Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

AMX0035

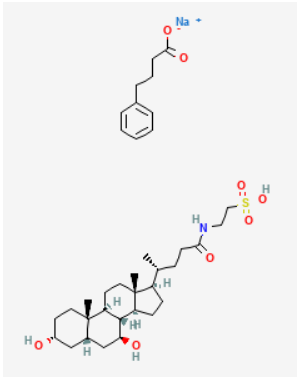
Evidence Summary

AMX0035 was approved for the treatment of ALS based on a phase 2 trial but did not meet primary or secondary endpoints in a phase 3 trial. The phase 2 study in AD met the safety and tolerability endpoint.

Neuroprotective Benefit: The phase 2 study in AD reported some AMX0035 effects on CSF biomarkers. While the phase 2 study in ALS reported slower rate of decline and prolonged survival, the phase 3 trial did not meet primary or secondary endpoints.

Aging and related health concerns: No studies with AMX0035 have been carried out for age-related diseases other than Alzheimer's disease and ALS.

Safety: The most common adverse events with AMX0035 are gastrointestinal in nature. AMX0035 may increase bile acid levels and fluid retention. In a minority of ALS patients, asymptomatic electrocardiographic changes have also been observed.

Availability: Approved for ALS but discontinued; in development for progressive supranuclear palsy, Alzheimer's and Wolfram Syndrome	**Dose**: In ALS patients, 1 packet (3 g of sodium phenylbutyrate and 1 g of tauroursodeoxycholic acid) daily is taken for the first 3 weeks, followed by 1 packet twice daily (Relyvrio.com).	**Chemical formula:** $C_{26}H_{45}NO_6S$ **MW**: 187.19 (sodium phenylbutyrate; top); 499.7 (TUDCA; bottom)  Source: PubChem
Half life: 45 minutes for sodium phenylbutyrate	**BBB**: penetrant	
Clinical trials: A phase 2 trial in AD enrolled 95 patients. A phase 3 trial in ALS enrolled 664 patients.	**Observational studies**: N/A	

What is it?

AMX0035 (marketed as Relyvrio™) is a combination therapy of two active compounds, sodium phenylbutyrate and tauroursodeoxycholic acid (TUDCA; also known as taurursodiol, or TURSO). This combination therapy is designed to reduce neuronal death through two mechanisms: sodium phenylbutyrate decreases endoplasmic reticulum (ER) stress (by upregulating the master chaperone regulator DJ-1) and TUDCA mitigates mitochondrial dysfunction (by incorporating into the mitochondrial membrane and increasing apoptotic threshold)(Paganoni et al., 2020; Jiang et al., 2022).

After the completion of the phase 2 study for ALS, the company developing AMX0035, Amylyx Pharmaceuticals, submitted a New Drug Application to the US FDA (before completion of phase 3 trials). ALS patient advocacy groups also submitted over 50,000 signatures to the FDA, calling on the agency to approve AMX0035 for the treatment of ALS. In September 2022, the FDA convened an advisory committee meeting, at which members voted in favor of approving the drug (7-2). On September 29, 2022, the FDA approved AMX0035 (Relyvrio) for the treatment of ALS (FDA.gov). On March 8, 2024, Amylyx Pharmaceuticals announced the topline results from a global phase 3 trial (PHOENIX trial) of AMX0035 in ALS and reported that the study did not meet prespecified primary or secondary endpoints

(Amylyx press release, March 8, 2024). In April 2024, Amylyx Pharmaceuticals announced they will voluntarily discontinue and remove AMX0035 (Relyvrio) from the market in the US and Canada (NeurologyLive, April 4, 2024).

AMX0035 is also under clinical development for Alzheimer's disease, progressive supranuclear palsy, and Wolfram syndrome, a rare genetic disorder that causes insulin-dependent diabetes mellitus and progressive optic atrophy (Amylyx pipeline).

For details on the individual components of this combination therapy, please see Cognitive Vitality Reports on sodium phenylbutyrate and tauroursodeoxycholic acid (TUDCA).

