

Biogen Must Prove Tofersen in Genetically Defined ALS, Establish New Surrogate Endpoint

The FDA is taking time to review the drug for SOD1-ALS with data from clinical trials and an open-label study extension, considering neurofilament as a surrogate endpoint.

By Jessica Kim Cohen

IN TAKING UP Biogen's application to market an investigational drug for a genetic form of amyotrophic lateral sclerosis (ALS), the US Food and Drug Administration will have to contend with a new biomarker for the disease.

The FDA accepted Biogen's new drug application for tofersen last summer and granted the drug priority review. The company is studying the antisense drug as a treatment for superoxide dismutase 1 ALS (SOD1-ALS), a rare form of the disease with an underlying genetic cause, and if approved, it could be the first drug for this subset of ALS patients, according to Biogen.

ALS, which is also known as Lou Gehrig's disease, is a progressive and fatal neurodegenerative condition that causes muscle

weakness, atrophy, and loss of control. Patients eventually lose their ability to move, speak, and even breathe. While the majority of cases are sporadic, around 10 percent have a familial origin. Mutations in more than 40 genes have been associated with ALS, though mutations in SOD1 – which was first linked to ALS in 1993 – appear to be the most common. According to one study, SOD1-ALS accounts for about 2 percent of ALS cases globally.

Biogen is developing tofersen for SOD1-ALS because it is one of the better understood genetic forms of the disease, said Toby Ferguson, head of the neuromuscular development unit at Biogen and lead on the tofersen program. The drug binds to and degrades SOD1 mRNA

in an effort to reduce the production of SOD1 proteins.

The tofersen program builds on lessons learned from dexamipexole, a failed ALS therapy that Biogen stopped developing in 2013. With dexamipexole, the company was trying to develop a drug in an all-comer ALS population. But after dexamipexole did not improve ALS patients' function or survival in a Phase III trial, Biogen began studying the underlying genetic causes of ALS in an effort to identify better drug targets.

"We changed how we thought about targets," Ferguson said. Biogen wanted to continue its work in ALS, "but we were quite anxious about these more general approaches." ▶

Despite the shift in focus, tofersen has had some bumps in its development path. In a Phase III trial, the drug failed to improve patients' physical functions. Still, Biogen remains committed. "The available data show that tofersen has the potential to make a meaningful difference for people with SOD1-ALS," said Priya Singhal, who recently became the head of Biogen's drug development efforts, in a statement last year.

Biogen is seeking tofersen's market authorization through the FDA's accelerated approval pathway, a program designed to more quickly approve drugs that treat serious conditions using surrogate endpoints – markers that are expected to predict that a drug will benefit patients but aren't a direct measure of clinical benefit. In the case of tofersen, Biogen is using levels of neurofilament, a marker of neurodegeneration, as a surrogate endpoint in its clinical trials, and in its FDA application, the company will have to convince the agency that changes in this protein are reasonably likely to be a proxy for treatment benefit in patients.

"This will be the first time that an application has [used] neurofilament" as a surrogate endpoint for ALS, said Frank Diaz, an assistant professor of neurology at Cedars-Sinai who researches ALS biomarkers. "It will be very interesting to hear what they [the FDA] have to say."

A promising biomarker

Even though tofersen, which Biogen licensed from Ionis Pharmaceuticals in 2018 in a collaborative development and license agreement, failed to meet its primary endpoint in a six-month Phase III randomized study, there were trends in the data that suggested to Biogen that the drug may be reducing disease progression.

Specifically, the drug failed to significantly improve patients' physical functions as measured by the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), compared to placebo in the study, dubbed VALOR. But Biogen noted that secondary endpoints, including reductions in plasma neurofilament light chain and SOD1 protein levels in cerebrospinal fluid, suggested it might be having an effect.


Based on this, Biogen is pursuing accelerated approval through the FDA using neurofilament as a surrogate endpoint. However, since tofersen didn't improve patient function in the VALOR trial, some neurologists are questioning whether it is appropriate for the FDA to approve the drug based on a novel biomarker.

Neurofilament is still an experimental biomarker for neurodegeneration, said Stephen Scelsa, director of the ALS Center at Mount Sinai Downtown Union Square and a professor

of neurology at the Icahn School of Medicine at Mount Sinai in New York. Scelsa was a co-investigator on a recently approved ALS drug, Amylyx's Relyvrio (sodium phenylbutyrate and taurursodiol), which in studies appeared to put the brakes on functional decline in ALS patients but didn't appear to change neurofilament levels, he said.

