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# BrainStorm's ALS Treatment NurOwn, Filed Over Protest, Will Get US FDA Panel Review

by Sue Sutter

A November 2022 refuse-to-file letter cited clinical and statistical issues for the stem cell therapy, which failed its Phase III clinical efficacy endpoint. However, BrainStorm has consistently asserted that NurOwn demonstrated benefit in patients with less advanced disease at baseline, and it is encouraged by regulatory flexibility FDA recently has shown for the neurodegenerative disease.

*BrainStorm Cell Therapeutics Inc.* is taking an unusual regulatory route to the US Food and Drug Administration advisory committee meeting it wanted for NurOwn, its stem cell therapy for amyotrophic lateral sclerosis.

The FDA has agreed to convene an advisory committee review of the NurOwn biologics license application, which is being filed over protest following a refuse-to-file action, the company said on 27 March.

"The FDA provided us with more than one path to an advisory committee meeting for NurOwn. Our goal has always been to make NurOwn available to people living with ALS as quickly as possible, therefore we chose the file-over-protest pathway since this offered the fastest path to an adcomm and regulatory decision relative to other pathways provided by FDA," BrainStorm president and CEO Chaim Lebovits said.

The meeting date has not yet been set.

## Headwinds …

BrainStorm is heading into the advisory committee review amid seemingly strong crosswinds.

The company brings with it a 189-patient Phase III trial that failed its prespecified clinical

efficacy endpoint, but for which it repeatedly has asserted are favorable findings in the subgroup of patients with less advanced disease at baseline.

However, the company's consistently bullish view of the data in talking to the ALS community led the Center for Biologics Evaluation and Research to publicly state that the failed study did not show evidence of efficacy.

NurOwn also is going into the advisory committee review with CBER's Office of Therapeutic Products (previously known as the Office of Tissues and Advanced Therapies) having found the original BLA deficient for filing.

In addition, the file-over-protest mechanism is little used, with little apparent success in getting products approved through this route.

*PTC Therapeutics, Inc.* invoked the file-over-protest mechanism for its Duchenne muscular dystrophy treatment Translarna (ataluren) following a February 2016 refuse-to-file letter and a rejected appeal of that letter. At a September 2017 meeting, an advisory committee voted 10-1 that the efficacy data were inconclusive. (Also see "*Patients Can't Clear Translarna's Data Hurdles As PTC Falls Short At FDA Panel*" - Pink Sheet, 28 Sep, 2017.) A complete response letter was announced in October 2017.

In December 2007, the FDA issued a "not approvable" letter for *Pharmacyclics, Inc.*'s anti-cancer agent Xcytrin (motexafin gadolinium), an application that was filed over protest after a refuse-to-file letter. (Also see "*Pharmacyclics Xcytrin Is "Not Approvable" For Brain Metastases*" - Pink Sheet, 1 Jan, 2008.)

In November 2006, *Oscient Pharmaceuticals Corporation* withdrew an sNDA for the fluoroquinolone Factive (gemifloxacin) for treatment of acute bacterial sinusitis following a negative advisory committee review. (Also see "*Factive Superiority Trials Needed to Evaluate Efficacy In Acute Sinusitis, FDA Committee Says*" - Pink Sheet, 13 Sep, 2006.) The sNDA had been filed over protest after the agency initially refused to file the application. (Also see "*Oscient's Factive To Get Advisory Committee Review For Acute Bacterial Sinusitis*" - Pink Sheet, 28 Jun, 2006.)

## … And Tailwinds

However, the current regulatory tailwinds in the ALS space may help BrainStorm.

News of the file-over-protest action and advisory committee came just days after an advisory committee unanimously supported accelerated approval of *Biogen, Inc.* and *Ionis Pharmaceuticals, Inc.*'s tofersen for ALS patients with the SOD1 genetic mutation. (Also see "*Accelerated Approval Is US FDA Panel's Preferred Path For Biogen/Ionis's Tofersen In ALS*" - Pink Sheet, 22 Mar, 2023.)

The Phase III trial for tofersen also failed its prespecified primary clinical endpoint, but Biogen is pursuing accelerated approval on the basis that reduction in plasma neurofilament light chain (NfL) is a surrogate endpoint reasonably likely to predict clinical benefit.

The tofersen advisory committee review shows that a failed efficacy trial may not be a hurdle to approvability in ALS, although the panel majority did not believe the currently available clinical and biomarker evidence supported regular approval of the drug.

> *"We are incredibly encouraged by the regulatory flexibility that the FDA is showing in the ALS space." – BrainStorm's Stacy Lindborg*

In addition, the FDA repeatedly has highlighted its willingness to exercise regulatory flexibility in the ALS space, both at the tofersen review and in its September 2022 approval of *Amylyx Pharmaceuticals, Inc.*'s Relyvrio (sodium phenylbutyrate/taurursodiol, also known as AMX0035).

