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## AMX0035 for ALS – FDA Advisory Committee Update

- On March 30, 2022, the FDA convened an Advisory Committee to review the available data supporting AMX0035, a pipeline drug seeking approval for the treatment of amyotrophic lateral sclerosis (ALS), also commonly known as Lou Gehrig's disease.

- ALS is a progressive neurodegenerative disorder that cause muscle weakness, paralysis, disability, and eventually death. The risk for ALS increases with age, especially after age 40 years with most patients having onset of symptoms between the ages of 55 – 74 years old.

    - Prevalence of ALS is 2.7 to 7.4 cases per 100,000 person-years.
    - Approximately 7,000 new cases of ALS are diagnosed each year in the U.S.
    - The life expectancy after symptom onset is 2 – 5 years.

- AMX0035 is a combination of two compounds, phenylbutyrate (currently available as Buphenyl® and generics) and taurursodiol (available as a dietary supplement), designed to reduce neuronal death in persons with ALS by simultaneously mitigating endoplasmic reticulum stress and mitochondrial dysfunction.

    - AMX0035 has been filed with the FDA seeking approval as a treatment for ALS and an approval decision is expected by June 29, 2022.

- The FDA Advisory Committee members were asked to review the supporting data for AMX0035, which consisted of one phase 2, randomized, double-blind clinical trial with an open label extension (the CENTAUR study).

    - A total of 137 patients were randomized (2:1 AMX0035 to placebo) for 24 weeks, then switched to open label extension where all patients received AMX0035 (77% completed 24 weeks, 40% completed 48 weeks, and only 2 patients completed the open label extension at 132 weeks).
    - The primary endpoint was the rate of change at 24 weeks in the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) scale (a 48-point scale that is the standard for ALS trials, though involves subjective assessments): AMX0035 showed 2.32-point improvement over placebo ($p = 0.034$).
    - No significant safety concerns were identified, and the most common side effects were mainly gastrointestinal (diarrhea, abdominal pain, nausea, salivation) and bitter taste.
    - A larger, international, phase 3 PHOENIX trial is underway and due to be completed in 2024.

- The Advisory Committee was asked if the data from the phase 2 trial and the open label extension was sufficient to determine that the drug is effective for the treatment of ALS. After much debate and discussion, the members voted 6-4 against AMX0035.

    - Those voting in favor of approval reasoned that ALS is a devastating illness, with few treatments, and a patient community willing to bear more risk for the hope of some benefit.
    - Those voting against approval had the following reasons:
        - Considerable concerns voiced by the FDA about the conduct of the single placebo-controlled study including randomization problems, missing data, imbalances between groups, high drop our rates (only 2 people completed the open label extension), and improper statistical analysis.

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- Modest effect size on the primary endpoint and no confirmatory support from any of the secondary endpoints.
- The unmet need in ALS is clear and the patient testimonies were compelling, but the regulatory guidance is also clear and the single CENTAUR trial did not provide persuasive evidence that AMX0035 was effective in treating ALS.
- A larger trial is underway and should provide confirmatory evidence of efficacy.

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