NEW DRUG APPROVAL

Brand Name	Relyvrio™
Generic Name	sodium phenylbutyrate and taurursodiol
Drug Manufacturer	Amylyx Pharmaceuticals, Inc.

New Drug Approval

FDA approval date: September 29, 2022

Review designation: Priority; Orphan

Type of review: Type 1 - New Molecular Entity, New Drug Application (NDA): 216660

Dispensing restriction: Speciality Pharmacy Required, Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Many people know ALS as Lou Gehrig's disease, named after the famous baseball player who got the illness and had to retire in 1939 because of it. ALS is a disease that affects the nerve cells that make muscles work in both the upper and lower parts of the body. This disease makes the nerve cells stop working and die. The nerves lose the ability to trigger specific muscles, which causes the muscles to become weak and leads to paralysis.

No one knows what causes most cases of ALS. Scientists have been studying many factors that could be linked with ALS such as heredity and environmental exposures. Other scientists have looked at diet or injury. Although no cause has been found for most cases of ALS, a number of inherited factors have been found to cause familial ALS. In the future, scientists may find that many factors together cause ALS.

As of 2017, the Registry has found up to 31,843 cases of ALS in the United States with a mean of 24,821 and a lower estimate of 17,800. ALS is not a reportable disease in the majority of states and CDC/ATSDR is not notified of these cases at this time. ALS is slightly more common in men than women. ALS is age related; most people find out they have it when they are between 55 and 75 years of age and live from 2 to 5 years after symptoms develop. How long a person lives with ALS seems to be related to age; people who are younger when the illness starts live slightly longer.

Efficacy

Relyvrio™ is an oral, fixed-dose combination therapy that is thought to target endoplasmic reticulum stress and mitochondrial dysfunction for the treatment of ALS. The approval of Relyvrio™ is based on data from the Phase 2 CENTAUR trial (NCT03127514) and the CENTAUR open-label extension (OLE) study (NCT03488524).

Table 1. Phase 2 CENTAUR (NCT03127514) Study Design and Results	
Study Design	Phase 2, multicenter, randomized, placebo-controlled study
Study Population	• Diagnosis of definite ALS* with onset of symptoms within the previous 18 months • SVC >60% • 18–80 years of age

Key Exclusion Criterion	• Presence of tracheostomy
Interventions	• Relyvrio™ (3 g PB, 1 g TURSO per packet) (n = 89) or placebo (n = 48) for 24 weeks • Dosing: One packet once daily, increasing to one packet twice daily after 3 weeks if tolerated • Participants were allowed to continue taking riluzole and/or edaravone (77% of participants were taking riluzole or edaravone at baseline)
Efficacy Results: Primary Endpoint	Least-squares mean ALSFRS-R total score at Week 24: • Relyvrio™: 29.06 • Placebo: 26.73 **After 24 weeks, patients treated with Relyvrio™ scored on average 2.32 points higher on the ALSFRS-R than the placebo group (*P* = 0.03), which equated to a 25% slowing of disease progression over this time period.**
Efficacy Results: Key Secondary Endpoints	Least-squares mean change in SVC at Week 24 (% of predicted normal value): • Relyvrio™: 66.17% • Placebo: 61.06% Estimated % of patients with the event of death, tracheostomy, or hospitalization: • Relyvrio™: 19.3% • Placebo: 33.1% Estimated % of patients with the event of death or tracheostomy: • Relyvrio™: 2.8% • Placebo: 4.4% Estimated % of patients with the event of hospitalization: • Relyvrio™: 17.5% • Placebo: 29.7% Plasma pNF-H level at Week 24: • Relyvrio™: 406.95 pg/mL • Placebo: 374.25 pg/mL **None of the secondary endpoints were statistically different between the two groups.**

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (higher scores = more physical function); PB, sodium phenylbutyrate; pNF-H, phosphorylated axonal neurofilament H subunit; SVC, slow vital capacity; TURSO, taurursodiol.

*As defined by the revised El Escorial World Federation of Neurology criteria (clinical evidence of both upper and lower motor neuron signs in at least three body regions).

CENTAUR-OLE Study

The CENTAUR-OLE trial was a single-arm, open-label extension study in which participants completing the 6-month randomized phase (the CENTAUR trial) were eligible to receive Relyvrio™ for up to 30 months (132 weeks). Overall, 66% of participants originally randomized in the CENTAUR trial enrolled in the OLE, which included 56 participants (64%) from the Relyvrio™ arm and 34 participants (71%) from the placebo arm. The post-hoc, long-term, intention-to-treat (ITT) survival analysis showed a difference in median survival of 4.8 months in the group

originally randomized to Relyvrio™ compared to those originally randomized to placebo (23.5 months and 18.7 months, respectively; HR, 0.64; 95% CI, 0.42–0.995, *P* = 0.0475).

Ongoing Phase 3 PHOENIX Trial

The ongoing Phase 3 PHOENIX trial (NCT05021536) is a 48-week, randomized, placebo-controlled trial that will evaluate the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) as a primary outcome measure along with survival. The PHOENIX trial has an estimated enrollment of 600 patients with definite or clinically probable ALS within 24 months of symptom onset, which is a less stringent inclusion criteria set compared with the CENTAUR trial. The estimated primary completion date for the PHOENIX trial is in November 2023.

Safety

In the CENTAUR trial, adverse events (AEs) occurring in ≥2% of patients in the Relyvrio™ arm were primarily gastrointestinal (diarrhea, nausea, salivary hypersecretion, and abdominal discomfort). Gastrointestinal AEs were reported more frequently in the Relyvrio™ arm than in the placebo arm during the first 3 weeks, and then were reported less frequently for the remainder of the trial. A total of 19% of the participants in the Relyvrio™ arm prematurely discontinued the trial due to AEs, compared to 8% in the placebo arm. The most common AEs leading to discontinuation of the trial regimen were diarrhea (6% in the Relyvrio™ arm versus none in the placebo arm) and respiratory failure (6% in the placebo arm versus none in the Relyvrio™ arm).

Safety

ADVERSE EVENTS

Most common adverse reactions (at least 15% and at least 5% greater than placebo) are diarrhea, abdominal pain, nausea, and upper respiratory tract infection.

WARNINGS & PRECAUTIONS

- Risk in Patients with Enterohepatic Circulation Disorders, Pancreatic Disorders, or Intestinal Disorders: In patients with disorders that interfere with bile acid circulation, consider consulting with a specialist. Monitor for new or worsening diarrhea in these patients. These conditions may also lead to decreased absorption of either of the components of Relyvrio™.
- Use in Patients Sensitive to High Sodium Intake: Relyvrio™ has a high sodium content. In patients sensitive to salt intake, consider the amount of daily sodium intake in each dose of Relyvrio™ and monitor appropriately.

CONTRAINDICATIONS

None reported

Clinical Pharmacology

MECHANISMS OF ACTION

The mechanism by which Relyvrio™ exerts its therapeutic effects in patients with ALS is unknown.

Dose & Administration

ADULTS

The recommended initial dosage of Relyvrio™ for oral suspension is 1 packet (3 g sodium phenylbutyrate and 1 g taurursodiol) daily for the first 3 weeks. After 3 weeks, increase to the maintenance dosage of 1 packet twice daily.

PEDIATRICS

None.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); use with caution.

HEPATIC IMPAIRMENT

There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); use with caution.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Oral suspension: 3 g sodium phenylbutyrate and 1 g taurursodiol in single dose packets.