24 May 2023 | **Analysis**

Sarepta's DMD Gene Therapy: Approval Delayed And Indication Narrowed, But Still On Track

by Derrick Gingery

As Sarepta again brings a product application from the brink of rejection to the cusp of approval, the one-month review delay creates more assurance the confirmatory EMBARK trial will be completed as well as providing more time for label negotiations with the US FDA.

Sarepta Therapeutics, Inc. must wait another month for the likely accelerated approval of its proposed gene therapy for Duchenne muscular dystrophy, as well as deal with a restricted patient population, at least at the start of marketing.

The company announced on 24 May that the US Food and Drug Administration needed more time to complete its review of the pending biologics license application for SRP-9001 (delandistrogene moxeparvovec), including final label negotiations and postmarket commitment discussions. A decision now is expected by 22 June.

Sarepta had been given a 29 May user fee goal.

Key Takeaways

- The FDA needs more time to complete labeling negotiations and postmarketing discussions
- SRP-9001 is expected to be limited to DMD patients age four and five pending the completion of the EMBARK trial
- The delay increases the certainty that EMBARK will be completed on time

SRP-9001 is proposed for ambulatory patients with DMD and a confirmed mutation of the DMD gene. For safety reasons, Sarepta proposed a contraindication in patients with a deletion fully including exons 9

through 13 in the DMD gene.

Sarepta intends the gene therapy to change the DMD disease trajectory to a milder Becker muscular dystrophy-like phenotype.

Sarepta said in a press release that after discussions with the FDA, an accelerated approval is possible, but initially only in patients age four and five. The indicated population may be expanded upon completion of the EMBARK study, which is intended to confirm the benefit as part of the accelerated approval.

"The agency has informed Sarepta that, in addition to confirming the results of the initial BLA approval, if the trial meets its objectives the agency intends to entertain a non-age-restricted expansion of the SRP-9001 label based upon the review of the EMBARK data," the company said in the statement.

Guggenheim analysts said in a note that about 700 to 800 patients may be eligible for the gene therapy after 22 June and that the delayed decision was not material.

"While the outcome may not be in line with 'time-is-muscle,' it might be the right regulatory decision, based on the available clinical evidence," they said.

An age restriction upon accelerated approval is a set-back for Sarepta, but reflects the questions FDA reviewers have raised about the product's efficacy.

DMD patients and advocates vowed to fight for the indicated population to be expanded.

"While we are optimistic for a potential approval for four- to five-year-olds, we recognize the heartbreak that many families outside of this criteria feel today," Parent Project Muscular Dystrophy said in a statement. "We will continue to advocate for appropriate expanded eligibility."

Commercial Fate Of Sarepta's DMD Gene Therapy Remains Tied To EMBARK

By Jessica Merrill

24 May 2023
The company guided investors to expect a narrow initial label under a US FDA accelerated approval for SRP-9001, with expansion possible based on EMBARK.

Read the full article here

Agency officials were not convinced SRP-9001 was effective at stabilizing DMD, stating that the disease's natural history suggests patients improve on the North Star Ambulatory Assessment (NSAA), Sarepta's endpoint for measuring disease progression, until about age six and then

begin to decline.

SRP-9001 administration began at age four, when patients would be expected to be improving. And while patients on the gene therapy also showed improvement compared to placebo, the natural history data made discerning the benefit difficult. The treatment did not show efficacy in patients age six and seven. (Also see "*Unpredictable DMD Progression Complicates Sarepta's Gene Therapy Efficacy Claims*" - Pink Sheet, 16 May, 2023.)

The Center for Biologics Evaluation and Research's Cellular, Tissue and Gene Therapies Advisory Committee narrowly voted to recommend accelerated approval for the product despite the efficacy questions. (Also see "*Slim Adcomm Majority Boosts Sarepta's Gene Therapy In Duchenne Muscular Dystrophy*" - Pink Sheet, 12 May, 2023.)

More Certainty About EMBARK's Completion

The delay also could be beneficial for Sarepta's efforts to confirm clinical benefit.

