Potential New Therapies for Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a rare genetic disorder characterized by progressive muscle deterioration and disabling muscle weakness affecting many parts of the body. The disease is caused by a mutation in the DMD gene which results in an absence or defect of the dystropin protein. Dystropin works together with other proteins to act like a shock absorber in muscle cells, helping protect them from the wear and tear of typical muscle movements. Missing or defective dystropin causes DMD symptoms like muscle weakness to appear in early childhood between 2 and 5 years of age. As the disease progresses most patients will need to use a wheelchair by the time they are teenagers. During adolescence, heart and breathing muscles weaken. Eventually, respiratory failure occurs, and patients usually develop cardiomyopathy before 30 years of age. Premature death from respiratory or cardiac failure is likely to occur by age 40 if not before. DMD primarily affects males, but in rare cases it can also affects females. Between 400 and 600 boys are diagnosed with DMD each year in the United States. In the UK, around 70,000 people have Muscular Dystrophy, with Duchenne Muscular Dystrophy being the most common. In the UK, about 100 boys are born with Duchenne MD each year, and there are about 2,500 people living with the condition in the UK at any one time.

Current pharmacological approaches can help delay damage to muscles or minimize symptoms of DMD. Corticosteroid therapy is considered the standard of care. Studies show that daily treatment with prednisone can increase muscle strength and respiratory function while also slowing the progression of weakness by several years. Other drugs are beginning to become available for Duchenne muscular dystrophy, including Translarna (ataluren), which is currently available in some European countries to slow down the progression of symptoms in boys with Duchenne muscular dystrophy.

The drug works for only a small group of boys who carry a particular mutation in the dystrophin gene ('nonsense' mutation – where a single letter change in the DNA code results in a premature stop codon). Other drugs targeting specific mutations may be approved in the coming years.

Intense research is continuing, in trying to find treatments for Duchenne muscular dystrophy. Some medicines are currently being tested in clinical trials.

In the U.S., Emflaza® (deflazacort) is another corticosteroid that was approved in 2017 to decrease inflammation and reducing the activity of the immune system in patients with DMD.

The most recently approved treatments for DMD in the U.S. have focused on correcting the gene mutations. Specifically, these medications use a process called exon-skipping to produce a usable dystrophin protein by skipping over the exon or part of the gene that causes problems with the muscle proteins. The US approved Exondys 51 (eteplirsen) for treatment of DMD in 2016, Vyondys 53 (golodirsen) in 2019, and Viltepso® (viltolarsen) in 2020. These treatments require weekly intravenous injections and may slow disease progression in about 30% of patients. They increase dystrophin production but have not yet been proven to improve survival or provide other clinical benefits.

Several new treatment options for DMD may become available in the U.S. within the next year. In May, the FDA is scheduled to review delandistrogene moxeparvovec (SRP-9001), an investigational one-time gene therapy treatment designed to treat the underlying cause of DMD. It works by delivering a gene to the muscle that encodes for a shortened, functional form of dystrophin. Last November, the FDA granted accelerated review of the Biologics License Application (BLA) for SRP-9001 based on efficacy and

safety data from three studies: Studies-9001-101, SRP-9001-102, and Study SRP-9001-103 (also known as ENDEAVOR).

Study 101 and Study 102 demonstrated the safety of SRP-9001 as well as an improvement in North Star Ambulatory Assessment (NSAA) in patients 4 to 7 years of age. The NSAA is a 17 item-based scale from 0 (worst) to 100 (best) designed to evaluate ambulatory performance in patients with DMD.

- The ENDEAVOR (Study 103 or SRP-9001-103) is an open-label trial evaluating the safety of SRP-9001 in 20 boys ages 4 to 7 and 12 older patients, both able and unable to walk. Patients are being followed for five years. The trial's primary goal is changes in micro-dystrophin protein levels from the study start to 12 weeks. Results demonstrated that 70.5% of muscle fibers were expressing micro-dystrophin at 12 weeks. Comparisons between the baseline of 12.8% and the post-treatment measure was statistically significant (p=0.001). Exploratory measures include changes in motor skills. At 52 weeks, the 20-patient cohort improved 4 points from their pre-therapy baselines on NSAA compared to the external control group. In addition, timed function tests at 52 weeks including time to rise and ten-meter walk/run improved by 0.5 seconds and 0.8 seconds respectively compared to the external control group. During this study, the safety and tolerability profile for SRP-9001 remained stable across treated patients.

