To Treat Duchenne Muscular Dystrophy with AGAMREE (VAMOROLONE)

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***Abstract*—The dystrophin protein, which is necessary for safeguarding muscle cells during contraction, is not produced in Duchenne due to mutations in the DMD gene. Patients experience increasing muscular degeneration and atrophy as a result. Over time, chronic inflammation plays a role in the development of this damage. For individuals with Duchenne muscular dystrophy (DMD) who are two years of age or older, the dissociative steroid agamree (vamorolone) is used to maintain muscle function and reduce inflammation. Santhera Pharmaceuticals sold the rights to market Agamree in North America to Catalyst Pharmaceuticals. The treatment was first created by ReveraGen BioPharma. Current clinical management guidelines state that mechanical ventilatory assistance is typically started at night to address hypoventilation and sleep-related breathing issues sometime in the second to third decade of a patient's life. All patients eventually require help breathing, even throughout the day, to survive as their respiratory muscles continue to degenerate. Because of the disease's morbidity and mortality, DMD is linked to a significant burden on afflicted individuals, unpaid caregivers, and society at large. Mainly, the DMD is caused by a genetic mutation in the DMD gene causes dystrophin, a protein necessary for muscle function, to be absent, leading to progressive muscle weakness and degeneration. This is the cause of Duchenne muscular dystrophy (DMD). The symptoms include in DMD include Muscle weakness, regular falls, walking on tiptoe, difficulty standing up, delayed onset of sitting, etc. Vamorolone is a corticosteroid class drug, and the formulation present in the market is named Agamree. And the administration form of this formulation is oral suspension.**

***Keywords*— DMD, Agamree, corticosteroid, Vamorolone, address hypoventilation.**

I. INTRODUCTION

For individuals with Duchenne muscular dystrophy (DMD) who are two years of age or older, the dissociative steroid agamree (vamorolone) is used to maintain muscle function and reduce inflammation. Santhera Pharmaceuticals sold the rights to market Agamree in North America to Catalyst Pharmaceuticals. The treatment was first created by ReveraGen BioPharma.

The dystrophin protein, which is necessary for safeguarding muscle cells during contraction, is not produced in Duchenne due to mutations in the DMD gene. Patients experience increasing muscular degeneration and atrophy as a result. Over time, chronic inflammation plays a role in the development of this damage.

Prednisone and Emflaza (deflazacort) are two examples of the powerful anti-inflammatory drugs known as corticosteroids, which imitate the actions of the hormone cortisol. They are believed to reduce inflammation and help maintain muscle mass, but long-term use is linked to a variety of negative effects. Agamree is a novel dissociative corticosteroid that aims to minimize the negative effects of corticosteroids while optimising their positive effects.

Numerous cellular pathways are activated as a result of interactions between cortisol and corticosteroids and cortisol receptors. While some of these routes can result in undesirable side effects, others have anti-inflammatory properties. By interacting with cortisol receptors, agrammatic avoids the adverse effects of standard corticosteroids while promoting anti-inflammatory pathways.

For instance, Agamree suppresses NF-kb pathways, which are implicated in causing inflammation, just like other corticosteroids do. Additionally, it aids in cell membrane stabilisation while avoiding transactivation, which is a rise in gene activity associated with other corticosteroids that is believed to be a contributing factor to adverse effects. By inhibiting activation at proteins known as mineralocorticoid receptors, which is not seen with other drugs in this family, agamemath may also assist in maintaining cardiac function in DMD [1].

With an estimated frequency of 1 in 3800–6300 live male births, Duchenne muscular dystrophy (DMD) is a neuromuscular illness that is X-linked recessive and extremely disabling. DMD is characterised by gradual muscle degeneration brought on by a lack of dystrophin protein, which can lead to catastrophic

cardiac and pulmonary problems, delayed motor milestones, and loss of independent ambulation.

Current clinical management guidelines state that mechanical ventilatory assistance is typically started at night to address hypoventilation and sleep-related breathing issues sometime in the second to third decade of a patient's life. All patients eventually require help breathing, even throughout the day, to survive as their respiratory muscles continue to degenerate. Because of the disease's morbidity and mortality, DMD is linked to a significant burden on afflicted individuals, unpaid caregivers, and society at large.

Life expectancy at birth in DMD has increased in recent decades, according to reports from multiple studies. Nevertheless, estimates differ significantly between samples, and no study has examined the literature on life expectancy in this indication to far. Furthermore, because of better care standards, especially the regular use of mechanical ventilatory support in later stages of disease, certain published figures might no longer be applicable. There may be considerable ambiguity surrounding the current survival outlook when medical professionals speak with the relatives of recently diagnosed patients. Our study's goal was to perform a comprehensive evaluation and analysis of the life expectancy of Duchenne muscular dystrophy by Agamree (vamorolone) to help close this data gap [2].

Causes:

A genetic mutation in the DMD gene causes dystrophin, a protein necessary for muscle function, to be absent, leading to progressive muscle weakness and degeneration. This is the cause of Duchenne muscular dystrophy (DMD).

Symptoms:

Early Warning Signs and Symptoms (usually ages 2-4):

1. Muscle Weakness:
a. Progressive weakness that first affects the legs and pelvis before spreading to other regions.
b. Having trouble running, walking, and climbing stairs.
c. Difficulty standing up after sitting or lying down (Gower's sign).
2. Problems with motor skills:
a. Regular falls.
b. Waddling gait, which involves spreading one's legs apart.
c. Walking on tiptoe.
3. Physical Appearance: a. Pseudohypertrophy, or enlarged calf muscles.
4. Additional Indications:
a. Delayed onset of sitting, walking, and talking milestones.
b. Behavioural and learning challenges.
c. Pain and stiffness in the muscles.
5. Later Stages:
a. Cardiomyopathy, or heart issues.
b. Issues with the breathing system (weakened muscles).
c. Scoliosis, or the spine's curvature.
d. Stiff joints, or joint contractures.
e. Reduced mobility.

