

Category

Best Pharmaceutical Product

Drug / Device Name

AMX0035

Compound/ Tech Name

Sodium phenylbutyrate [PB] and taurursodiol [TURSO]

Trade Name

RELYVRIO® in the United States; ALBRIOZA™ in Canada

Date of Approval

2022-09-29

Indications

Amyotrophic lateral sclerosis (ALS) in adults

Therapeutic Categories

Neurodegenerative disease

Attached Files:

- Prix Galien Video.mov

Background information and need for drug/device

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive and fatal neurodegenerative disorder caused by motor neuron death in the brain and spinal cord. The disease affects more than 29,000 adults in the U.S. alone, along with more than 120,000 individuals worldwide and is the most common neurodegenerative disorder of midlife. More than 90% of this population have sporadic disease, showing no clear family history. Time is the enemy for people living with ALS, who have a median survival of approximately two years from diagnosis, as a result of deteriorating muscle function, inability to move and speak, respiratory paralysis, and more, brought on by motor neuron loss. Innovation and development of therapies for ALS have been slow and riddled with failures. For decades, many compounds have been tested in clinical trials for ALS, but almost all have failed to show any statistically significant evidence of clinical benefit. Prior to the approval of AMX0035 in the U.S., there were only two approved therapies to treat ALS, and neither of them demonstrated both a statistically significant benefit on function and an observed benefit on survival in a clinical trial. For people living with ALS, every moment matters, and the potential to slow the loss of function and extend the amount of time they can live independently can make a significant impact for the individual and their loved ones.

History of the development of the drug/device

The co-founders of Amylyx, Joshua Cohen and Justin Klee, started the development of AMX0035 with one unanswered question, “Why do neurons die?” After poring over scientific literature, they hypothesized that simultaneously targeting two dysfunctional pathways could help slow progression of neurodegenerative disease and reduce neuronal death. This led to a focus on two organelles: the endoplasmic reticulum and the mitochondria. Pre-clinical studies on two separate compounds targeting these organelles showed promise in protecting against neurodegeneration – sodium phenylbutyrate (PB) and taurursodiol (TURSO; or ursodoxicoltaurine). Based on this background, Amylyx developed AMX0035, a proprietary, oral fixed-dose combination of PB and TURSO. Looking to design an effective trial, Amylyx collaborated with advocates and leaders in ALS and neurodegenerative diseases, including Merit Cudkowicz, MD, MSC, Chief of Neurology at Massachusetts General Hospital, co-founder of the Northeast ALS Consortium; Rudy Tanzi, PhD, director at Massachusetts General Hospital, professor at Harvard Medical School; and Sabrina Paganoni, MD, PhD, investigator at the Sean M. Healey & AMG Center for ALS at Mass General, professor at Harvard Medical School and Spaulding Rehabilitation Hospital. AMX0035 was assessed in the Phase 2 CENTAUR trial, which met its primary endpoint of slowing functional decline, represented by the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), as published in the New England Journal of Medicine; longer overall survival was seen, as published in Muscle and Nerve. Additional data, published in the Journal of Neurology, Neurosurgery and Psychiatry, showed that early administration resulted in a 49% lower risk of death, tracheostomy and permanent assisted ventilation and 44% lower risk of first hospitalization, suggesting treatment may help delay the need for intervention. AMX0035 is also being studied in a global, confirmatory Phase 3 ALS trial, PHOENIX, which completed enrollment in February 2023, and intends to generate more safety and efficacy data on AMX0035.

Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition

The data from CENTAUR provided the basis for FDA approval and approval with conditions in Canada of AMX0035, helping to address a critically unmet need presented by the relentlessly progressive disease. Researchers believe a combination approach of multiple therapies simultaneously targeting different pathways will be the key to stopping ALS, and AMX0035 is an innovation by being designed to target two pathways in ALS pathogenesis, serving as a proof point for that research. It is also designed to be either taken alongside other approved treatments, or as a monotherapy. AMX0035 is also being studied in Wolfram syndrome and Progressive Supranuclear Palsy, as the pathways targeted by AMX0035 are relevant for the treatment of other neurodegenerative diseases. In its assessment, CENTAUR showed AMX0035 was the first fixed dosed combination therapy to demonstrate both a statistically significant benefit on function as well as an observed benefit on survival. Additionally, many of the participant-centric aspects of ALS clinical trials that are standard today, such as limiting the number of participants on placebo with short durations and a 2:1 randomization ratio, open label extension phases for interested participants, and allowing the use of approved therapies during the trial, were originally implemented in CENTAUR. Understanding medical innovations are only as effective as how accessible they are once approved, Amylyx created the Amylyx Care Team (ACT) to help people living with ALS. People wanting to take AMX0035 are assigned a representative through the program, many of whom have personal connections to ALS themselves, to help navigate the insurance system and find a means of accessing the therapy. The study of AMX0035 has helped shift the ALS treatment paradigm, paving the way for future innovations as the community works toward making ALS a chronic, manageable disease, and ultimately, finding a cure.

Please provide appropriate references (ie Pubmed links)

- a. <https://www.nejm.org/doi/full/10.1056/nejmoa1916945>
- b. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7820979/>
- c. <https://jnnp.bmj.com/content/93/8/871>
- d. <https://pubmed.ncbi.nlm.nih.gov/36083004/>
- e. <https://onlinelibrary.wiley.com/doi/10.1002/mus.27569>
- f. <https://www.tandfonline.com/doi/full/10.1080/21678421.2022.2121167>
- g. <https://pubmed.ncbi.nlm.nih.gov/34338107/>
- h. <https://pubmed.ncbi.nlm.nih.gov/31795746/>