Sarepta's Elevidys Gene Therapy for Duchenne Muscular Dystrophy

An analyst and a neurologist specializing in neuromuscular disorders discussed Sarepta's Elevidys gene therapy, recent safety concerns involving patient deaths, and the expected impact on prescribing patterns for Duchenne muscular dystrophy patients.

Expert Background and Patient Population

The expert is a neurologist and neuromuscular specialist who has been practicing for approximately three years at an academic institution. Their clinic is essentially 99.9% neuromuscular patients, with all work being outpatient-based. The expert currently manages between five to seven Duchenne muscular dystrophy patients, all of whom are non-ambulatory adults, reflecting the expert's focus on adult neuromuscular care.

Disease Progression and Current Treatment Landscape

The expert explained that approved therapies haven't been available long enough to fully understand their impact on long-term disease progression. Disease severity varies depending on the specific mutation patients carry, with some mutations being more aggressive than others. Most patients are highly dependent on walking aids like lady walkers, and many become wheelchair users by their 20s and 30s. However, it remains unclear whether all patients eventually become non-ambulatory when treatments are started early enough.

The standard of care begins with steroid or steroid-like therapy for all patients. Traditionally, patients receive prednisone, though two alternative corticosteroids are now available on the market. Beyond steroids, treatment depends on the patient's specific gene mutation. Some patients qualify for exon-skipping therapy based on their mutation, with several such therapies available. Supportive care includes physical therapy, occupational therapy, and respiratory therapy, though these represent non-pharmacological interventions.

Exon-Skipping Therapies

Only four exon-skipping therapies exist, targeting exons 51, 53 (with two drugs), and 54. Patients are only eligible if they have mutations in these specific exons; otherwise, there's no clear benefit and insurance typically won't provide coverage. The expert noted that this limitation made Elevidys particularly valuable since it has broader applicability.

Exon-skipping therapies aim to convert patients into a Becker's phenotype—a less severe form of muscular dystrophy. Patients with Becker's can walk into their 20s, 30s, and

40s, experiencing much milder symptoms than Duchenne patients. The goal is minimizing damage by enabling production of more dystrophin protein, helping patients maintain functionality. These effects primarily impact the musculoskeletal system and strength, showing less improvement for cardiac and cognitive symptoms that can also occur with Duchenne.

Elevidys: Initial Impressions and Current Use

Elevidys received accelerated approval approximately two years ago, with expanded approval into the non-ambulatory population coming last summer. The expert's pediatric colleagues are prescribing the therapy, though the expert's own patients have not received it yet. Since most of the expert's patients were non-ambulatory before the expanded approval, they weren't previously considered candidates. Additionally, because these patients are typically seen annually, the expert hadn't yet had appointments with them since the expanded approval.

Despite this, the expert has considered recommending Elevidys to patients. The mechanism makes considerable sense, and depending on how developments unfold over the coming months and ongoing discussions, it remains something the expert would still consider for some patients. The expert believes there might be benefit even for non-ambulatory patients, noting that while dramatic improvements occur in ambulatory patients, non-ambulatory patients have much lower functional reserve. For these patients, losing even 1% of function means they can no longer complete certain tasks like feeding themselves or spreading their arms—they simply can't do it anymore rather than finding it difficult. Every small gain therefore counts significantly.

Patient Candidacy Assessment

The expert indicated that most—potentially all except one—of their five to seven Duchenne patients would probably be good candidates for Elevidys. Patients with many other active medical issues would require more careful risk-benefit consideration, but those who are relatively healthy aside from Duchenne would be reasonable candidates to consider. Of these patients, one is currently on an exon skipper while the rest are not.

Regarding combination therapy with exon skippers and gene therapy, the expert was uncertain but didn't think it would work well. Exon skipping is supposed to correct the problem by restoring the dystrophin protein, while Elevidys provides a much shorter, abbreviated dystrophin protein covering all main points. There may not be much benefit in combining both approaches.

