

QT interval prolongation is a potential safety concern with Duvyzat, as it may extend the corrected QT interval (QTc) on the electrocardiogram (ECG) and thereby increase the risk of ventricular arrhythmias. Caution is advised, and treatment should be avoided in patients with a known high risk for such arrhythmias. Regular ECG monitoring is recommended throughout therapy, and if the QT interval prolongation exceeds 500 ms, or if the increase from baseline is greater than 60 ms, discontinuation of the drug is warranted to prevent serious cardiac complications [78].

9. Warnings and Contraindications

Duvyzat should be administered with caution in patients with hepatic or renal impairment, as well as in special populations such as pregnant or lactating women. In cases of hepatic impairment, dose adjustments may be required for patients with mild to moderate dysfunction, while severe hepatic impairment is considered a contraindication [79]. For individuals with severe renal impairment (creatinine clearance <30 mL/min), use of Duvyzat should generally be avoided unless the potential therapeutic benefit clearly outweighs the risks. With respect to pregnancy and lactation, available data are limited; however, animal studies have indicated potential risks such as reduced fetal growth and labor complications. Therefore, use during pregnancy should be restricted to situations where it is absolutely necessary, and caution is also advised during lactation [80].

10. Management of Adverse Effects

Duvyzat therapy for Duchenne muscular dystrophy is generally well tolerated, but several adverse effects require close monitoring and management. Dose adjustments or discontinuation may be necessary in cases of severe diarrhea, vomiting, thrombocytopenia, or elevated triglyceride levels, and patients experiencing significant side effects should be monitored carefully and treated with supportive care. Regular assessments, including blood counts, liver function, lipid panels, and QTc intervals, are essential to detect complications early [81]. Commonly reported side effects include dizziness, nausea, vomiting, elevated triglycerides, and thrombocytopenia, which can arise from bone marrow suppression leading to reduced blood cell production, anemia, and neutropenia. Blood counts should be monitored every two weeks during the first two months of therapy, monthly for the following three months, and then every three months thereafter. If thrombocytopenia develops, the dose should be adjusted or treatment discontinued, and clinical signs such as excessive bleeding, easy bruising, petechiae, or blood in stool or urine should prompt immediate medical consultation [82].

Despite its therapeutic potential, Duvyzat poses

several risk factors that must be considered to optimize safety and effectiveness. Elevated triglyceride levels are a major concern, as they increase the risk of cardiovascular disease and stroke; thus, triglycerides should be monitored at 1, 3, and 6 months after initiation and every six months thereafter, with therapy adjusted or discontinued if levels exceed 300 mg/dL. Gastrointestinal disturbances such as nausea, vomiting, and diarrhea are also common, and patients should remain well hydrated and monitor symptom severity, with dose adjustments considered if supportive care is insufficient [83]. Cardiac risks include QT interval prolongation, which increases the likelihood of ventricular arrhythmias; therefore, treatment should be avoided in patients with pre-existing heart disease, arrhythmia risk, or electrolyte imbalances, and ECG monitoring is required, with discontinuation if QT prolongation exceeds 500 ms or if the increase from baseline is greater than 60 ms. Finally, the safety of Duvyzat in pregnancy and lactation remains uncertain, as animal studies indicate potential risks including reduced fetal growth and labor complications, and therefore its use should be avoided in these populations unless absolutely necessary [84].

11. Current Therapies for DMD

It is important to consult a doctor who specializes in neuromuscular disease when considering DMD treatment. Although there is currently no cure for DMD, certain medications can control symptoms and slow the progression of the disease. Corticosteroids, such as prednisone, are often used to improve muscle tone and function. Recently, the FDA has approved drugs such as eteplirsen (Exondys 51) and golodirsen (Vyondys 53) to treat patients with specific genetic mutations. Supportive care, including physical therapy, respiratory care, and cardiac care, remains important in managing the condition and improving quality of life [29,30,31,32]. Some of the therapies are reported in Table 1 [85].

