March 21, 2023

Food and Drug Administration,
10903 New Hampshire Avenue
Silver Spring, MD 20993

Docket No. FDA-2022-N-0691

PharmedOut, a rational prescribing project at Georgetown University Medical Center urges the FDA to reject Biogen's New Drug Application (NDA) for tofersen to treat amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene. The drug simply does not work. In its Phase III clinical trial, tofersen failed to delay decline in patients with ALS associated with SOD1 when compared to placebo. Don't be fooled by surrogate markers. There are many examples where surrogate markers fail to predict clinical outcomes. For example, flecainide reduced cardiac arrhythmias but increased deaths. Fluoride increases bone density, but increases hip fractures. In this case, because the drug significantly reduced the concentration of neurofilament light chains, a biomarker associated with SOD1, Biogen is now seeking approval for its failed drug. This should not happen.

ALS is a devastating disease that causes unimaginable pain to patients and their families. But the last thing that these families need is an expensive drug that does not work. You will hear statements from patients, families and advocacy groups in support of approval, but please keep the conflicts of interests of these groups in mind.

Patient advocacy groups are supposed to be champions for patients and their families: providing support, fighting for increased research and care, supporting access to effective, safe, and affordable treatments; and opposing ineffective or unsafe treatments. These groups should be a voice for those who cannot speak for themselves. Instead, groups created or co-opted by industry defend ineffective or unsafe drugs and express views more closely aligned with industry than public health. Patient advocacy groups such as the ALS Association and I AM ALS have been at the forefront of urging for expedited access to drugs that have been insufficiently tested.

I AM ALS published a guide on their site for its members to use to persuade this advisory committee to vote on emotions rather than evidence. The guide reflects industry-friendly perspectives, urging patients and families to, "share how urgent [it] is to bring new treatments to market for people living with ALS & the tremendous potential this has for moving all science forward," and to "explain how critical this new product is because [it] will be the first drug that targets a genetic cause of ALS..." The guide calls tofersen safe and effective, and suggests that those submitting testimony say things like, "this drug will be the first that can slow or even stop the most aggressive version of ALS…" or "new data shows a clinically meaningful benefit in individuals living with SOD1-ALS."

This committee knows that these statements are false. The "new data" published by Biogen researchers illustrates that the Phase III clinical trial failed to meet its primary endpoint of slowing decline in function at 28 weeks of the trial. The difference in ALS Functional Rating Scale (ALSFR-S) between tofersen and placebo was 1.2, an insignificant difference. What's

more, one in 14 (7%) of all participants who received the drug also experienced serious neurological harms including myelitis, meningitis, lumbar radiculopathy, increased intracranial pressure, and papilledema.

I AM ALS fails to disclose where they receive their funding from, but their sentiments echo those of the ALS Association, a leading voice in ALS that has received hundreds of thousands of dollars from Biogen and other companies over the years, and, naturally, supports the approval of this drug. According to their written testimony, the ALS Association provided funding for the development of tofersen and "may" receive financial payments under undisclosed circumstances. The ALS Association, admits that "…like most other rare disease organizations, [we] receive a portion of our funding from the pharmaceutical industry as [a] whole, and we may receive some funding from a specific sponsor that may also have a drug up for review." The ALS Association provides grants to pharmaceutical companies and notes that these grants "include pay-back provisions or other financial interests."

So it should come as no surprise the ALS Association has argued in their comment that "it would not be ethically or operationally possible to run a new larger and longer randomized trial" given the small number of people with this genetic type of ALS. In fact, by the ethical principles of beneficence and nonmaleficence, it would be unethical to unleash a treatment on a population when it has no proven benefits and has proven harms.

The ALS Association also argues that ALS patients cannot wait any longer for treatment. But waiting is the scientific, ethical, and rational response to a treatment that is no better than placebo. Instead, the Association is rallying behind the "ATLAS prevention trial of tofersen in pre-symptomatic SOD1 mutation carriers", rationalizing that an in-progress study in asymptomatic people somehow lends credence to a study that showed no clinical benefit in sick patients.

In short, the efficacy trial for tofersen failed to show benefit and the market for the drug would have been very small anyway. Now, Biogen is running a trial to test this drug in healthy individuals who have the SOD1 mutation — a much larger market. Approving tofersen before any benefits have been shown will not only put an ineffective drug on the market but will ensure that a larger market is exposed to a highly questionable drug.

The Les Turner ALS Foundation, another patient group that has also received funding from Biogen, writes in their comment that patients "…need hope" and that the foundation "look[s] forward to the day when a person is given a copy of their SOD1 lab report, a prescription for tofersen and new hope for this genetic form of ALS." But the false hope peddled by these advocacy groups is worse than no hope at all.

It is the duty of this FDA advisory committee to analyze the evidence objectively and make decisions based on data, not emotional appeals and hidden industry messaging. Of course, patient voices matter. Pharmaceutical companies understand this, and they have shamelessly used patients and patient advocacy groups to their advantage.

The interests of drug manufacturers and those of patients are not aligned. How can a patient group possibly turn around and criticize their funder for pushing a drug that does not work? They can't. They will support even the worst of drugs, urging their members to do the same, and they will pressure you, the committee, to vote to approve their sponsor's drug. The unconflicted patient advocacy groups that actually advocate for patients criticize drug companies for pushing drugs that do not work.

Tofersen is not the only example where groups and individual patients are mouthpieces for pharma messaging and "advocate" for a drug that does not work. The ALS Association pressured the FDA to approve Relyvrio on the basis of weak data; of course Amylyx, the manufacturer of the drug, funds the Association. We have seen it many times previously, most recently with aducanumab for Alzheimer's disease; the Alzheimer's Association invested a lot in a mediocre and harmful drug.

Pharma's patient advocacy "strategy" works. And patient advocacy groups that sometimes do good work in other areas do a disservice to their constituencies when they become megaphones for pharma messages. A "patient advocacy group" that is funded by industry is in essence not a patient advocacy group at all. Although there is seemingly overwhelming support for the approval of tofersen, we urge this FDA advisory committee to look past this industry-funded façade and make decisions based on data, not hope. ALS patients are desperate for an effective treatment, but unfortunately tofersen is not it. Patients and their loved ones deserve better.

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