The diagnosis is:

1. First Assessment and History:
a. Health History and Physical Examination:

In addition to asking about the child's symptoms and family history of muscular dystrophy, the doctor will conduct a physical examination to evaluate muscle strength and search for symptoms such as Gowers' sign, which involves using hands to "walk" up the legs to stand up, and calf enlargement.

b. Neurological Exam: To evaluate reflexes and muscle strength, a neurological examination will be performed.
2. Examinations of the Blood:
a. Creatine Kinase (CK) Test: A powerful marker of DMD is elevated levels of CK, an enzyme generated by injured muscle tissue.
b. Genetic Blood Test: This test looks for mutations in the dystrophin gene, which is the root cause of DMD, by analysing DNA.
3. If required, a muscle biopsy:
a. A muscle biopsy may be carried out if genetic testing yields conflicting results or if the child's symptoms are unusual.
b. To check for symptoms of DMD, such as the lack of dystrophin protein, a tiny sample of muscle tissue is removed and seen under a microscope.
4. Additional Examinations:
a. Electrocardiogram (ECG/EKG): An ECG is performed to assess cardiac rhythm and function because DMD can impact the heart.
b. Echocardiography: This type of cardiac ultrasound can identify structural alterations in the heart, including valvular heart disease.
c. Electromyography (EMG): This test helps distinguish between nerve and muscle injury by measuring the electrical activity of muscles.
d. Imaging Studies: To find scoliosis and check for

anomalies in the heart and other organs, CT or MRI scans might be utilised.

Brand name:	Agamree
Chemical name:	Vamorolone
Usage:	Therapy for Duchenne Muscular Dystrophy
Administration:	Oral liquid suspension
Formula:	C22H28O4
Other names:	: VBP; VBP-15; 17α,21-Dihydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione
Trade names:	Agamree
Class:	Corticosteroids

Fig 1. Physiotherapy for mental well-being during DMD.

Ayurvedic perspective on DMD:

- Classification:

In Ayurveda, DMD is viewed through the concepts of genetic disorders ("Bijabhagavayay dushtijanya Vyadhi") and inherited diseases ("Adibalapravritta Vyadhi") rather than being directly linked to any particular disease entity.

- Pathogenesis:

Genetic abnormalities and gamete deficiencies ("Shukra-short dosha") are thought to be the cause of the disease's development, which vitiates the Vata dosha.

- Thanasamshraya (Location):

Muscle tissue is where the sickness is primarily found ("Mamsa Dhatu").

- Vita Dosha Vitiation:

Muscle tissue impairment ("Mamsa-dhatvagni") and the development of defective muscle tissue are caused by vitiated vata dosha, which controls movement and tissues. Symptoms such as muscle

wasting ("Mamsa Dhatu Kshaya"), paresthesia ("Gatranam Sadanam"), loose and flabby arteries ("Dhamni Shaithilya"), debility of the sense organs ("Aksha Glani"), joint pain ("Sandhi Vedana"), and muscle wasting in the hip and cervical region ("Sphic Griva Shushyata") are caused by the impaired muscle tissue ("Mamsa Dhatu").

- Ayurvedic Management:

Using a mix of Panchakarma treatments and Ayurvedic oral medications, Ayurvedic treatment of DMD aims to encourage regeneration in neuromuscular disorders.

- Panchakarma:

This detoxifying and rejuvenating treatment is meant to address the underlying imbalances and encourage recovery.

- Rasayana and Rasa Oushadhi:

Rasa Oushadhi (herbal medicines) and Rasayana (rejuvenation) are used to enhance general health and assist the body's natural healing processes.

- Particular Ayurvedic Therapies:

To enhance muscle function and mobility, Ayurvedic treatments such as Abhyanga with Bala taila, Shashika shali Pinda swedana followed by Vasti, and Nadi Sweda with Dashmool Qwath and Swedana Karma are utilised [3].

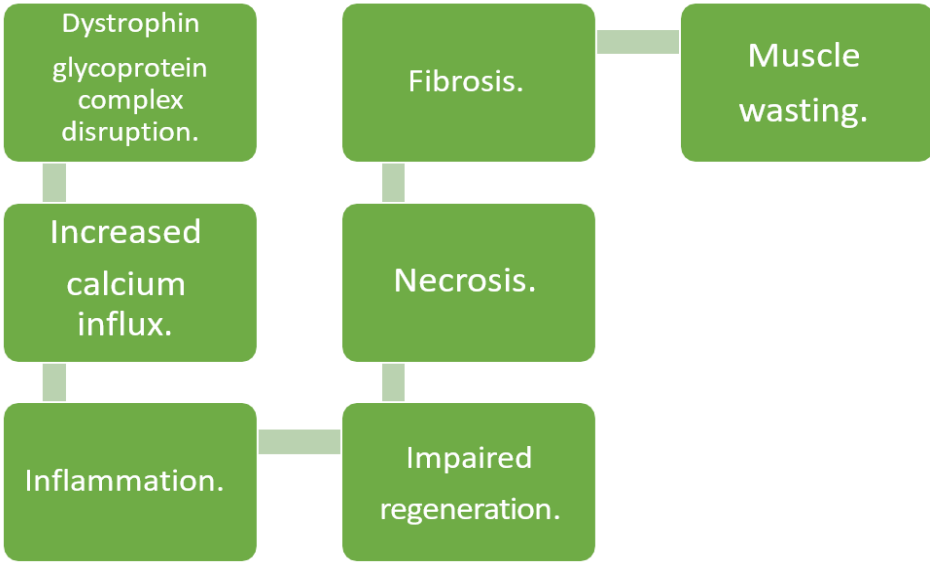


Chart 1: Occurrence of Muscular Dystrophy.