11.1. Glucocorticoids

Corticosteroids, such as prednisone and deflazacort (trade name Calcort) are one of the main treatments for Duchenne Muscular Dystrophy (DMD). These drugs are known to weaken muscles, improve muscle strength temporarily, and can delay walking for years. The usual dose for prednisone is 0.75 mg/kg/day and for deflazacort at a dose of 0.9 mg/kg/day. The choice of these two glucocorticoids may depend on their availability, cost, and side effects. Long-term use of glucocorticoids can cause side effects such as weight gain, bone fragility, and growth suppression [86].

11.2. Exon-Skipping Treatments

Exon-skipping treatments are a class of drugs designed to prevent certain exons from being shipped during the splicing of the pre-mRNA transcript of the dystrophin gene. This can keep production from working, but some work well. Eteplirsen (Exondys51) was the first FDA-approved drug of its kind to treat people with DMD patients who have a confirmed exon 51 translocation. It is administered as a weekly intravenous infusion. Golodirsen (brand name Vyondys 53) and viltolarsen (brand name Viltepso) are similar drugs approved for patients with exon 53 and exon 53 transition mutation, respectively [87].
Casimersen (brand name Amondys 45), is approved for use in people with DMD who have proven mutations that cause exon 45 skipping. These treatments are mutation-specific and therefore suitable for certain DMD patients. The effectiveness of exon-skipping therapy in DMD histology is currently under investigation, and is generally successful with few side effects [88].

11.3. Supportive Therapy

Supportive therapy is important in the treatment of DMD and includes physical therapy, occupational therapy, and respiratory therapy. Stretching and strengthening routines are essential components of physical therapy because they maintain muscle function and prevent contractures. Occupational therapy helps to maintain independence in daily living. As the disease progresses, respiratory therapy becomes more important because the respiratory muscles are weaker, and interventions may include cough assist devices night time breathing, or delayed tracheostomy [90].

11.4. Cardiovascular Management

Due to the prevalence of myocardial pathology in these patients, cardiac management is an important aspect of DMD treatment. Angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and aldosterone antagonists are common medicines used to treat the early signs of heart failure. Periodic monitoring with echocardiography and cardiac MRI is recommended to guide treatment [91].

11.5. Bone Health

Bisphosphonates are often used to treat osteoporosis, and long-term glucocorticoids can lead to osteoporosis. Calcium and vitamin D supplements are also recommended to improve bone health [92].

11.6. Experimental Treatments

Several experimental treatments for DMD are currently being investigated. These include gene therapy designed to insert copies of the dystrophin gene into muscle cells. Trials of micro-dystrophin gene therapy are ongoing, and while initial results are promising, these treatments have not yet been approved by the FDA [93].

Gene therapy is one of the best ways to treat DMD. This approach involves inserting genetic material into a patient's body to replace the defective or missing dystrophin gene. Scientists are investigating different methods, such as using adeno-associated viruses (AAVs) as vectors to deliver the correct genes to the muscles. While clinical trials have shown some success in improving muscle mass, significant challenges still need to be overcome before gene therapy can be considered as a treatment, including blocking the vectors to prevent all muscle pain and long-term expression of the gene [94].

Other experimental strategies include the use of dystrophin modification, myostatin inhibition, and stem cell therapy. Utrophin is a protein similar to dystrophin, and increasing its expression in muscle tissue may compensate for the lack of dystrophin in DMD. Myostatin inhibitors are designed to increase muscle mass and strength because myostatin is a negative regulator of muscle contraction [95].

11.7. Stem Cell Therapy

Stem cell therapy is another area of research in treating DMD. The idea is to turn stem cells into muscle cells that can differentiate, regenerate muscle tissue, and restore dystrophin production for patients. While some progress has been made in understanding how stem cells can be directed to become muscle cells, translating this into a treatment for DMD is still a work in progress, with a lot of science and detailed work to be done Stem cell therapy research is investigating the ability of different types of stem cells to regenerate muscle tissue [96].