Dystrophin Production Comparison

When comparing dystrophin production between gene therapy and exon skippers, the expert explained that in theory, exon skipping should be better for the patient than the mini-dystrophin or micro-dystrophin provided by Elevidys. This is because exon skipping bypasses the broken part of the gene, though outcomes also depend on where the specific issue is located. The expert acknowledged lacking head-to-head comparison data between Elevidys and exon skippers regarding dystrophin production levels.

Safety Concerns: Patient Deaths and Liver Injury

The conversation focused extensively on recent patient deaths, which the expert found challenging to interpret given the viral delivery mechanism for the gene. While the company checks beforehand to ensure patients don't have resistance to the virus, complications can still occur. In clinical trials, approximately 40% of patients experienced some liver injury, though most cases were relatively mild and none were severe. The expert was uncertain why non-ambulatory patients experienced more severe reactions. The most recent death involved an adult with a different mutation who wasn't a Duchenne patient, for whom the therapy was being tested.

The expert theorized that non-ambulatory patients are typically sicker because they're less active and have more progressed disease, making them more prone to various complications. The reduced mobility itself might contribute, though the expert wasn't certain. The striking aspect was that ambulatory patients in trials weren't affected at all by severe liver injury.

Clinical trials did demonstrate varying degrees of liver injury among participants. The mildest form involves elevated liver enzyme markers without significant other effects. The next level includes more significant liver injuries where metabolism slows or toxic effects begin appearing. The most severe form is acute liver failure.

Monitoring Challenges with Muscular Dystrophy Patients

The expert identified a significant complication in monitoring liver function in muscular dystrophy patients. Many of these patients already have underlying issues that could resemble liver problems, but tracking becomes very difficult because muscle dystrophy patients can have elevated liver enzyme markers that actually overlap with muscle breakdown markers. When muscles break down or burst, contents spill out, causing elevated creatine kinase (CK) levels. The typical markers for liver injury—AST and ALT transaminases—are also among the first signs of muscle dystrophy. Pediatricians often discover muscle dystrophy when they order CK levels after finding elevated AST and ALT.

This creates a challenge: AST and ALT (liver enzyme markers) may be elevated due to CK from muscle injury rather than actual liver problems. This makes it genuinely difficult to

track liver health in these patients and identify which patients might be at higher risk beyond the ambulatory versus non-ambulatory distinction.

Current and Anticipated Monitoring Requirements

The expert was not aware of specific current monitoring requirements for the liver beyond standard practice. With most infusions, clinicians perform a comprehensive metabolic panel that includes liver enzymes. However, as mentioned, people with muscular dystrophy—particularly those with very high CK levels like most Duchenne patients—can have elevated AST and ALT, the very markers used to detect liver injury.

Regarding labeling, the expert didn't think Elevidys currently carried a black box warning. However, based on how other drugs are regulated, once two or three high-risk issues or patient complications occur, the FDA typically adds either a relative warning or black box warning, or includes the drug in a REMS (Risk Evaluation and Mitigation Strategy) program. This program establishes monitoring criteria accompanying drug use, requiring clinicians to be well aware of risks, educate patients thoroughly, and be proactive about monitoring.

The expert identified liver monitoring as the main component likely to be added to a REMS program, though acknowledged that standard blood work may not be very effective. Ultrasound represents another monitoring option. If regulators want to enable non-ambulatory patients to access the therapy while managing risks, they would either block it off completely or add it to a REMS program, add a black box warning, or implement both measures.

Impact on Prescribing Patterns

When asked whether a black box warning and REMS program would impact prescribing ability, the expert thought it would add some burden but not significantly more difficulty. Clinicians already must discuss potential side effects with patients. Importantly, many patients eligible for Elevidys aren't eligible for other drugs, and they often become quite desperate for anything that might help with their disease. The expert didn't think these additional requirements would significantly decrease prescribing. After prescribing to their first few patients, clinicians would likely become more comfortable and potentially realize the complications aren't as common as initially feared.

Patient Sentiment and Reactions

The expert had not yet spoken with any patients about the recent deaths since they hadn't come into the office in the weeks following these reports. However, the expert believed most patients eligible for Elevidys would remain very interested in hearing about it.

