FDA Places Hold on Phase 1/2 Trial of Sarepta’s Gene Therapy for DMD

A Phase 1/2 trial evaluating Sarepta’s microdystrophin gene therapy candidate for Duchenne muscular dystrophy (DMD) was placed on clinical hold by the U.S. Food and Drug Administration.

The FDA found trace amounts of plasmid DNA in the raw material used to make the drug. The fragments don’t seem harmful in preliminary tests and the dosing of patients by the end of 2018 remains on track, according to Sarepta officials.

Nationwide Children’s Hospital in Columbus, Ohio, working with Sarepta, has developed an action plan to be submitted to the FDA. It includes the use of GMP-Source plasmids only to ensure the quality and controlled composition of the DNA used in the therapy.

Based on the proposed plan and rapid response to FDA, Sarepta believes there will be no delays in the dosing of patients originally planned for the end of 2018.

“Patient safety is our top priority at Sarepta as we know it is for Nationwide Children’s Research Institute,” Doug Ingram, Sarepta’s president and CEO, said in a company news release.

“We intend to rapidly respond to the FDA’s clinical hold letter, including a commitment to the Agency to only use GMP-s plasmid,” he said. “Independently, we will also request a meeting with the Agency to discuss the micro-dystrophin program with the goal of commencing a pivotal trial by year-end 2018.”

After positive results on animal models, the gene therapy that delivers a functional version of the dystrophin gene (DMD), missing in people with Duchenne muscular dystrophy, advanced to clinical trials in patients.
The investigative therapy, called rAAVrh74.MHCK7.micro-dystrophin, is based on a viral carrier — the adeno-associated virus, or AAV — to deliver a shorter version of the DMD gene, called microdystrophin.

This shorter gene contains enough information to produce a protein that is able to restore the function of dystrophin.

A Phase 1/2 clinical trial (NCT03375164) was initiated at Nationwide Children’s Hospital with the support of Sarepta Therapeutics.

The trial is currently recruiting patients and is expected to enroll 12 male children, equally divided into two age groups: 3 months to 3 years, and ages 4 to 7.

A single dose of the gene will be infused into the blood of each patient, who will also receive a regimen of corticosteroids to prevent immune responses against the drug.

A muscle biopsy will be done at the start of the study, before gene therapy, and again 90 days after treatment to see if the therapy replaced the missing dystrophin protein.

Patients will be followed over three years, during which time they will be monitored for side effects and changes in muscular capacity through physical examinations.

Recently, promising interim results of the trial were announced by Sarepta. The therapy was able to increase the production of a functional dystrophin protein and reduce muscle damage in three boys ages 4-7.

Now, the trial has been put on hold by the FDA due to the presence of trace amounts of DNA in the raw material used to produce the DNA components of drug. These components are called plasmids, small circular, closed DNA molecules that can be used to produce proteins and create viral vectors for gene therapy.

Preliminary testing indicates that these trace fragments are quickly cleared by the body and do not present any safety concerns.

The Phase 1/2 trial is currently recruiting patients. For more information, visit the clinical trial’s official website here.