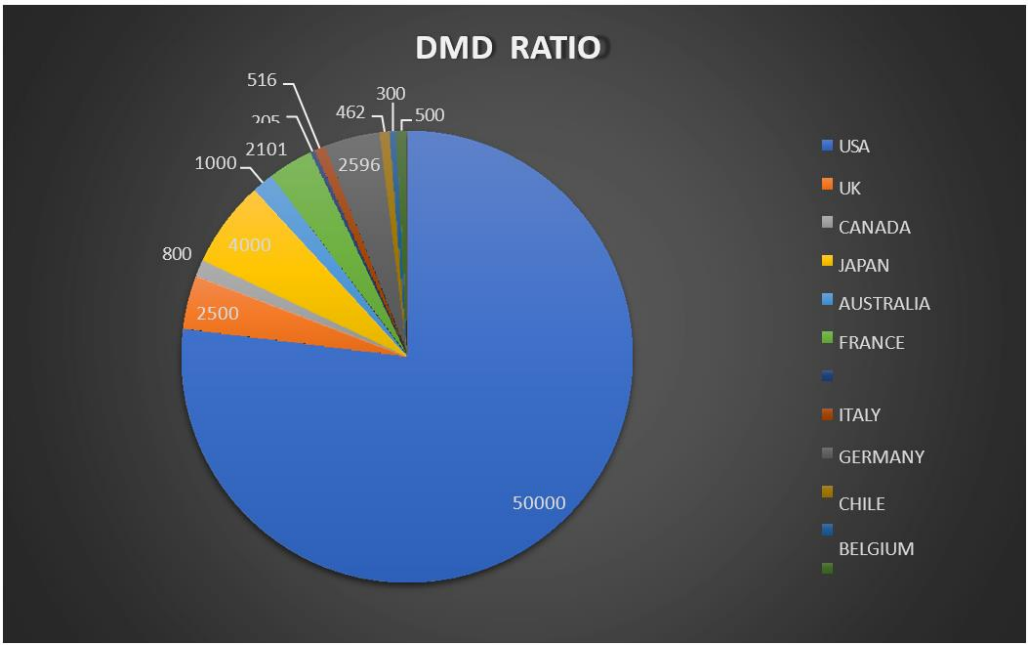


Chart 2: Presenting the ratio of DMD.

Table 1: Ratio of DMD patients in different countries [4].

Setting	Design	Sample	Life expectancy results	Risk of bias
USA	Prospective observational study	101 patients with DMD with end-stage respiratory muscle failure receiving NIV treated at the University Hospital in Newark (New Jersey, USA) in July 2010	Median survival (total sample; n = 101): 30.6 years	Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊◊
UK	Retrospective chart review	165 patients with DMD treated at the Newcastle Muscle Centre (Newcastle upon Tyne, UK) who died between 1967 and 2002, and 18 living patients	Median survival (died in the 1960s without ventilatory support; n = 9): 14.4 years Median survival (died in the 1970s without ventilatory support; n = 49): 18.0 years Median survival (died in the 1980s without ventilatory support; n = 68): 18.7 years Median survival (died after 1990 without ventilatory	Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊◊
			support; n = 33): 19.1 years Median survival (died after 1990 with ventilatory support; n = 24): 26.2 years	
UK	Retrospective chart review	75 patients with DMD treated at the Newcastle Muscle Centre (Newcastle upon Tyne, UK) born between 1970 and 1990	Median survival (spinal surgery and ventilatory support; n = 27): 30.0 years Median survival (ventilatory support; n = 13): 22.2 years Median survival (no spinal surgery or ventilatory support; n = 35): 17.1 years	Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊◊
USA	Retrospective chart review	57 patients with DMD with non-invasive IPPV, of which 14 subsequently underwent tracheotomy, were treated at a university hospital neuromuscular disease clinic since 1983	Median survival (total sample; n = 57): 28.9 years	Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊◊
Canada	Retrospective chart review	44 patients with DMD treated at the Pediatric Neurology Division at Dalhousie University in Halifax (Nova Scotia, Canada), born between 1963 and 2006, who had	Median survival (bisphosphonate treatment; n = 16): 27.0 years Median survival (no bisphosphonate treatment; n =	Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊◊

		received at least 1 year of corticosteroid therapy. One patient was mechanically ventilated	28): 21.0 years	
Japan	Retrospective chart review	187 patients with DMD treated at a medical institution in Yakumo (Hokkaido, Japan) between 1964 and 2010	Median survival (died between 1964 and 1984 without ventilatory support; n = 56): 18.1 years Median survival (died between 1984 and 1991 without ventilatory support; n = 11): 17.3 years Median survival (died between 1984	Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊◊
			and 1991 with tracheotomy; n = 24): 29.7 years Median survival (died after 1991 without ventilatory support; n = 8): 21.9 years Median survival (died after 1991 with NIV; n = 88): 39.6 years	
Australia	Retrospective chart review	38 patients with DMD treated at the Orthopaedical Clinic at the Women's and Children's Hospital or the Muscular Dystrophy Clinic at the Regency Park Centre for Young Disabled (Adelaide, South Australia) between 1960 and 1993	Median survival (spinal surgery; n = 17)19.0 years. Median survival (no spinal surgery; n = 21): 19.0 years	Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊◊
France	Retrospective chart review	119 adult patients with DMD treated at the AFM Yolaine de Kepper centre (Saint-Georges-Sur-Loire, France) between 1981 and 2011	Median survival (born before 1970 with/without ventilatory support; n = 43): 25.8 years Median survival (born after 1970 with/without ventilatory support; n = 76): 41.0 years Median survival (ventilatory support; n = 77): 36.2 years Median survival (no ventilatory support; no = 42): 22.2 years	Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊◊
Switzerland	Prospective observational study	43 patients with DMD residing at the Mathilde-Escher-Heim centre (Zurich, Switzerland) between 1999 and September 2006. 22 patients received long-term assisted	Median survival (total sample; n = 43): 35.0 years	Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊ (follow-up was too short)