Neuroprotective Benefit: The phase 2 study in AD reported some AMX0035 effects on CSF biomarkers. While the phase 2 study in ALS reported slower rate of decline and prolonged survival, the phase 3 trial did not meet primary or secondary endpoints.

Types of evidence:

- 1 phase 3 study in ALS patients
- 1 phase 2 study in Alzheimer's disease patients
- 1 phase 2 study and an open-label extension study in ALS patients
- Numerous laboratory studies for sodium phenylbutyrate and TUDCA, individually

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:
None available.

Human research to suggest benefits to patients with dementia:
Results from the phase 2 double-blind, randomized, controlled trial of AMX0035 (PEGASUS trial; NCT03533257) in mild cognitive impairment or Alzheimer's disease were announced at the 14th Clinical Trials on Alzheimer's Disease (CTAD) conference held in November 2021 (BusinessWire; NeurologyLive). This study was co-funded by the ADDF and the Alzheimer's Association. The study met the primary end point of safety and tolerability (discussed below under "Safety" section). This phase 2 study was not designed to evaluate differences between placebo and treatment groups in efficacy outcomes, and there were no differences found in cognitive or functional measures, or in hippocampal volume. This clinical trial did have some baseline imbalances. A greater baseline level of cognitive impairment was

present in the AMX0035 group compared with the placebo group (ADAS-Cog14, MoCA, and mild/moderate Alzheimer's disease composite scale; p<0.01 for all). The proportion of APOE4 carriers was also higher in the AMX0035 group (77.1%) compared with placebo (61.4%).

For exploratory outcomes, CSF and plasma biomarkers were evaluated (NCT03533257). When compared with placebo, significant reductions were seen in CSF total tau (p=0.0005) and p-tau181 (p=0.0008) in patients treated with AMX0035, as well as an increase in Aβ42/Aβ40 ratio (p<0.05), suggesting less accumulation of amyloid in the brain (NeurologyLive).

There was an increase in an oxidative stress marker, 8-OHdG, in the CSF of the AMX0035 group compared to the placebo group (p<0.01)(BusinessWire). This increase was unexpected and potentially a cause for concern, as studies have reported that CSF levels of 8-OHdG are elevated in several neurodegenerative diseases including Alzheimer's disease (Isobe et al., 2010) and Parkinson's disease (Gmitterova et al., 2009). An alternative possibility is that 8-OHdG levels are higher in the AMX0035-treated group due to increased apoptotic threshold, leading to increased survival of brain cells that have high oxidative stress. It is also not clear if AMX0035 treatment is responsible for the elevated 8-OHdG levels or if the level difference is related to the baseline imbalance between the AMX0035 and placebo groups.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
For mechanisms of action of the individual components of AMX0035, please see Cognitive Vitality Reports on sodium phenylbutyrate and tauroursodeoxycholic acid (TUDCA).

ALS: AMX0035 has been tested in clinical trials for ALS patients. ALS is characterized by motor neuron degeneration that leads to progressive muscle weakness, with respiratory failure being the predominant cause of death several years after symptom onset. Based on strong phase 2 trial (CENTAUR trial) data, the FDA approved AMX0035 (Relyvrio) for the treatment of ALS in September 2022 (FDA.gov). However, on March 8, 2024, Amylyx Pharmaceuticals announced that their global phase 3 trial (PHOENIX trial) of AMX0035 in ALS did not meet prespecified primary or secondary endpoints (Amylyx press release, March 8, 2024).