In clinical results from more than 80 treated patients, SRP-9001 has demonstrated positive results at multiple time points, including one, two, and up to four years after treatment, in addition to demonstrating a consistent safety profile. Sarepta, the manufacturer, recently announce that the FDA is not requiring SRP-9001 to go through an advisory board committee prior to its review on May 29th. If approved, it would be the first gene therapy approved for DMD. Based on the cost of other approved gene therapy products, the estimated price for the one-time treatment is between $2,000,000 and $3,000,000.

While not a potential cure, in October the FDA is scheduled to review vamorolone as an additional supportive therapy for DMD. Vamorolone is a first in-class dissociative corticosteroid that was designed to have the anti-inflammatory activity of corticosteroids, but with fewer side effects. It is administered orally as a flavored liquid.

The submission for FDA approval was supported by the results from the Phase 2b VISION-DMD trial which enrolled 121 boys between the ages 4 and 6 who were able to walk. Each was randomly assigned to either receive vamorolone, prednisone, or placebo daily. The trial met its primary endpoint of improvement in change of time to stand velocity with vamorolone versus placebo at 24 weeks. Specifically, investigators observed improvements from 6.0 to 4.6 seconds in the treated group and a small decline in the placebo group from 5.4 to 5.5 seconds. Vamorolone also met its secondary efficacy endpoints including no statistically significant difference observed in efficacy or safety between vamorolone and prednisone in time to stand velocity, 6-minute walk test, or time to run/walk 10 meters. After the first 24 weeks of treatment, the group given vamorolone also showed improvements compared with those on placebo in several additional motor function assessments. These included the time to stand test and the six-minute walk test. In the trial extension, in which all participants received vamorolone for an additional 24 weeks, the treatment continued to show sustained improvements. Efficacy observed at 24 weeks for vamorolone was maintained across multiple endpoints over 48 weeks.

In both parts of the trial, vamorolone treatment showed a good safety and tolerability profile. The most commonly adverse events reported were Cushingoid features like a rounded face, as well as vomiting and vitamin D deficiency. Adverse events were generally mild to moderate in severity, and the treatment was associated with fewer side effects than prednisone. The safety and efficacy profile of vamorolone indicates it has the potential to offer an alternative therapy to current standard of care. If approved in October, the manufacturer Santhera plans to launch the medication in late 2023. An early estimated annual cost could range between $100,000 and $300,000.

Another new potential therapy for DMD may submit its application to the FDA soon. Givinostat is an investigational HDAC inhibitor. It blocks enzymes called histone deacetylases (HDAC) which are involved in turning genes on and off within cells. By inhibiting HDAC activity, givinostat may help activate muscle repair mechanisms to increase muscle fiber regeneration, reduce inflammation, and reduce fibrosis. Topline results from the completed Phase 3 EPIDYS trial were announced in June of last year. The primary objective of the study was to evaluate the effects of givinostat on slowing disease progression in ambulant DMD boys aged 6 years and older on chronic steroids. The study compared givinostat to placebo in 179 males. The study met its primary endpoint which was the change from baseline in the time to climb 4 stairs after 18 months of treatment. The results demonstrated a slower decline to perform this functional task in the givinostat-treated group (difference vs placebo of 1.78 seconds, p=0.0345). A variety of secondary endpoints were analyzed that showed results consistent with the functional primary endpoint including NSAA and time to rise tests along with muscle strength analysis. The majority of adverse events were mild to moderate with the most common being diarrhea, abdominal pain, thrombocytopenia, and high triglycerides. Italfarmaco, the manufacturer, intends to use these results in its application to the FDA which may happen yet this year. Givinostat has already received a Fast Track designation from the FDA allowing for its approval to potentially occur 6 months after submitting its application to the FDA.

The life expectancy of patients with DMD has considerably increased the past couple of decades due to treatment advances, such as standard use of corticosteroids, assisted ventilation, and the management of cardiomyopathy-related heart failure. DMD patients are living past their second decade of life. However, additional treatment strategies are still needed to reduce pathology, improve quality of life, and ultimately prolong survival. Gene therapy offers the potential to cure DMD by slowing or halting disease progression and thereby improving overall survival but will need to be proven as an enhancement to current standard of care and with the anticipated high cost of gene therapy, be cost-effective. More studies are needed to determine if this will be achievable with SRP-9001 or a different gene therapy. Meanwhile, both vamorolone and givinostat show promise as additional supportive therapy options to slow disease progression.

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