Some recent research suggests that neurofilament levels can rise as far back as a year before a patient's first ALS symptoms emerge. But neurofilament isn't specific to SOD1-ALS, or even ALS generally, since the biomarker has also been detected in other neurodegenerative conditions. Neurofilament levels can increase in blood and cerebrospinal fluid when neurons and axons are damaged, and though higher levels of the protein are associated with faster ALS progression and decreased survival, it is also found in healthy neurons.

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With the VALOR trial results, Biogen claims to have demonstrated a "trend toward improving the clinical outcomes" based on neurofilament levels, said Martina Wiedau, who leads the ALS clinic and research center at the University of California, Los Angeles Health's neurology department. She's hoping to see additional research on the drug with more participants and longer follow-up as well as studies on whether patients enrolled earlier in the disease course have better outcomes.

"I'm still hopeful that this medication will work," she said. "The neurofilament findings are definitely hopeful ... but I do think that they [Biogen] need more data."

In its application to the FDA, Biogen also included data from an open-label extension of the VALOR study, in which researchers continued to follow a subset of participants from the six-month VALOR trial for at least 12 months. The open-label extension was not randomized and all participants were administered tofersen. In this analysis, the company reported that patients who started tofersen during the initial VALOR trial, as opposed to six months later in the open-label extension, experienced slower declines in clinical function as well as in respiratory function, muscle strength, and quality of life.

"Neurofilament reduction in and of itself is not sufficient – you need to have some clinical data, as well," Biogen's Ferguson said.

"That's why the context of what we observed in VALOR and also what we observed in the extension are quite important," he added. "It's that neurofilament data, our prior knowledge of what happens in ALS with neurofilament ... and the clinical data developed in the extension together that makes this compelling. It's not any one individual piece."

Biogen had always planned to do an open-label extension of the VALOR study, according to Ferguson. "We knew that the six-month duration of the study was short in VALOR," he said. "We wanted to make sure that we looked at a longer time point, as well."

These findings suggest to Biogen and others that it may take longer for patients to demonstrate clinical benefits to tofersen treatment. "It's possible that just six months is just too short of a time [and] it's not enough to really see clinically significant changes," Cedars-Sinai's Diaz said.

Proving surrogate endpoints

Today, the "gold standard" for clinical trial endpoints for ALS therapies is a change in function for daily activities, according to an FDA guidance from 2019. This is often measured using ALSFRS-R – the primary endpoint in VALOR. ALSFRS-R measures various aspects of physical and clinical function on a 48-point scale, with 48 representing normal function. In the open-label extension, researchers observed that the patient cohort that began taking tofersen at the start of the VALOR trial and the cohort that got on the drug six months later both experienced a decrease in ALSFRS-R scores. However, scores for patients who started tofersen earlier and were on the drug longer decreased by fewer points, suggesting that their physical functions were declining more slowly. The patient cohort that started the drug at the outset of VALOR experienced a decrease in ALSFRS-R score of 6.0 points from baseline, compared to a decrease of 9.5 points for those who started it later.

The 12-month results from the extension also demonstrated changes in key biomarkers, including reductions in total SOD1 protein and neurofilament, that preceded clinical changes.

To gain traditional FDA approval based on changes in a surrogate endpoint that endpoint must undergo "extensive testing" to validate that it can reliably predict clinical outcomes. There's a lower evidence bar for surrogate endpoints used to gain accelerated approval – what Biogen is attempting with tofersen – in that the endpoint must only be "reasonably likely to predict a

clinical benefit,” according to the FDA. Even if a drug receives accelerated approval based on a surrogate endpoint that meets this “reasonably likely” bar, the sponsor will ideally conduct a confirmatory trial in the post-market setting to demonstrate that the drug actually improves clinical outcomes in order to convert the accelerated approval to full approval.

The use of surrogate endpoints to garner accelerated approval has been controversial. Biogen’s use of amyloid plaque as a surrogate endpoint in its application for the Alzheimer’s drug Aduhelm (aducanumab) in 2021 was met with significant skepticism over whether the drug had demonstrated adequate clinical benefits. This led Medicare to restrict insurance coverage of the drug and similar therapies and caused Biogen to eliminate many marketing and commercialization efforts for it.

In other areas, such as oncology, the use of progression-free survival as a surrogate endpoint for accelerated approval of drugs has increased. According to a study published last year, however, improvements in progression-free survival don’t seem to correlate strongly with improvements in overall survival.

In light of the open-label extension results from VALOR, Diaz is willing to consider the likelihood that, as Biogen has said, neurofilament is “reasonably likely” to predict clinical benefit. But he’d also like to see more research on how neurofilament correlates with clinical function and ALS symptoms before it is routinely used as a surrogate endpoint in clinical trials. Neurofilament light chain is “definitely not a validated surrogate endpoint,” Diaz said. “I don’t think we’re there. We don’t have the evidence that it correlates with function.”