A phase 2 double-blind, randomized controlled trial (the CENTAUR trial) enrolled 137 ALS patients who received AMX0035 (n=89) or placebo (n=48) for 24 weeks (Paganoni et al., 2020). Patients were within 18 months after symptom onset and had clinical evidence of both upper and lower motor neuron signs in at least 3 body regions. The AMX0035 dose was 3 g of sodium phenylbutyrate and 1 g of TUDCA per

sachet, that was dissolved in room temperature water, and taken orally or through a feeding tube, once daily for the first 3 weeks and 2 sachets per day (1 in the morning, 1 in the evening) thereafter. Most participants were receiving riluzole or edaravone concurrently, with 28% of participants receiving both. A higher percentage of the placebo group (50%) were receiving edaravone than the AMX0035 group (25%). This trial was designed by and conducted through the Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS; www.neals.org) in collaboration with Amylyx Pharmaceuticals Inc. Amylyx Pharmaceuticals Inc. provided AMX0035 and placebo and was involved in the trial design, data analysis, and manuscript development. Statistical analyses were performed by Pentara Corp, the Massachusetts General Hospital Biostatistics Center, and an independent consultant.

For the phase 2 primary outcome, AMX0035 treatment significantly slowed the mean rate of change in the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised score (ALSFRS-R-score; 48-point scale), indicating slower functional decline than placebo over a 24-week period (-1.24 points per month with AMX0035; -1.66 points per month with placebo; difference of 0.42 points per month; 95% CI, 0.03-0.81; p=0.03)(Paganoni et al., 2020). In a sensitivity analysis, correcting for the use of edaravone gave a similar result as the primary analysis, with an estimated between-group difference of 2.15 points in the ALSFRS-R score (95% CI, -0.05 to 4.35). A sensitivity analysis that corrected for the use of riluzole showed an estimated between-group difference of 2.34 points in the ALSFRS-R score (95% CI, 0.19 to 4.48). The ALSFRS-R-score consists of 4 subdomains and the change that was most prominent was the fine-motor subscale.

For secondary outcomes, there were no statistically significant differences between the AMX0035 and placebo groups, even though the direction of change was mostly in the same direction as the primary outcome. Secondary efficacy outcomes were assessed in the following hierarchical order: rate of decline in isometric muscle strength as measured by the Accurate Test of Limb Isometric Strength (ATLIS) device; the rate of decline in plasma levels of the phosphorylated axonal neurofilament H subunit (pNF-H; a potential biomarker of motor neuron degeneration); the rate of decline in the slow vital capacity (SVC); the time to death, tracheostomy, permanent assisted ventilation, or hospitalization; the pharmacokinetics of sodium phenylbutyrate and TUDCA; and 18-kD translocator protein (TSPO) uptake on the MR-PET scan (in a subgroup). The hierarchical analysis with the first secondary outcome (rate of decline in isometric muscle strength) failed to reach statistical significance, with the mean rate of change per month at -3.03% with AMX0035 treatment and -3.54% with placebo (difference, 0.51% per month; 95% CI, -0.12 to 1.14). Thus, subsequent secondary outcomes were analyzed without p-values.

The mean rate of change in the plasma pNF-H concentration was 3.58 pg/mL per month with AMX0035 and −2.34 pg/mL per month with placebo (difference, 5.92 pg/mL per month; 95% CI, −4.41 to 16.26). The mean rate of change in the SVC was −3.10% of the predicted normal value per month with AMX0035 and −4.03% of the predicted normal value per month with placebo (difference, 0.93% per month; 95% CI, −0.10 to 1.95). The cumulative hazard ratio for death, tracheostomy, or hospitalization in the AMX0035 group compared with the placebo group, was 0.53 (95% CI, 0.27 to 1.05). Death occurred in 5 participants (6%) who received AMX0035 and in 2 participants (4%) who received placebo. The most common cause of death was respiratory failure, accounting for 4 out of the 7 deaths, consistent with ALS pathology.