FDA reviewers questioned whether the company could complete the EMBARK trial following an accelerated approval, in part because patients could drop-out to ensure they received the gene therapy instead of placebo.

Sarepta argued that drop-outs are not likely because the company would need about four months to make the product commercially available after approval, which would be about the time of final study visits for the first part of EMBARK. The company also suggested patients would not give up guaranteed treatment to try navigate the many hurdles to commercial access. (Also see "*Gene Therapy: Four-Month Lag In Commercial Access Protects EMBARK Study, Sarepta Says*" - Pink Sheet, 13 May, 2023.)

With the decision delayed, fewer patients could be in position to withdraw from EMBARK upon approval. By 1 July, 53 US patients will have completed the 52-week primary endpoint visit, leaving only 27 that could theoretically withdraw. On 1 June, just after the original decision date, 38 US patients will have completed the 52-week endpoint visit and 42 could theoretically withdraw.

EMBARK already is fully enrolled and has moved much faster than the confirmatory studies for Sarepta's other DMD treatments. (Also see "*Why Sarepta's Gene Therapy Trial Enrollment Has Been More Successful Than Its Other DMD Therapies*" - Pink Sheet, 9 May, 2023.)

A Test For Accelerated Approval In Gene Therapy

SRP-9001 also may be a test case for CBER Director Peter Marks' vision for using accelerated approval for gene therapies treating rare diseases. Marks has made clear that he wants the pathway used in the sector.

“The science that’s inherent in the development of gene therapy really lends itself to accelerated approval,” he said 17 May during the Food and Drug Law Institute Annual Conference.

“What you’re doing often, it’s really simple stuff in some ways,” he added. “Sometimes it’s very complex, but sometimes it’s as simple as something is empty and you have to fill it or something is filled and you have to empty it. Because you can measure those things, if you can convince yourself that you’re able to measure the difference and that measuring that difference is able to be correlated with some clinical outcome, you basically have what you need for accelerated approvals.”

Marks warned that CBER still will be “following the science” when making decisions.

“We won’t be able to have a magic wand and say ‘Poof’ everything gets an accelerated approval,” he said.

But Marks also said rare diseases deserve some regulatory flexibility.

“For these really small populations where there’s no alternative, the choice is something or really inexorable decline or death, that’s a different benefit-risk calculus than if it’s a product for something where we have a lot of other therapies around for it,” he said.

The Center for Drug Evaluation and Research embraces a similar policy allowing regulatory flexibility in rare diseases. When SRP-9001 reached the application assessment stage, stakeholders told CBER that their reviewers should follow the same policy. (Also see "*Sarepta’s DMD Gene Therapy, Like Exondys 51, Is Foundational, Advocates Argue*" - Pink Sheet, 7 May, 2023.)

Sarepta’s Familiar Path From No To Yes

SRP-9001 has undergone a substantial transformation in perception at the FDA over the past few months. Review staff initially did not want to file the application, but Marks overruled them and forced an assessment. (Also see "*CBER Director Marks’ Intervention On Sarepta Gene Therapy Filing Decision Appears To Backfire*" - Pink Sheet, 15 Apr, 2023.)

Reviewers again raised multiple questions during the review that appeared to endanger the application, including the worry that patients who take the product may not be able to receive another gene therapy using the same vector. (Also see "*Sarepta’s DMD Gene Therapy: FDA Says Concluding Effectiveness Or Ineffectiveness Is ‘Challenging’*" - Pink Sheet, 10 May, 2023.)

But thanks in part to patients and advocates pushing for approval, after a favorable advisory committee vote the product appears to be on the cusp of becoming the first gene therapy available for DMD. (Also see "*The Power Of The Open Public Hearing*" - Pink Sheet, 21 May, 2023.)

Sarepta's initial DMD treatment, Exondys 51 (eteplirsen), also saw the FDA raise efficacy questions. That product also received an accelerated approval, which remains controversial because of the FDA's internal disagreements. (Also see "*Woodcock's 'Bias' In Sarepta Case Made Jenkins Worry About Future Drug Reviews*" - Pink Sheet, 31 Jul, 2017.)