		mechanical ventilation for chronic respiratory failure		
Italy	Retrospective chart review	516 patients with DMD treated at the Centre of Cardiology and Medical Genetics of the Second University of Naples (Naples, Italy) between 1961 and 2006	Median survival (born in the 1960s; n = NR): 18.0 years Median survival (born in the 1970s; n = NR): 22.1 years Median survival (born in the 1980s; n = NR): 28.0 years	Selection: ◊◊◊◊ Comparability: ◊ (ventilatory support details NR) Outcome: ◊◊◊
Germany	Retrospective chart review; cross-sectional observational study	67 patients with DMD born between 1970 and 1980 treated at the Department of Human Genetics, University of Würzburg (Würzburg, Germany)	Median survival (total sample; n = 67): 24.0 years. Median survival (no ventilatory support; n = 22): 19.0 years. Median survival (ventilatory support; n = 44): 27.0 years	Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊◊
Chile	Retrospective observational study	462 patients with DMD treated at the Teletón Institute of Santiago (Santiago, Chile) between 1993 and 2013	Median survival (total sample; n = 462): 20.3 years. Median survival (low socio- economic status; n = 351): 19.0 years. Median survival (medium socio- economic status; n = 82): 23.3 years. Median survival (high socio- economic status; n = 15): 22.7 years	Selection: ◊◊◊ (uncertain diagnosis) Comparability: ◊ (ventilatory support details NR) Outcome: ◊◊◊
Belgium	Prospective observational study	42 patients with DMD with nasal IPPV receiving mouth IPPV since end-diurnal hypercapnia, treated at the Neuromuscular Excellence Centre (Brussels, Belgium) between 1996 and 2005	Median survival (total sample; n = 42): 31.0 years	Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊◊
The Netherlands	Cross-sectional observational study	293 patients with DMD born between 1961 and 1974 (a pathway for identification NR), and 336	Median survival (born 1961–1974; n = 293): 18.0 years	Selection: ◊◊◊◊
		Patients with DMD born between 1980 and 2006 registered in the Dutch Dystrophinopathy Database	Median survival (born 1980–2006; n = 336): 29.0 years	Comparability: ◊ (ventilatory support details NR) Outcome: ◊◊ (caregiver-reported)
Japan	Retrospective chart review	80 patients with DMD who died between 1980 and 1995, and 19 living patients with IPPV	Median survival (no ventilatory support; n = 65): 20.1 years. Median survival (NPV support; n = 7)21.0 years.	Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊◊

			Median survival (IPPV support; n = 27): 30.4 years	

CINRG	Cooperative International Neuromuscular Research Group
CTCAE	Common Terminology Criteria for Adverse Events
DMD	Duchenne muscular dystrophy
DNHS	Duchenne Natural History Study
NF-KB	Nuclear factor-κB
NSAA	North Star Ambulatory Assessment
SAE	Serious adverse event
6MWT	6-minute walk test
TEAE	Treatment-emergent adverse event
TTRW	Time to run/walk 10 m
TTSTAND	Timed stand from supine

Clinical Pharmacology of vamorolone:-

Mechanism of Action:

Vamorolone is a corticosteroid that suppresses the immune system and reduces inflammation by acting on the glucocorticoid receptor. There is no known exact mechanism by which vamorolone works in DMD patients.

Pharmacodynamics:

In clinical trials, vamorolone resulted in a dose-dependent reduction in morning cortisol levels. Endogenous cortisol levels are suppressed, and the hypothalamic-pituitary-adrenal (HPA) axis is impaired when corticosteroid treatment is administered. In clinical trials using vamorolone, a dose-dependent rise in leukocyte and lymphocyte counts was noted.

Cardiac Electrophysiology:-

Vamorolone does not cause a mean increase in the QTc interval >20 milliseconds (ms) at 1.6 times the approved recommended dose.

Pharmacokinetics:

Metabolism is the main method of elimination, and metabolites are then excreted into urine. The exposure to vamorolone increases proportionately to either a single dosage (0.1 to 20 mg/kg) or several doses (0.25 to 20 mg/kg), exhibiting linear pharmacokinetics (PK). Repeated once-daily dosages of vamorolone do not cause accumulation.

Absorption:

The median Tmax following oral treatment with meals is approximately two hours (range: 0.5 to 5 hours).

Food Effect:

When vamorolone (2 mg/kg) was taken with a high-fat/high-calorie meal, the Cmax decreased by 18%, the AUC increased by 13%, and the Tmax was delayed by one hour. Combining a low-fat/low-calorie meal with vamorolone (2 mg/kg) resulted in a 4% decrease in Cmax, a 14% increase in AUC, and an hour-long delay in Tmax [see Dosage and Administration].

Distribution:

According to the population PK analysis, the apparent volume of distribution of vamorolone for a 20 kg DMD patient taking AGAMREE with a meal is 162 L. In vitro, protein binding is 88.1%. The ratio of blood to plasma is roughly 0.87.

Elimination:

According to the population PK analysis, the vamorolone clearance for a 20 kg DMD patient taking AGAMREE with a meal is 58 L/h. Vamorolone has a terminal elimination half-life of roughly two hours.

Metabolism:
Glucuronidation, hydroxylation, and reduction are some of the Phase I and Phase II metabolic pathways that are used to break down vamorolone. Both direct glucuronidation and hydrogenation, followed by glucuronidation, are used to create the primary metabolites in plasma and urine. By means of CYP3A4/5, CYP2C8, UGT1A3, UGT2B7, and UGT2B17, vamorolone is metabolized.

Excretion:
About 48% of the vamorolone dose is eliminated in urine as metabolites (<1% unmodified), and about 30% of the dose is eliminated in faeces (15.4% unchanged). Glucuronides are the main metabolites found in urine.

Particular Populations:
Race and sex did not appear to have any clinically meaningful effects on vamorolone pharmacokinetics.
Paediatric Patients:
On Days 1 and 14, the Cmax values (arithmetic mean, SD) of vamorolone were 856 ng/mL (471) and 970 ng/mL (270), respectively, and the AUC24 values (arithmetic mean, SD) of vamorolone were 3279 mgh/mL (1693) and 3606 mgh/mL (897), respectively, in children aged 4 to 7 years (N=12) who were given 6 mg/kg of AGAMREE every day. Additionally, the pharmacokinetics of vamorolone were described in children with DMD aged 2–4 (N=6). When compared to older children, younger children showed similar PK values following administration of 6 mg/kg AGAMREE.