Both the Relyvrio and tofersen applications were handled by the Center for Drug Evaluation and Research's Office of Neuroscience, so the extent to which CBER's OTP would similarly view regulatory flexibility in the context of a stem cell therapy for ALS remains to be seen.

"We are incredibly encouraged by the regulatory flexibility that the FDA is showing in the ALS space," BrainStorm co-CEO Stacy Lindborg said in an interview with the *Pink Sheet*.

"ALS is an incredibly heterogeneous disease, complicated to study," she said. "We have a very comprehensive dataset, one that we're very confident in but that has complexities that we have long believed … would really benefit by a rigorous discussion with multiple parties, including FDA reviewers, company experts and investigators that conducted the program, and then input from the stakeholders in the community. So this strategy of seeking an adcomm has really been central to our actions, and we think the robust and complicated dataset would benefit by deep and thoughtful discussion."

As with any ALS drug adcomm, there is likely to be outpouring of patient community support for the product's approval. At the tofersen advisory committee, 26 individuals spoke during the open public portion, 22 of whom advocated for approval.

In December, I AM ALS delivered a petition with more than 30,000 signatures to CBER director Peter Marks requesting the agency hold an advisory committee review of NurOwn.

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Brian Wallach, an individual living with ALS who founded the advocacy group, thanked the FDA and BrainStorm for convening the NurOwn review. "The ALS community has waited years for this adcomm. It is time to let the science have a full, fair and transparent hearing so that we can get this treatment to people who are living with and dying from ALS as soon as possible," he said in a statement.

## Complex Regulatory History

NurOwn consists of mesenchymal stem cells derived from adult bone marrow and induced to secrete high levels of neurotrophic factors (MSC-NTF). It is administered intrathecally.

In November 2020, BrainStorm announced that a Phase III trial failed its prespecified primary endpoint.

The randomized, placebo-controlled study enrolled 189 individuals with rapidly progressing ALS. The primary efficacy endpoint was a responder analysis evaluating the proportion of participants who experienced an improvement of 1.25 points per month in the post-treatment Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) slope.

BrainStorm reported the primary endpoint was achieved in 34.7% of NurOwn subjects versus 27.7% of those receiving placebo (p=0.453), a difference that was not statistically significant.

> ***BrainStorm submitted the NurOwn BLA on 9 September, two days after an FDA advisory committee voted 7-2 that the available evidence was sufficient to support regular approval of Amylyx's Relyvrio for treatment of ALS.***

Despite the miss on the primary analysis, the company has consistently suggested a potential path to approval via subgroup efficacy, specifically in a prespecified subgroup of patients with less severe disease.

However, in March 2021 CBER posted a statement on its website saying that with completion of the Phase III trial, "it has become clear that data do not support the proposed clinical benefit of this therapy. Data indicated that none of the primary or secondary endpoints were met in the group of patients who were randomized."

The agency also cited a "modest excess in deaths." (Also see "*BrainStorm's Phase III Data Do Not*

*Support Clinical Benefit Of NurOwn In ALS, US FDA Says*" - Pink Sheet, 3 Mar, 2021.)

CBER's statement was unusual in that the FDA generally is unwilling to publicly discuss the status of an investigational drug outside of the setting of an advisory committee review.

In August 2022, the company announced plans to file a BLA, citing the increasingly positive regulatory environment for ALS drugs, as well as newly corrected subgroup analyses for a secondary endpoint in its Phase III trial. (Also see "*ALS 'Urgency', US FDA Regulatory Environment Justify Filing NurOwn, BrainStorm Says*" - Pink Sheet, 24 Aug, 2022.)

BrainStorm said it submitted the NurOwn BLA on 9 September. This was two days after the Peripheral and Central Nervous System Drugs Advisory Committee voted 7-2 that the available evidence was sufficient to support regular approval of Amylyx's Relyvrio for treatment of ALS. (Also see "*Second Time's The Charm: Amylyx's ALS Drug Wins US FDA Panel Nod*" - Pink Sheet, 7 Sep, 2022.)

The September meeting marked the second panel review of Relyvrio in the same review cycle. At a 30 March meeting, the committee voted 6-4 that data from the CENTAUR trial and the open-label extension do not establish a conclusion that AMX0035 is effective. (Also see "*Amylyx's Relyvrio: The Road To Regulatory Flexibility And US FDA Approval*" - Pink Sheet, 29 Sep, 2022.)

The FDA approved Relyvrio on 29 September. (Also see "*Regulatory Flexibility: US FDA Approves Amylyx's Relyvrio For ALS Despite 'Degree Of Residual Uncertainty'*" - Pink Sheet, 29 Sep, 2022.)