In the phase 2 (CENTAUR) study, the effects of AMX0035 on plasma biomarkers of inflammation were also assessed in ALS patients (Bowser et al., 2023). YKL-40 has been shown to be elevated in ALS and correlated with disease severity (Andres-Benito et al., 2018). CRP is a marker of systemic inflammation, also elevated in ALS and correlated with its disease progression (Kharel et al., 2022). After 24 weeks of treatment, mean plasma YKL-40 levels decreased by approximately 20% (p=0.008) and CRP decreased by 30% (p=0.048) in the AMX0035 versus placebo group (Bowser et al., 2023). Plasma YKL-40 (r=-0.21; p<0.0001) and CRP levels (r=-0.19; p=0.0002) also correlated with the ALSFRS-R total score (primary outcome). Levels of chitinase 1 (another mediator of inflammation) were not significantly different between groups and did not correlate with ALSFRS-R total score or slope. Levels of neurofilament light, a marker of neurodegeneration, were not significantly changed with AMX0035 treatment in this phase 2 study.

In an open-label extension study of the CENTAUR trial patients who were followed for up to 35 months post-randomization, patients who were originally randomized to AMX0035 treatment had a 44% lower risk of death than those randomized to placebo (HR=0.56; 95% CI, 0.34 to 0.92; p=0.023; *see graph below*)(Paganoni et al., 2021). Vital status was obtained for 135 out of 137 participants originally randomized in the CENTAUR trial. Median overall survival was 25.0 months among participants originally randomized to AMX0035 and 18.5 months among those originally randomized to placebo. Thus, initiation of AMX0035 treatment at baseline resulted in a 6.5-month longer median survival compared with placebo.

The estimated probability of survival at 12 months among participants originally randomized to AMX0035 and placebo was 80.9% (95% CI, 71.1 to 87.7%) and 72.9% (95% CI, 58.0 to 83.3%), respectively. At 24 months, the estimates were 51.6% (95% CI, 38.9 to 62.9%) and 33.9% (95% CI, 19.4 to 49.1%), respectively. In patients originally randomized to AMX0035, the mean AMX0035 exposure

duration was 10.6 months; and in the group originally randomized to placebo, the mean AMX0035 exposure duration was 4.7 months.

In an update to the open-label extension study of CENTAUR trial participants, after 6 months of AMX0035 treatment followed by an open-label extension of up to 30 months resulted in a 47% lower risk of any key event in those originally randomized to AMX0035 versus placebo (HR=0.53; 95% CI, 0.35 to 0.81; p=0.003)(Paganoni et al., 2022). Median event-free durations were 14.8 (6.5-29.1) and 10.0 (4.0-15.0) months, respectively; thus, 4.8 months longer in participants originally randomized to AMX0035. Risks of death or tracheostomy or permanent assistant ventilation (PAV) were 49% lower in those originally randomized to AMX0035 (HR=0.51; 95% CI, 0.32 to 0.84; p=0.007), with median tracheostomy/PAV-free survival durations of 25.8 (14.8–33.6) months and 18.5 months (11.7 months–not reached), respectively. First hospitalization was 44% lower in those originally randomized to AMX0035 (HR=0.56; 95% CI 0.34 to 0.95; p=0.03), with median hospitalization-free duration not reached (6.9 months to not reached) in those originally randomized to AMX0035 versus 14.1 months (4.2 months to not reached) in those originally randomized to placebo. Consistent with the earlier publication, early AMX0035 treatment prolonged tracheostomy/PAV-free survival and delayed first hospitalization in ALS patients. Riluzole and edaravone are two other FDA-approved therapies for ALS, but only riluzole has shown a survival benefit in randomized clinical trials (Miller et al., 2012). It is worth noting that AMX0035 treatment demonstrated a dual benefit on survival and function (Paganoni et al., 2022).

In a further follow-up to the CENTAUR study, a posthoc survival analysis was carried out to determine the AMX0035 treatment effect while eliminating the placebo-to-active crossover in the original phase 2 study (Paganoni et al., 2023). A propensity score-matched AMX0035-naïve external control participants were selected from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database; these control participants were matched 1:1 with the AMX0035-treated CENTAUR participants using prognostically significant covariates. Baseline characteristics between the CENTAUR AMX0035-treated group (n=89) and the matched external controls (n=85) were well balanced. Estimated median overall survival was 23.54 months in the CENTAUR AMX0035 group and 13.15 months in the PRO-ACT external control group, with a difference of 10.39 months. Mortality risk was 52% lower in the CENTAUR AMX0035-treated group compared to the PRO-ACT external control group (HR= 0.48; 95% CI, 0.31-0.72; p=0.00048).