Hepatic Impairment Patients:
In a clinical study (N=16), subjects with moderate hepatic impairment (Child-Pugh Class B) had vamorolone Cmax and AUC0-inf values that were roughly 1.7 and 2.6 times higher, respectively, than those of healthy matched controls [see Dosage and Administration and Use in Specific Populations]. Vamorolone has never been used with patients who have severe liver impairment.

Research on Drug Interactions:
Effect of Strong CYP3A4 Inhibitors on Vamorolone
Compared to administration of vamorolone alone, administration of vamorolone following multiple doses of a strong CYP3A4 inhibitor (itraconazole) increased vamorolone Cmax and AUC by 8% and 44%, respectively [see Drug Interactions]. There is no experience with vamorolone when co-administered with moderate and weak CYP3A4 inhibitors.

Metabolising Enzymes:
The FDA may not have recently approved this label. CYP3A4 is induced in vitro by vamorolone. Co-administration of AGAMREE may result in lower plasma concentrations of other substances that are CYP3A4 substrates. Nevertheless, no research on clinical medication interactions with CYP3A4 substrates was carried out. At clinically significant concentrations, vamorolone does not inhibit the CYP or UGT isoenzymes.

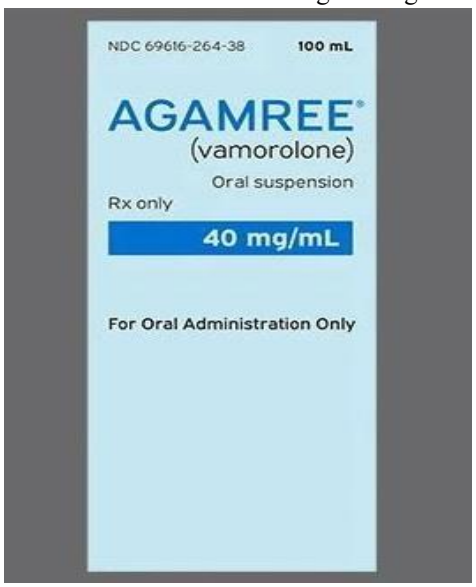
Transporter Systems:
At clinically relevant concentrations, vamorolone does not inhibit P-gp, BCRP, OATP1B1, OATBP1B3, OCT2, OAT1, OAT3, MATE1, MATE2-K, or BSEP. P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, MATE2-K, and BSEP do not bind to vamorolone [5].

Table 2: Effect of vamorolone on patient motor function tests and body.[5]

Week 24 changes from baseline					
	Group 1, 0.25 mg/kg/d (n=12)	Group 2, 0.75 mg/kg/d (n=12)	Group 3, 2.0 mg/kg/d (n=12)	Group 4, 6.0 mg/kg/d (n=12)	CINRG DNHS" (n=31)
TTSTAND					
No.	10	12	12	11	29
Mean	-0.01	0.00	0.05	0.04	0.01
SD	0.066	0.062	0.061	0.045	0.068
MMRM p-value vs DNHS	0.4062	0.9554	0.0397	0.1048	

MMRM p-value vs group 1		0.5067	0.0192	0.0442	
6MWT					
No.	10	12	10	09	
Mean	-11.6	18.9	29.2	43.9	
SD	29.45	41.08	35.91	43.72	
MMRM p-value vs group 1		0.0644	0.0153	0.0019	
TTCLIMB					
No.	12	12	12	11	31
Mean	0.00	0.01	0.04	0.05	0.01
SD	0.076	0.066	0.090	0.061	0.062
MMRM p-value vs DNHS	0.8532	0.6581	0.0811	0.0507	
MMRM p-value vs group 1		0.6107	0.1180	0.0747	

Fig 2. Images of the vamorolone formulation.



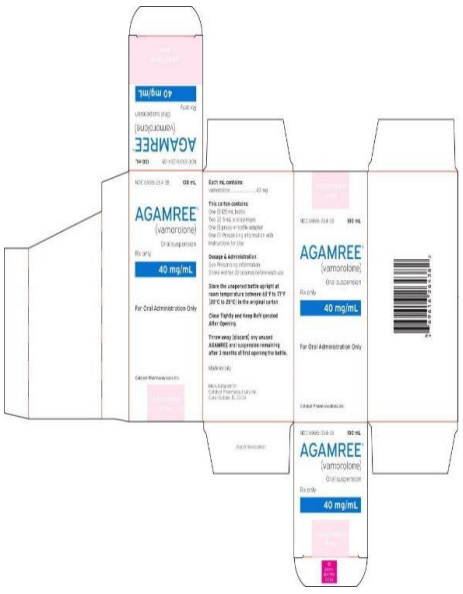
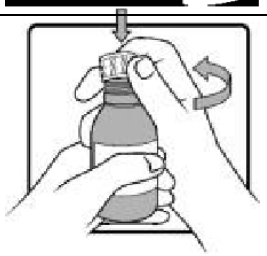
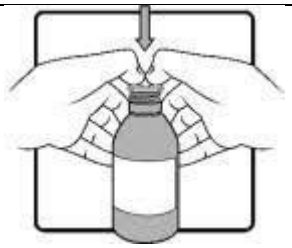
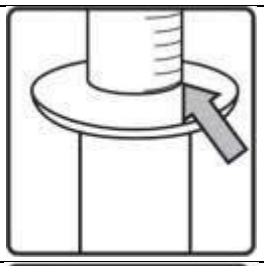
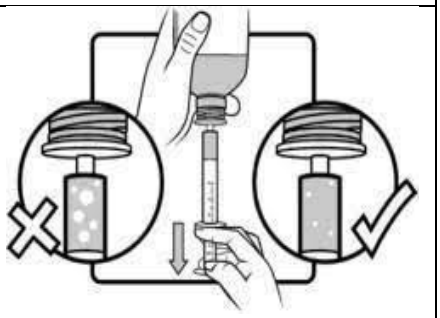
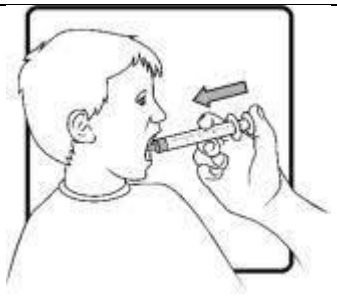
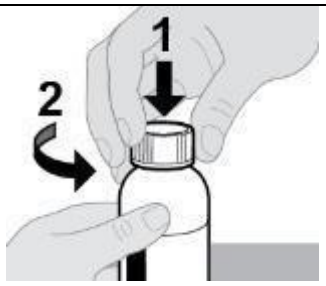
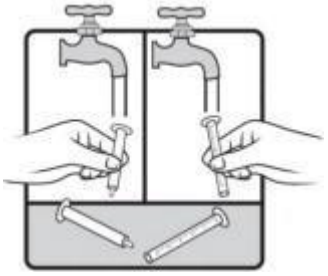


Figure 3: Preparing the AGAMREE bottle.

