Life in the Fast Track
Two companies, two drugs for Duchenne muscular dystrophy in the expedited approval process. The stakes are high, especially for patients and their families.

By Thomas Reinke

Orphan drugs are one of the fastest-growing segments of the specialty market. Drug manufacturers are lured by the potential riches of being the exclusive agent for a particular, if rare, condition and a variety of incentives, ranging from research grants to expedited approval from the FDA.

But that is only half of the story. Orphan drugs are a risky business. Years of research and clinical trials plus investments of hundreds of millions of dollars can come up short.

Duchenne muscular dystrophy is a prime example. Muscular dystrophy has some name recognition because of the Jerry Lewis telethons. Duchenne muscular dystrophy is a rare variant of the disease. It is an X-linked recessive genetic condition, so women are carriers but are hardly ever affected. More than 2 million male infants are born each year in the United States, and somewhere between 350 and 620 of them have Duchenne muscular dystrophy (a milder version, called Becker muscular dystrophy, is even rarer). The signs and symptoms of the progressive muscle weakness that characterize muscular dystrophy typically begin when children are toddlers. Many of those with the disease end up in wheelchairs in their teens. While people with Duchenne muscular dystrophy are living longer—some are surviving into the 40s and 50s—most die in their 20s or 30s from respiratory or heart failure.

The race is on
Corticosteroids can slow the muscle loss and are used to treat the debilitating symptoms, but until recently there wasn’t even a candidate for a targeted treatment of Duchenne muscular dystrophy. Now two companies, BioMarin Pharmaceuticals in San Rafael, Calif., and Sarepta Therapeutics in Cambridge, Mass., are in neck-and-neck competition to fill the void.

In 2014, BioMarin spent $680 million to get into the race by acquiring Prosensa, the original developer of drisapersen (Kyndrisa), the drug it is now promoting. BioMarin went out on a limb after GlaxoSmithKline pulled out because of poor clinical trial results.

Sarepta has no approved drugs and reported no revenue in 2015 through September. It is losing $200 million annually bringing its candidate, eteplirsen, to market.

Decades of research has identified only a questionable and very limited pathway for modifying the progression of Duchenne muscular dystrophy. Both companies have developed “exon-skipping” agents that fix a break in the gene that produces dystrophin, a protein that is thought to be critical to maintaining muscle mass and function. Exon skipping is a treatment strategy in which sections of genetic code are “skipped,” allowing cells to manufacture dystrophin that is partially functional. This approach won’t cure Duchenne muscular dystrophy but it could help slow down the muscle weakness and atrophy that gets worse and worse.

While exon-skipping therapy may be the best available strategy for treating Duchenne muscular dystrophy, only a small proportion—about 13%—of patients have the mutation targeted by these agents. So we are talking a relatively rare mutation among those with a rare disease—a fraction of a fraction.

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The two companies have come to a point where their FDA approval decisions may be very close to one another. Of course, achieving first-in-class approval is often a huge market advantage, and drug developers pursue one or more the FDA’s expedited review designations to grab it. On the surface, pursuing an expedited review is a no-brainer. But in this case, it may prove to haunt one or both of these companies and their medications.

The FDA has created several types of faster reviews—fast track, breakthrough, accelerated, priority—and a single drug may be given several designations at the same time. More designations may mean more technical assistance from the agency. BioMarin’s drisapersen received three and Sarepta’s eteplirsen just one, so it seemed like BioMarin was ahead of the game.

In addition to streamlining the approval process, these shortcut designations are important because they can create a close—perhaps too close, say critics—working relationship between the drug developer and the FDA. The agency emphasizes that a faster process does not mean automatic approval, but drug developers figure once they are in a speedier approval track, they will get some helpful guidance from the FDA on trial design and endpoints and perhaps benefit from nontraditional efficacy and safety measurements.

Drisapersen was reviewed by the FDA’s advisory panel of outside experts on Nov. 24, 2015. Despite the three expedited review designations, the drug got a tough review. The panel focused on dystrophin levels as a biomarker and clinical results from a 6-minute walk test (6MWT). The reviewers, in looking at one small study with the 6MWT, found that “the overall persuasiveness of this study appears to be low.” A second study came to a similar conclusion, and a third larger study produced negative results.

The drug was designed to increase dystrophin levels, and here is what the advisory panel said: “Drisapersen has little effect on increasing dystrophin levels, the putative mechanism of action,” and “any effect on dystrophin appear so small as to be unlikely to have resulted in clinical benefit.”

Regarding safety, the federal agency’s reviewers found that “even in the context of an invariably disabling and fatal disease such as DMD [Duchenne muscular dystrophy], the safety profile of drisapersen is concerning.”

The briefing document says the drug caused proteinuria and other renal abnormalities in 61% of patients and thrombocytopenia, which occurred in 2% of subjects 14 to 26 months after the first dose, possibly suggesting that the risk increases with duration of therapy.

BioMarin was expected to get an FDA decision before New Year’s Day. But in mid-December, the company announced that the agency had delayed making a decision until some time this month.

Meanwhile, Sarepta Pharmaceutical’s eteplirsen is scheduled to come before the same FDA advisory review panel that reviewed drisapersen this month.

The FDA has not yet issued its briefing document on eteplirsen. In October 2015, Sarepta reported results from a phase 2 study that trial participants who were treated with eteplirsen experienced a slower rate of muscle decline and were generally able to walk farther than control patients. In addition, pulmonary function remained relatively stable over the 3-year study period and muscle biopsy data confirmed dystrophin production in nearly all patients.

Importantly, though, this study included only 12 patients. It’s impossible to conduct large trials for rare diseases, but that’s a very small study, which, quite naturally, raises some concern about the validity and generalizability of the results.

Patients still waiting
There’s a lot riding on the competition between BioMarin and Sarepta for those companies, their investors, and their employees. And for people who watch the pharmaceutical industry, two companies in a tight race is great drama.

But that all pales in comparison to what patients and their families have at stake. Decades of research have not identified a definitive therapeutic target for Duchenne muscular dystrophy. Gene therapy is years—maybe even decades—away. Exon-skipping therapy offers a glimmer of hope. It’s safe to say that the patients and families really don’t care who wins, BioMarin or Sarepta. They just hope that at least one of them has an effective drug that can help some Duchenne muscular dystrophy patients.