In March 2024, topline results from the phase 3 randomized, placebo-controlled trial (PHOENIX; NCT05021536) were announced. Further results were presented at the 2024 AAN conference (Amylyx's AAN slides, April 16, 2024). The trial enrolled 664 ALS patients who were treated with AMX0035 or

placebo (3:2 ratio) for 48 weeks, with both groups receiving standard-of-care (e.g., stable dosing regimen of riluzole and/or edaravone). The study also has an optional open-label extension. The primary endpoint was the change from baseline in ALSFRS-R at week 48. Secondary endpoints included quality of life patient-reported outcome assessments (ALSAQ-40 Total Score), overall survival, and respiratory function as measured by slow vital capacity (SVC). Safety and tolerability were also assessed. The phase 3 trial did not meet prespecified primary or secondary endpoints (Amylyx press release, March 8, 2024; Amylyx's AAN slides, April 16, 2024). There was no statistically significant difference observed between patients treated with AMX0035 (-14.98) and placebo (-15.32) in ALSFRS-R total score change from baseline to week 48 (p=0.667). There was also no significant difference in the same measure in a subset of participants who met the phase 2 (CENTAUR) trial criteria. There were no statistically significant differences between AMX0035 and placebo groups on secondary endpoints. Complete secondary endpoint survival data will not be available until 2025-2026. Amylyx plans to publish the results in a medical journal later in 2024. Amylyx Pharmaceuticals will continue to engage with regulatory authorities and the ALS Community to share their data. In April 2024, Amylyx Pharmaceuticals announced they will voluntarily discontinue and remove AMX0035 (Relyvrio) from the market in the US and Canada (NeurologyLive, April 4, 2024). AMX0035 will no longer be available for new patients with ALS, but those already on therapy in the US and Canada who wish to stay on treatment can be transitioned to a free drug program.

In primary skin fibroblasts of sporadic ALS patients, exposure to AMX0035 changed more genes and metabolites than either phenylbutyrate or TUDCA individually (Fels et al., 2022). The gene expression changes unique to AMX0035 affected nucleocytoplasmic transport, unfolded protein response (promoting cell survival under ER stress), mitochondrial oxidative phosphorylation, RNA metabolism, and innate immune activation (clearing misfolded proteins). Modulation of these pathways could underlie the neuroprotective benefits seen with AMX0035 in ALS patients. The weighted gene co-expression correlation analysis showed significant correlations between ALS gene expression modules and clinical parameters that were reversed by AMX0035 administration.

APOE4 interactions: Unknown.

Aging and related health concerns: No studies with AMX0035 have been carried out for age-related diseases other than Alzheimer's disease and ALS.

Types of evidence:

- 2 clinical trials in ALS patients
- 0 laboratory studies

AMX0035 has not been studied for age-related diseases other than the neurodegenerative diseases discussed under the "Neuroprotective Benefit" section above.

As discussed above, the open-label extension study in ALS patients who were followed up for a maximum of 35 months reported that AMX0035 provided survival benefits in ALS patients (Paganoni et al., 2020). Median overall survival was 25.0 months among participants originally randomized to AMX0035 and 18.5 months among those originally randomized to placebo (HR=0.56; 95% CI, 0.34 to 0.92; p=0.023).

However, the pivotal phase 3 trial (PHOENIX) in ALS patients did not meet prespecified primary or secondary endpoints. Overall survival was one of the secondary endpoints, which was not significantly different between AMX0035 and placebo groups (Amylyx press release, March 8, 2024).

Safety: The most common adverse events with AMX0035 are gastrointestinal in nature. AMX0035 may increase bile acid levels and fluid retention. In a minority of ALS patients, asymptomatic electrocardiographic changes have also been observed.