Step 1	Place the child-resistant bottle cap on the bottle. Make sure the child-resistant bottle cap is tightly secured and shake the bottle well for about 30 seconds.	
Step 2	Open the bottle by firmly pressing down on the child-resistant bottle cap and turning it to the left (counterclockwise). Do not throw away the child-resistant bottle cap.	
Step 3	Place the open bottle on a flat surface. Firmly insert the bottle adapter into the bottle by pushing it tightly into the top of the bottle. The top edge of the bottle adapter should be even with the bottle top. Do not remove the bottle adapter after it is inserted into the bottle. Write the date of first opening on your AGAMREE bottle when you first open it.	
Step 4	Check your dose in millilitres (ml) as prescribed by your healthcare provider. Each mark on the oral syringe is equal to 0.1 ml. Do not take more than the prescribed daily dose.	
Step 5	Place the bottle on a flat surface. Before inserting the tip of the oral syringe into the bottle adapter, push the plunger completely down toward the tip of the oral syringe. Use 1 hand to hold the bottle upright. Insert the oral syringe tip firmly into the opening of the bottle adapter.	

		
Step 6	Hold the oral syringe in place and carefully turn the bottle upside down. Pull the plunger down slowly until you reach the ml markings on the plunger for the prescribed dose. Do not pull the plunger out of the oral dispenser.	
Step 7	If there are large bubbles in the oral syringe or if you draw up the wrong dose of AGAMREE, push the plunger all the way up so that AGAMREE flows back into the bottle. Pull the plunger down slowly until you reach the ml markings for your prescribed dose. Repeat Step 7 if any large air bubbles remain or if you draw up the wrong dose of AGAMREE.	
Step 8	Leave the tip of the oral syringe in the bottle and turn the entire bottle to an upright position. Slowly remove the oral syringe tip from the bottle by pulling the oral syringe straight up. Do not hold the oral syringe by the plunger, because the plunger may come out. Take or give AGAMREE right away after it is drawn up into the oral syringe. Do not store the filled oral syringe.	

Step 9	The child or adult should sit upright to take a dose of AGAMREE. Place the oral syringe tip in the mouth towards the cheek and slowly push the plunger down until the oral syringe is empty. Do not forcefully push on the plunger. Do not give AGAMREE too fast into the back of the mouth or throat. This may cause choking.	
Step 10	Put the child-resistant bottle cap back on the bottle and turn the cap to the right (clockwise) to close the bottle. Keep the bottle tightly closed after each use.	
Step 11	Remove the plunger from the barrel of the oral syringe. Rinse the barrel and plunger with running warm water only and let them air dry on a paper towel. When the oral syringe and plunger are dry, put the plunger back in the oral syringe for the next dose. Store the oral syringe in a clean, dry place.	

The drug prescribed:
Adults and children two years of age and up who have Duchenne muscular dystrophy (DMD), a degenerative condition in which the muscles do not function properly, are treated with vamorolone. Vamorolone belongs to the group of drugs known as corticosteroids. It functions by altering the immune system's functioning and decreasing inflammation, or swelling.

The medication to be taken:
Vamorolone is available orally as a suspension (liquid). Typically, it is taken with a meal once a day. Take vamorolone daily at approximately the same time. Pay close attention to the instructions on your prescription label, and ask your pharmacist or doctor to clarify any parts you don't understand. Follow the directions on vamorolone exactly. Never take more or less of it, or take it more frequently than your doctor has suggested. Before using, give the suspension a good shake for around 30 seconds to ensure the drug is uniformly distributed. Only the included oral syringe should be used to measure the vamorolone dosage.

Depending on how well vamorolone works for you, your doctor may decide to lower your dosage. Additionally, if you undergo surgery, get sick, or get infected, your doctor might need to adjust your dosage. Throughout your therapy, let your doctor know if your symptoms improve or worsen, if you become ill, or if your health changes.

Never discontinue taking vamorolone without first consulting your physician. Abruptly stopping the medication might result in symptoms like headache,

fever, joint and muscular discomfort, peeling skin, nausea, vomiting, drowsiness, confusion, and weight loss. Before quitting the medication entirely, your doctor will most likely gradually reduce your dosage to give your body time to adjust. If you are stopping vamorolone suspension and reducing your dosage gradually, be aware of these negative effects. Contact your physician right away if any of these issues arise. Ask your pharmacist or doctor for a copy of the manufacturer's information for the patient.

