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DIVE BRIEF // ALS drug development

FDA staff hold ‘major concerns’ with Brainstorm ALS therapy, documents show

A panel of expert advisers will meet Wednesday to review the stem cell treatment, which has become the latest test case in a debate over regulatory flexibility.

Published Sept. 25, 2023

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Courtesy of U.S. Food and Drug Administration

Food and Drug Administration scientists have “major concerns” with an application filed by biotechnology company BrainStorm Cell Therapeutics for approval of a personalized stem cell treatment for amyotrophic lateral sclerosis, documents posted online Monday show.

According to the documents, FDA staff found BrainStorm’s approval application, filed last September, to be “scientifically incomplete.” They also determined the company’s manufacturing data were “grossly deficient,” and cited missing biomarker results in dismissing after-the-fact analyses that BrainStorm conducted to support its application.

Those concerns led the FDA in November to turn back BrainStorm’s application, issuing the company a “refuse to file” letter. BrainStorm then took the rare step earlier this year of submitting its application over the FDA’s protest.

On Wednesday, the agency will convene a panel of expert advisers as part of its review of BrainStorm’s therapy, called debamestrocel or NurOwn. While the FDA isn’t required to follow the advice of its advisory committees, it usually does.

The documents released ahead of Wednesday’s meeting show the FDA will make a strong case for why BrainStorm’s accumulated clinical trial evidence doesn’t meet its bar for approval. Shares in BrainStorm fell by one-third in Monday morning trading following the documents’ release.

Yet the medicine has become a flash point in an at times contentious debate over how accommodating the agency should be in reviewing drugs of ALS, a devastating neurological disease that typically leads to death three to five years after symptoms begin.

The FDA has pledged to take a flexible approach in its review of ALS drugs, and recently approved medicines from Amylyx Pharmaceuticals and Biogen despite mixed results in support of their effectiveness. BrainStorm cited those drugs, and the FDA’s concerns about their trial evidence, in making its case for NurOwn’s approval.

Amylyx was helped by a positive clinical trial result for its drug, while the FDA and its advisers agreed Biogen’s drug showed an effect on levels of an important protein that are “reasonably likely” to predict a clinical benefit.

In BrainStorm’s case, NurOwn failed to met its primary and secondary goals in a Phase 3 study of nearly 200 people with ALS. Notably, the FDA found that, at study completion, more trial participants in the arm receiving BrainStorm’s drug had died than in the group who got a placebo.

Agency staff were also unconvinced by “retrospective” evidence BrainStorm claims show NurOwn helped certain patients, noting

that post hoc and subgroup analyses come with high risk of false positive conclusions.

”[S]uch exploratory analyses provide little confidence on which to base regulatory decisions, and though they may serve to generate hypotheses for testing in future trials, cannot compensate for negative results in a well-controlled study,” FDA staff wrote.

The agency also detailed its issues with how BrainStorm intends to manufacture NurOwn, which is built from mesenchymal stem cells collected from each patient. These stem cells, once injected into the cerebrospinal fluid, are meant to secrete proteins that help neurons survive.

In its own briefing document, BrainStorm does not directly address the FDA’s concerns about its ability to reliably produce NurOwn.

At Wednesday’s meeting, BrainStorm and the FDA will each make presentations, as will a director of a stem cell research center who was invited to speak on manufacturing issues. Advisers will also hear from patients and patient advocates during an open public hearing.

The panel of 20 voting advisers will be asked to vote on whether BrainStorm’s clinical trial data meet the FDA’s bar for “substantial evidence of effectiveness” and, if not, how a subsequent trial should be designed.