Learning from Aduhelm

Given the use of a never before used surrogate endpoint, Biogen is treading an unpaved regulatory path. Unsurprisingly, the FDA initially said it expected to complete its review of the drug by late January, but has since extended its review to April.

The FDA declined an interview for this story and said it cannot discuss products undergoing review at the agency.

It’s not unusual for companies to submit data on novel surrogate endpoints in FDA applications, particularly for drugs against complex, incurable diseases like ALS, about which scientists are still learning, said John Serio, a partner at the law firm Withers who has expertise in biotech and pharmaceutical intellectual property matters. Nearly half of drugs approved by the FDA use surrogate endpoints, many of them novel, he said.

Typically, when a drugmaker intends to

apply to the FDA with a surrogate endpoint, the company will reach out to the agency early in the drug development process to discuss the scientific rationale for using the surrogate endpoint and ensure that the agency will accept the data they produce in studies, Serio said. In these interactions, the FDA will want to see an explanation of the relationship between the surrogate endpoint and a clinical outcome.

The FDA may also be taking its time with the tofersen application after the criticism it faced upon granting accelerated approval to Biogen’s Aduhelm based on a surrogate biomarker. A congressional investigation last year concluded that the drug’s approval was “rife with irregularities” and that the FDA did not properly record many of its meetings and interactions with Biogen about the drug.

The FDA “got a lot of flak” for greenlighting Aduhelm based on biomarker data without clear clinical outcomes and is likely not eager to leave the agency open to similar criticism with tofersen, Mount Sinai’s Scelsa predicted. “I can’t imagine [the agency] again approving a drug just based on a biomarker without some clinical evidence of efficacy,” Scelsa said. “They’re not going to approve it just based on neurofilament data.”

Biogen has “learned from the development and launch of Aduhelm,” a Biogen spokesperson wrote in an email. “We believe a successful organization learns and moves forward, and that is what we intend to do. That process is continuing to inform our work as Biogen introduces new innovative treatments to the market.”

Balancing risk with access

Whether the FDA and Biogen’s Aduhelm experience will ultimately impact tofersen’s prospects remains to be seen. Meanwhile, the unmet need for new, effective treatments for ALS is a pressure that hangs over the process.

When considering approval, the FDA must weigh all the risks of a new drug – the fact that it may not work as expected or come with side effects – against the risks of not approving a treatment that could possibly help patients diagnosed with a rare and fatal disease.

“The [ALS] drugs that are commercially available now have very limited benefit,” noted Said Beydoun, a neurologist and division chief for neuromuscular disorders at Keck Medicine of USC, though he declined to comment on tofersen or other treatments specifically. “There’s no cure ... [The available drugs] slow disease progression.”

Even if ALS patients lack treatment options, Scelsa expressed disappointment that tofersen’s effect isn’t more substantial. There has been a lot of hope that genetically targeted treatments could


yield greater benefits for patients, since they’re designed to target specific mutations driving the disease, rather than a range of pathways.

For now, UCLA Health’s Wiedau remains cautious, particularly since the drug is not without toxicities, including reports of serious neurologic events like inflammation of the spinal cord. In VALOR and the open-label extension, such serious neurologic events were reported in 6.7 percent of participants. But she remains hopeful about tofersen’s potential to become an option for a genetically defined subset of ALS patients and urged the industry to have “a little bit more patience with the drug development process.”

“It’s really important that we get good data that gives us confidence, and not just approve medications that show a trend or that show a really mild benefit,” she said.

Between 10 percent and 20 percent of patients diagnosed with ALS and with a family history of the disease have SOD1 mutations, but they have also been observed in between 1 percent and 2 percent of those without a family history, according to the ALS Association. “I’m really very optimistic that we will have much better treatments in hand in the next few years to treat at least our patients with gene mutations,” Wiedau said.

Scelsa is hopeful that a Phase III trial Biogen is currently conducting, dubbed ATLAS, could have better implications for patients. In that study, Biogen will evaluate whether tofersen delays the clinical onset of ALS when administered to presymptomatic patients with a SOD1 mutation. As part of the study, Biogen will monitor neurofilament light chain and start treatment when it reaches a certain level, rather than treating patients who already have symptoms and suffer from nerve damage.

“The future will be treating patients who have the genetic risk,” before onset of the disease, Scelsa said. The industry will have to wait and see whether tofersen can delay the onset of ALS’ debilitating symptoms in patients. 



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