BrainStorm received a refuse-to-file letter for the NurOwn BLA on 8 November. The company said the letter raised primarily clinical and statistical issues that were already known, namely that the pivotal clinical trial did not meet its primary endpoint. (Also see "*BrainStorm Hoping For Advisory Committee After FDA Refuses To File BLA For Its ALS Cell Therapy*" - Pink Sheet, 14 Nov, 2022.)

The agency and company held a type A meeting on 11 January. On 25 January, BrainStorm met with CBER as part of a dispute resolution proceeding, during which the agency provided multiple options to return the BLA to active review and to convene an advisory committee.

Lindborg said the company could have chosen to revise the BLA and resubmit, but that approach "could present substantial delays to the overall regulatory pathway. We certainly have seen other sponsors that have experienced lengthy delays. The file-over-protest option not only provided the shortest amount of time to adcomm [but] also provides the ability to address the matters identified by the FDA in the refusal-to-file letter through amendments to the BLA."

Lindborg said the agency is working to set a date for the adcomm, which in turn will give

BrainStorm clarity as to the regulatory timeline for the BLA review.

She said it is premature to speculate on an accelerated approval versus a regular approval pathway. However, the company is making plans for a rigorous, controlled postapproval study.

"While we're confident in the data, we certainly understand that there will be outstanding questions. We have opted to file and to seek the ability to allow access to NurOwn while doing a study in parallel and will be prepared in the future and certainly by the time of an adcomm to talk about what would be a post-commitment study if approved."

## Quantum Of Evidence

BrainStorm intends to present the agency's external advisors with "a strong set of evidence," including clinical efficacy and biomarker data, Lindborg said.

"We have a well-conducted Phase III trial that really, by almost every standard, has operated exactly as planned," she said. "Randomization was very effective. We have a very high completion rate. We have fewer deaths than we expected. We have a very strong safety profile."

"We did enroll a set of patients that were more reflective of the broader ALS community, and a subset of those patients had advanced ALS, which impacted the analyses that are focused on the entire study population," she sad.

When the company looked at a prespecified group of patients with less disease activity at baseline (ASLFRS-R ⩾35), there was a large treatment effect across all endpoints with NurOwn compared to placebo, and a statistically significant difference on a key endpoint, the average change from baseline, Lindborg said.

In addition, the company has continued to conduct sensitivity analyses and recently presented data showing the impact of the floor effect of the ALSFRS-R scale.

"In these participants that started the trial with advanced ALS, what that means is that they started with many items on the ALS Functional Rating Scale that had zeroes, so the scale is not able to measure ongoing progression in in those dimensions," Lindborg said. "As that accumulates across, we see a plateauing and a scale-wide floor effect."

"When we look at assessing the treatment effect by focusing on participants that are not impacted by the floor effect … more than half of the study that actually has no presence of zeros on their baseline items, and therefore the scale is effectively able to measure disease progression at the start of the trial."

Among study participants who had no evidence of a floor effect at baseline, 40.8% in the NurOwn

arm met the primary endpoint, compared with 22.8% in the placebo group.

“The biomarker data also is another point of very, very important data because it's not hindered as this clinical scale is with a floor effect,” Lindborg said. “We actually see strong and consistent biomarker effects and biological effects of NurOwn in all patients. And we see that there are biomarkers that are predictive of clinical response observed in the trial that are very important to ALS, the markers of neuroinflammation, neurodegeneration and neuroprotection.”

One of the biomarkers that showed a treatment-related effect was NfL, she said.

## Bolus Of Neurodegenerative Disease Adcomms

The BrainStorm announcement means that three neurodegenerative disease treatments will be the focus of high-profile advisory committee meetings in the coming months.

The agency is expected to convene its Peripheral and Central Nervous System Drugs Advisory Committee to consider conversion from accelerated to regular approval for *Eisai Co., Ltd.* and Biogen’s Alzheimer’s drug Leqembi (lecanemab-irmb), which has a 6 July user fee date. (Also see "*Transparency In Alzheimer’s: AdComm Expected On Regular Approval For Eisai/Biogen’s Leqembi*" - Pink Sheet, 6 Mar, 2023.)

In addition, *Sarepta Therapeutics, Inc.*'s Duchenne muscular dystrophy gene therapy SRP-9001 will be vetted by the Cellular, Tissue and Gene Therapies Advisory Committee. The product’s user fee date is 29 May. (Also see "*Sarepta’s DMD Gene Therapy Adcomm Likely To Focus On Dystrophin As A Surrogate Endpoint*" - Pink Sheet, 19 Mar, 2023.)