11.8. Medications for Specific Mutations

Ataluren (brand name Translarna) is a drug designed for patients with DMD with malignant transformation, which accounts for 10-15% of pain in the population. It promotes the read-through of premature stop codons in mRNA, resulting in full-length, functional dystrophin. Ataluren is approved in some countries outside the United States but is not yet FDA-approved [97].

11.9. New Therapies

Newer therapies not yet FDA-approved, include CRISPR/Cas9 and other gene-editing techniques that can genetically changes in DNA. Antisense oligonucleotides (AONs) are also being investigated to modulate splicing and reverse transcription of the dystrophin gene [98].

11.10. Investigational Drug

Agamree is an investigational drug that has not been approved by the FDA. It is a recombinant adeno-associated virus that delivers a short version of the dystrophin gene into muscle cells (micro-dystrophin). AGAMREE is a corticosteroid approved for the treatment of Duchenne muscular dystrophy (DMD) in individuals aged 2 years and older. The treatment is currently undergoing clinical trials to evaluate its safety and effectiveness in people with DMD [99].

Duchenne Muscular Dystrophy (DMD) treatment is individualized and based on genetic diversity and clinical presentation. Glucocorticoids are used, but mutation therapies are being developed. Supportive care is crucial for managing symptoms and quality of life. Research and clinical trials are ongoing to find a cure, but these treatments are still in the research or trial phases [100].

This Figure 4 outlines available therapies for Duchenne muscular dystrophy (DMD), categorized by therapy type, patient eligibility, and treatment effectiveness. It emphasizes that while most treatments offer limited dystrophin restoration or symptom management, eligibility often depends on specific genetic mutations or clinical criteria [89].

Therapy	Eligibility	Effectiveness
•Corticosteroids (e.g., prednisone, deflazacort)	•Most patients with DMD	•May slow muscle degeneration
•Calcort (Deflazacort)		•Similar to other corticosteroids
•Exondys (Eteplirsen)	•Most patients with DMD	• Dystrophin is produced in a small number of patients
•Vyondys (Golodirsen)	•Patients with confirmed mutations are eligible for exon 51 skipping	•Dystrophin is produced in a small number of patients
•Viltepso (Viltolarsen)	•Patients with confirmed mutations are eligible for exon 53 skipping	•Dystrophin is produced in a small number of patients
•Amondys 45 (Casimersen)	•Patients with confirmed mutations are eligible for exon 53 skipping	•Dystrophin is produced in a small number of patients
•Cardiac medications (e.g., ACE inhibitors, beta-blockers)	•Patients with confirmed mutationare eligible for exon 45 skipping	•Manages heart-related symptoms
•Physical Therapy	•Patients with cardiac involvement	•Improves mobility and delays contractures
•Experimental gene therapy	•All patients with DMD	•Varies; still under investigation
•Agamree (Poloxamer)	•Patients selected in clinical trials	•Experimental; efficacy not established.

Figure 4: Overview of current and emerging therapies for Duchenne muscular dystrophy, their eligibility, and relative effectiveness.

12. Plan for Distributing Duvyzat

PantheRx® Rare, a healthcare company specializing in rare diseases, will manage the distribution of DUVYZAT. Due to the rarity of Duchenne muscular

dystrophy (DMD) and the complexity of the payment process, patients, caregivers, and doctors often work with a specialty pharmacy to navigate treatment access. To support the community, several programs are available to help patients receive treatment once insurance evaluations are complete. These programs include $0 co-payments for patients with commercial insurance and options for eligible patients who experience delays in starting treatment due to insurance or other factors, allowing them to switch doctors or explore alternative therapies, including transplants [101].

13. Challenges and Future Perspectives

Duvyzat is a drug investigated for the treatment of Duchenne muscular dystrophy (DMD), a severe form of muscular dystrophy characterized by fast muscle degradation. The approval process for any new drug, including Duvyzat, involves several challenges and future perspectives that need to be considered [102].