Special precautions should be followed:
Before taking vamorolone,

1. If you have an allergy to vamorolone, any other drugs, or any of the substances in vamorolone suspension, let your doctor and pharmacist know. Request an ingredient list from your pharmacist.
2. Share your current and future prescription and over-the-counter medications, vitamins, nutritional supplements, and herbal products with your physician and pharmacist. Your doctor might need to adjust the dosages of your prescription drugs or keep a close eye out for any negative effects.
3. The following over-the-counter or herbal medicines may interact with vamorolone: Aspirin or other NSAIDS, including naproxen (Aleve, Naprosyn) and ibuprofen (Advil, Motrin). Before beginning vamorolone, be careful to inform your pharmacist and doctor that you are taking these drugs. When taking vamorolone, avoid starting any of these medications without first talking to your doctor.
4. Inform your doctor if you have or have ever had any of the following conditions: hepatitis B (HBV, a virus that infects the liver and can cause severe liver damage); cataracts (clouding of the eye's lens); glaucoma (an eye disease); high blood pressure; heart failure; a recent heart attack; diabetes; emotional issues, depression, or other mental illnesses; myasthenia gravis (a condition in which the muscles become weak); osteoporosis (a condition in which the bones become weak and can break easily); pheochromocytoma (tumour on a small gland near the kidneys); ulcers. A blood clot in your legs, lungs, or eyes; liver, kidney, heart, adrenal, or thyroid disease; diverticulitis (swelling of the lining of the large intestine); any type of surgery on your stomach or intestines; or any other gastrointestinal issue. Additionally, if you have an untreated bacterial, fungal, parasitic, or viral illness anywhere on your body, let your doctor know.
5. Inform your physician if you are nursing a baby, intend to get pregnant, or are already pregnant. Contact your physician if you become pregnant while taking vamorolone.
6. Inform the physician or dentist that you are taking vamorolone if you are undergoing any type of surgery, including dental work.
7. To find out if you require any immunisations, consult your physician. Before starting vamorolone medication, it is crucial that you have had all age-appropriate vaccinations. Consult your doctor before receiving any immunisations while undergoing therapy.

You should be aware that vamorolone may impair your defences against infection and may stop you from experiencing symptoms if you do get one. When using this medication, avoid contact with sick persons and wash your hands frequently. Avoid those who have measles or chicken pox. If you believe you may have meet someone who has measles or chicken pox, call your doctor right away.

Side effects of Vamorolone Medication:

1. Headache
2. Vomiting
3. Diarrhoea
4. Increased appetite
5. Runny nose
6. Difficulty falling asleep or staying asleep
7. Sore throat, fever, chills, cough, or other signs of infection
8. Rash; hives; itching; swelling of face, eyes, lips, or throat; difficulty swallowing or breathing
9. Confusion
10. Extreme changes in mood, changes in personality
11. Inappropriate happiness
12. Depression
13. Changes in weight (gain or loss)
14. Stomach pain
15. Shortness of breath
16. Sudden weight gain
17. Swelling of feet, ankles, or lower legs
18. Changes in vision

Vamorolone may cause children's growth and development to stall. The doctor will keep a close eye on your child's development. Discuss the dangers of providing your child with vamorolone with their physician. Long-term vamorolone users may develop cataracts or glaucoma. Discuss with your doctor the dangers of vamorolone use and the frequency of eye exams while undergoing treatment. Vamorolone may make osteoporosis more likely to occur. Discuss the dangers of using this drug with your doctor. Other

adverse effects are possible with vamorolone. If you have any odd side effects while taking this medicine, contact your doctor.

Storage and disposal of this medication:
Keep this medication tightly closed, out of children's reach, and in the container it came in. Do not freeze unsealed vamorolone suspension bottles; instead, keep them upright in the refrigerator. After three months, discard any leftover liquid suspension.
Since many prescription containers (including those for eye drops, creams, patches, and inhalers, as well as weekly pill minders) are not child-resistant and are readily opened by small children, it is crucial to keep all medications out of children's sight and access. Always lock the safety caps and put the medication in a secure location right away, out of young children's reach and sight, to prevent poisoning.
It is important to dispose of unnecessary prescriptions in a way that prevents children, dogs, and other people from consuming them. This drug should not, however, be flushed down the toilet. Instead, participating in a pharmaceutical take-back program is the easiest approach to get rid of your prescription drugs. To find out about take-back programs in your area, speak with your pharmacist or get in touch with the recycling and waste department [6].

How Supplied/ Storage, and Handling:
How Supplied:
40 mg/ml of vamorolone is present in the orange-flavoured, homogenous, white to off-white AGAMREE oral suspension. 100 ml of AGAMREE comes in a 125 ml glass bottle together with two 5 ml oral syringes, a bottle adapter, and usage instructions.
Handling and Storage:
Keep the bottle upright at room temperature, about 20 to 25 degrees Celsius (68 to 77 degrees Fahrenheit). Within the original cartoon, excursions are allowed between 15°C and 30°C (59°F and 86°F). Check out the USP- USP-controlled room temperature. Once the bottle is open, keep it upright in a refrigerator between 2°C and 8°C (36°F and 46°F). Avoid freezing. Discard any leftover AGAMREE oral suspension three months after the bottle was originally opened [7].

II. CONCLUSION

When compared to the placebo group, our pooled analysis showed a statistically significant correlation between the vamorolone group and higher TTSTAND, TTRW, and TTCLIMB velocities. Similarly, when compared to the glucocorticoid group, the pooled analysis revealed a statistically significant correlation between the vamorolone group and higher TTRW velocity and height percentile for age. The pooled study, however, revealed no statistically significant change in TTSTAND velocity, TTCLIMB velocity, or BMIZ score between the vamorolone and glucocorticoid groups. As a result, we propose that vamorolone be utilised to treat DMD patients. To validate our findings, additional randomised clinical trials are required.
Future Scope:
1. Gene Therapy and Exon Skipping:

- Gene Therapy:

This approach aims to replace the faulty dystrophin gene with a functional copy, potentially correcting the genetic defect at the root of DMD.

- Exon Skipping:

This strategy focuses on restoring the reading frame of the dystrophin gene by "skipping" over a specific exon (a section of the gene) that is causing the mutation, allowing the cell to produce a partially functional dystrophin protein.

- Current Status:

Several clinical trials are underway for both gene therapy and exon skipping approaches, with some treatments already approved for specific mutations, like Sarepta's EXONDYS 51 (eteplirsen), VYONDYS 53 (golodirsen), AMONDYS 45 (casimersen), and ELEVIDYS.

