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Tofersen comments submitted by Fred Fisher to the Food and Drug Administration

"I am grateful for the opportunity to express my support for the approval of Tofersen for the treatment of ALS. As the President and CEO of an organization that serves the country's largest ALS population (about 2,000 patients per year), I am all too familiar with the devastating impact of an ALS diagnosis, both on the patient and their family and friends.

The full data set, as reported in the New England Journal of Medicine, reveal the real promise of Tofersen for those with the SOD1 gene mutation. I have attached two pages with a total of six tables that demonstrate that Tofersen had a statistically significant effect on both the biologic effect and clinical effect of the drug over a 52-week period.

Regarding the Biologic Effect of Tofersen:

- Table A on page 1 reveals that over a 52-week period, Tofersen significantly knocked down the level of SOD1 concentration in CSF for those who started on the drug early, as well as those who started after the placebo arm ended.
- Table B on page 1 reveals that l the biomarker Nfl in plasma was significantly reduced in the early starters as well as those that started on Tofersen after the placebo arm.

The statistically significant improvement in these two biologic measures clearly indicates that the drug was hitting its target.

Regarding the Clinical Effect of Tofersen:

- Page 2, table A, clearly shows a slower decline in ALSFRS-R over a 52 week period, and the gap between the early starters verses the late starters over the 52-week period reached statistical significance.
- Page 2, table B, demonstrates a clear slowing in breathing degradation for early starters.
- Page 2, table C, shows that hand strength was significantly preserved for those who started on Tofersen early.
- Page 2, table D, shows the probable life extension for those who started Tofersen early.

The full data set over the 52-week period clearly shows that those who started Tofersen early showed a clear biologic effect and a clear clinical benefit. While the trial did not meet its ALSFRS-R primary endpoint over 28 weeks, it is clear that those who started early and stayed on the drug for 52 weeks did show statistically significant improvement. Those with the SOD1 form of ALS should not be denied access to a drug that clearly works. The Tofersen data clearly show that it has a significant biologic and clinical benefit, thus approval of the drug should not be denied due to a primary endpoint treatment effect that was not statistically significant at 28 weeks, precisely because it clearly demonstrated an overwhelmingly positive effect over a 52-week period."