13.1. Challenges

The approval of Duvyzat (givinostat) for Duchenne muscular dystrophy (DMD) faces multiple challenges but also opens avenues for future developments. Key challenges include demonstrating significant efficacy in improving or stabilizing muscle function, ensuring long-term safety with minimal adverse effects for patients requiring lifelong treatment, and designing robust clinical trials that can provide compelling evidence despite the rarity of DMD and patient heterogeneity [103]. Navigating complex regulatory requirements from agencies like the FDA and EMA, providing comprehensive preclinical and clinical data, and addressing specific regulatory concerns further complicate the approval process. Additionally, genetic and phenotypic variability among patients necessitates identifying predictive biomarkers for treatment response. Economic considerations, including cost-effectiveness, pricing, reimbursement, and convincing healthcare systems of the drug's value, are critical to ensuring broad patient access once approved [104].

13.2. Future Perspectives

Duvyzat, a novel therapeutic for Duchenne Muscular Dystrophy (DMD), has demonstrated promising clinical results by improving muscle function and slowing disease progression, offering potential to significantly enhance patient quality of life. Its approval by regulatory agencies like the FDA and EMA could expedite progress in neuromuscular research, validating therapeutic targets and mechanisms [105]. Future developments will focus on biomarker identification to predict and monitor treatment response, exploring combination therapies with gene- or exon-skipping treatments, and conducting long-term follow-up studies to assess durability and safety. Patient-centered approaches, including involvement of patients and caregivers, are essential to address their needs holistically. Regulatory flexibility and global accessibility are also crucial to ensure equitable distribution and timely access, particularly in rare diseases like DMD. The future of Duvyzat depends on collaborative efforts among researchers, regulators, healthcare providers, and patient organizations to overcome challenges and maximize patient benefit [106].

Conclusion

The FDA approval of Duvyzat (givinostat) for Duchenne Muscular Dystrophy (DMD) marks an important milestone in treatment development. As the first non-steroidal HDAC inhibitor approved for DMD, Duvyzat has demonstrated substantial benefits in clinical trials, including improvements in motor function and a slower disease progression. However, while these results are promising, the treatment still faces several challenges that need to be addressed moving forward. Long-term effects remain a key concern, as the durability of Duvyzat's benefits beyond the 18-month treatment period of the EPIDYS trial is not yet clear. Moreover, its safety profile, although generally well-tolerated, includes gastrointestinal issues, thrombocytopenia, and elevated triglycerides, which may impact patient quality of life and require careful monitoring and dose adjustments. Cost and accessibility are also significant barriers to the widespread use of Duvyzat. The high cost of treatment could limit access for many families, particularly in lower-income regions. Additionally, Duvyzat's efficacy needs to be assessed in comparison to other emerging therapies, such as exon-skipping drugs and gene therapies that target the root cause of DMD. The combination of these therapies with Duvyzat could enhance its therapeutic impact, but this requires further investigation. As Duvyzat becomes part of the broader treatment landscape for DMD, future research should focus on long-term safety data, biomarker identification 87 to personalize treatment, and the exploration of combination therapies. Additionally, ensuring global accessibility and patient-centered approaches will be crucial to maximizing the drug's impact. In conclusion, while Duvyzat offers a promising new treatment option, ongoing research, and a balanced approach to its use, cost, and accessibility are essential to fully realize its potential in improving the lives of those affected by Duchenne Muscular Dystrophy. Although the EPIDYS trial by Duvyzat confirms that the drug enhances functionality, the variation of its secondary outcomes among ages poses doubts on the extent of effectiveness of the drug. In addition, its comparative efficacy to exon-skipping therapies is poorly studied in direct comparisons. The next step of research should be given the consideration of combination strategy to combine the specific mechanisms such as epigenetic modulation, gene correction in a synergistic way.

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Ethical Approval and Consent to Participate

Ethical approval was not required for this study as it did not involve human participants, animals, or identifiable personal data.

Consent for Publication

I hereby give my consent for the publication.

Availability of Supporting Data
All data will be provided in the manuscript file.

Competing Interests
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