- Future Directions:

Research continues to explore different gene therapy vectors, such as AAV (adeno-associated virus), and to develop more efficient and targeted exon-skipping therapies [8].
2. Emerging Therapies and Approaches:

- Mini/Micro-dystrophin Therapy:

This approach involves delivering engineered versions of the dystrophin protein, known as mini- or micro-dystrophins, to muscle cells, which can potentially restore some muscle function.

- Antifibrotic Drugs:

As DMD progresses, muscle tissue is replaced by fibrous tissue, leading to further weakness and disability. Antifibrotic drugs, which can reduce the formation of scar tissue, are being explored as potential treatments.

- AI and Personalised Medicine:

Artificial intelligence (AI) and other advanced

technologies are being used to analyse large datasets and identify new therapeutic targets and biomarkers for DMD.

- Stem Cell Therapy:

Induced pluripotent stem cells (iPSCs) offer the potential to create muscle cells in the lab that can be used to study DMD and develop new therapies.

- Stitchr Technology:

A new technology called "Stitchr" delivers two halves of a gene separately, which then join together in the cell to restore the expression of a missing or inactive protein.

3. Improving Clinical Outcomes:

- Early Intervention:

Starting glucocorticoid therapy (a type of steroid medication) in younger children with DMD before significant muscle decline can help to slow down disease progression.

- Addressing Complications:

DMD can lead to a variety of complications, including heart and lung problems. Research is focused on developing treatments for these complications.

- Improving Quality of Life:

As treatments improve, it is also important to focus on improving the quality of life for people with DMD, including addressing cognitive and behavioural issues.

- Clinical Trials:

MDA has created a dedicated DMD Clinical Research Network that aims to advance human clinical trials in this disease.

- International Studies:

International studies are being conducted to better understand the progression of DMD and to identify potential new treatments [9].

4. Market Trends and Opportunities:

- Growing Market:

The DMD market is expected to continue to grow as new treatments are developed and approved.

- Sarepta Therapeutics:

Sarepta Therapeutics is a major player in the DMD treatment landscape, with several approved therapies and a robust pipeline of new treatments in development.

- Other Companies:

Other companies are also involved in DMD research and development, including Pfizer, Solid Biosciences, and Regenexbio.

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I would like to express my special gratitude to my teacher, Ms. Madhuri Kawade and the principal, who gave me a golden opportunity to do this wonderful project on the topic of treating Duchenne Muscular Dystrophy with Agamree (vamorolone). It also helped me do a lot of research, and I learned so many new things.

REFERENCES

[1] Catalyst Pharmaceuticals Reports FDA Approval of AGAMREE® (vamorolone) for Duchenne Muscular Dystrophy Granted to Santhera Pharmaceuticals. Catalyst Pharmaceuticals. News Release October 26, 2023. Accessed on October 26, 2023

[2] Vamorolone Phase 2b (VISION-DMD): A Study to Assess the Efficacy and Safety of Vamorolone in Boys with Duchenne Muscular Dystrophy (DMD). Hub Summary. Article. Accessed on October 26, 2023. https://dmdhub.org/trials/vamorolone-phase-2b/

[3] Santhera Pharmaceuticals. Santhera Receives U.S. FDA Approval of AGAMREE® (vamorolone) for the Treatment of Duchenne Muscular Dystrophy. [Press Release]. 27 October 2023. Accessed 27 October 2023.

[4] Santhera Pharmaceuticals. Our Pipeline: AGAMREE® (vamorolone). 2023. Accessed 27 October 2023

[5] Duan D, Goemins N, Takeda S, et al. Duchenne muscular dystrophy. Nat Rev Dis Primers. Feb 2021; 7(1):13.

[6] Heier CR, Damaskin JM, Yu Q, et al. VBP15, a novel anti-inflammatory and membrane stabiliser, improves muscular dystrophy without side effects. EMBO Mol Med. Sep 2013; 5(10):1569-85

[7] FDA. FDA Roundup: October 27, 2023. [Press Release]. 27 October 2023. Accessed 3 November 2023.

[8] Hench PS, Kendall EC, Slocumb CH, Polley HF. The effect of a hormone of the adrenal cortex (17 hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocortical hormone in arthritis: preliminary report. Ann Rheum Dis 1949;8:97–104. - PMC – PubMed

[9] The Nobel Prize in Physiology or Medicine 1950. Nobelprize.org. Nobel Media AB. 2014.

Available at: nobelprize.org/Nobel prizes/medicine/laureates/1950/. Accessed May 27, 2018.

[10] Hoffman EP, Brown RH Jr, Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. Cell 1987;51:919–928. – PubMed

[11] Guglieri M, Bushby K, McDermott MP, et al. . Developing standardised corticosteroid treatment for Duchenne muscular dystrophy. Contemp Clin Trials 2017;58:34 39. – PMC

[12] TomeÂ FMS: The saga of congenital muscular dystrophy. Neuropediatric 1999; 30:55±65.

[13] Hayashi YK, Tezak Z, Momoi T et al: Massive muscle cell degeneration in the early stage of merosin-deficient congenital muscular dystrophy. Neuromuscular Disorder 2001; 11:350±359.

[14] Muntoni F, Blake D, Brockington M et al: 85th ENMC International Workshop on Congenital Muscular Dystrophy 6th International CMD Workshop 1st Workshop of the Myo Cluster Project `GENRE' 27±28th October 2000, Naarden, The Netherlands. Neuromuscular Disorder 2001; 12:69±78.

[15] He Y, Jones KJ, Vignier N et al: Mild congenital muscular dystrophy with primary partial laminin a2 chain deficiency: molecular study. Neurology 2001; 57: 1319±1322.

[16] Guicheney P, Vignier N, Zhang X et al: PCR-based mutation screening of the laminin alpha2 chain gene (LAMA2): application to prenatal diagnosis and search for founder effects in Congenital muscular dystrophy. J Med Genet 1998; 35: 211±217. Brockington M, Blake DJ, Prandini P et al: Mutations in the Fukien-Related Protein Gene (FKRP) cause a form of congenita muscular dystrophy with secondary laminin a2 deficiency and Abnormal glycosylation of a-dystroglycanopathy. Am J Hum Genet 2001; 69: 1198±1209.