The majority would highly consider the therapy regardless of recent events, primarily because of the lack of alternative options for most patients.

FDA Actions and Regulatory Outlook

The analyst noted that on Friday, the FDA asked Sarepta to stop sending shipments of the gene therapy, though Sarepta had declined to do so as of that point. The expert viewed this as just an ask rather than a demand. If no further adverse events occur, the therapy would likely continue with extra restrictions through a black box warning and/or REMS program. Insurance coverage would likely become more challenging, with insurers requiring multiple criteria to be met before approving payment.

The expert anticipated approval might become somewhat harder to obtain. Unless more cases emerge and better methods are developed to identify unsuitable candidates (beyond non-ambulatory status), the therapy would likely continue for ambulatory patients at lower risk. Regulators might block use for all non-ambulatory patients while ensuring ambulatory patients understand the possibility of complications.

Implications of Additional Deaths

Regarding the potential for additional patient deaths, the expert drew comparisons to other neuromuscular drugs with serious risks. One particular drug carries a black box warning and REMS program for potentially fatal meningococcal infection. With that drug, extra precautionary steps are required, and the drug cannot be administered until all steps are fulfilled. After the first few reported cases, following proper steps has prevented or minimized subsequent serious events.

The expert wondered whether similar protocols might work for Elevidys: performing liver ultrasounds beforehand, conducting comprehensive labs, and doing additional tests to ensure nothing is amiss. Serial monitoring for a certain number of weeks or months post-infusion could help ensure patients aren't developing liver injury. However, the expert acknowledged uncertainty about outcomes—a couple more deaths could shut down the entire program, or these might be the only three deaths over the next five to six years.

Enthusiasm Level Assessment

Before the reported patient deaths, the expert rated their enthusiasm for Elevidys at a nine out of ten. Currently, the expert placed it at approximately 6.5 to 7.5 out of ten, settling on 7.5. Before the deaths, the therapy appeared to be all benefits with almost no drawbacks. Now there's some risk, though it remains relatively low. The expert philosophically noted to patients that nothing in life is free, everything has side effects, and it's just a matter of time before discovering what they are.

Management of Liver Injury

For managing minor cases of liver injury when they occur, several approaches are available. Clinicians can follow labs for longer periods, decrease the dose, hold medications, and potentially send patients to specialists to determine if additional interventions are needed. These represent standard approaches taken with other drugs. However, the expert acknowledged limited flexibility with gene therapy dosing compared to traditional medications.

Regarding the recent severe cases, the expert noted they appeared to develop quite quickly—within approximately two months according to reports. The expert hadn't examined these cases closely enough to know whether patients had steroids on board or preexisting conditions that might have been helpful or harmful. These factors would likely be investigated. The key observation was that clinical trials described liver injury that did not progress to the severity seen in these three cases.

Timeline for Risk and Monitoring Duration

When asked about the timeframe during which liver injury risk exists, the expert acknowledged this was speculative but suggested that risk likely decreases over time. Most incidents appear to occur within two months, possibly extending to two to four months. By six to eight months, the likelihood might be lower, though this was presented as an estimation rather than established fact.

If a REMS program were required, the expert expected liver monitoring for approximately one to two years afterward rather than lifelong monitoring. More emphasis would likely be placed on prescreening—ensuring nothing is wrong before starting treatment—to give patients the best possible chance of avoiding complications.

Final Clinical Approach

The expert described their general approach to patient care: presenting all available information and allowing patients to make decisions since they're the ones living with and managing the disease. The expert would explain how things went in trials, how things went outside trials (including the three patient deaths), and then let patients decide. For patients on the fence, the expert provides their assessment of relative safety, but ultimately leaves the decision to patients.

If a patient came in feeling strongly about wanting Elevidys and was eligible, the expert would be comfortable prescribing it. As a precautionary measure beyond current requirements, the expert would likely obtain a liver ultrasound, conduct labs, and if everything looked acceptable, proceed with treatment. This represented the expert's

practical approach to balancing the therapy's potential benefits against recently emerged safety concerns.