FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) Meeting
March 22, 2023

DRAFT QUESTIONS

1. **DISCUSSION:** Discuss whether the available evidence supports that a reduction in plasma neurofilament light chain (NfL) concentration observed in tofersen-treated patients with amyotrophic lateral sclerosis (ALS) secondary to a mutation in SOD1 (SOD1-ALS) is reasonably likely to predict clinical benefit for these patients.

2. **VOTE:** Is the available evidence sufficient to conclude that a reduction in plasma NfL concentration in tofersen-treated patients is reasonably likely to predict clinical benefit of tofersen for treatment of patients with SOD1-ALS?

3. **DISCUSSION:** Discuss the strengths and limitations of the available clinical data from the placebo-controlled study and long term extension regarding the effectiveness of tofersen for SOD1-ALS.

4. **VOTE:** Does the clinical data from the placebo-controlled study and available long-term extension study results, with additional supporting results from the effects on relevant biomarkers (i.e., changes in plasma NfL concentration and/or reductions in SOD1), provide convincing evidence of the effectiveness of tofersen in the treatment of patients with SOD1-ALS?

5. **DISCUSSION:** Discuss the overall benefit-risk assessment for tofersen in patients with amyotrophic lateral sclerosis (ALS) secondary to a mutation in SOD1 (SOD1-ALS). If the available evidence supports a benefit, discuss if the risks appear to be acceptable given the observed treatment benefit. If the benefit-risk assessment does not appear favorable, discuss what additional data would be needed for the benefit-risk assessment to be favorable.