Types of evidence:

- 1 phase 3 study in ALS patients
- 1 phase 2 study in Alzheimer's disease patients
- 1 phase 2 study and an open-label extension study in ALS patients
- Several clinical and laboratory studies for sodium phenylbutyrate and TUDCA, individually

AMX0035 may cause serious side effects, including changes in bile acid levels. If you already have problems with liver, bile ducts, or pancreas, AMX0035 may increase bile acid levels, causing worsening diarrhea (Drugs.com). AMX0035 also contains a high amount of salt, which may lead to fluid retention. People with heart failure, high blood pressure, or kidney problems may need to limit dietary intake of

salt. The most common side effects with AMX0035 are diarrhea, abdominal pain, nausea, and upper respiratory tract infection. AMX0035 may make you dizzy or drowsy (WebMD.com).

Based on the phase 3 trial (PHOENIX trial) enrolling 664 ALS patients, AMX0035 was "generally safe and well-tolerated", with no new safety signals (Amylyx press release, March 8, 2024; Amylyx's AAN slides, April 16, 2024). Of patients in the AMX0035 group, 89% experienced any adverse events, 53% experienced drug-related adverse events, and 26% experienced serious adverse events. Of patients in the placebo group, 88% experienced any adverse events, 28% experienced drug-related adverse events, and 28% experienced serious adverse events. Diarrhea occurred more frequently in the AMX0035 group (31%) compared to the placebo group (10%).

In a phase 2 double-blind, randomized controlled trial (the CENTAUR trial) enrolling 137 ALS patients, adverse events with AMX0035 (n=89) were mainly gastrointestinal (Paganoni et al., 2020; *see table below*). In the modified intention-to-treat population, 69% of the subjects in the AMX0035 group and 77% of the subjects in the placebo group completed the trial regimen. Death occurred in 5 subjects (6%) who received AMX0035 and in 2 subjects (4%) who received placebo. The most common cause of death was respiratory failure (4 out of 7), a finding consistent with ALS pathology.

A total of 97% of the participants in the AMX0035 group and 96% in the placebo group had one or more adverse events during the trial (Paganoni et al., 2020). Events occurring at greater than 2% frequency in the AMX0035 group were primarily gastrointestinal (diarrhea, nausea, salivary hypersecretion, and abdominal discomfort). Gastrointestinal adverse events were reported more frequently in the AMX0035 group than in the placebo group during the first 3 weeks, with nausea, diarrhea, and abdominal pain accounting for most events; thereafter, these events were reported less frequently in the AMX0035 group than in the placebo group for the remainder of the trial. Mean changes in body weight from baseline to week 24 were similar in AMX0035 and placebo groups.

Digital electrocardiography showed asymptomatic electrocardiographic changes, including left anterior hemiblock, left bundle-branch block, and nonspecific T-wave changes in 7 participants in the AMX0035 group and 3 participants in the placebo group (Paganoni et al., 2020). Corrected QT intervals remained stable and did not differ significantly between the AMX0035 and placebo groups at any time point.

Serious adverse events were less frequent in the AMX0035 group than in the placebo group (12% vs. 19%)(Paganoni et al., 2020). The incidence of respiratory serious adverse events was 8% in the placebo group and 3% in the AMX0035 group. A total of 19% of the participants in the AMX0035 group

prematurely discontinued the trial regimen owing to adverse events, as compared with 8% in the placebo group. The most common adverse events leading to discontinuation of the trial were diarrhea (6% in the AMX0035 and 0% in the placebo) and respiratory failure (6% in the placebo group and 0% in the AMX0035 group).

In an open-label extension study of the CENTAUR trial ALS patients who were followed for up to 35 months post-randomization, the AMX0035 and placebo groups had similar rates of death-equivalent events (Paganoni et al., 2020). Six (6.7%) patients originally randomized to AMX0035 and 4 (8.3%) patients originally randomized to placebo experienced death-equivalent events.

In the phase 2 double-blind, randomized, controlled trial that tested AMX0035 (PEGASUS trial; NCT03533257) in mild cognitive impairment or Alzheimer's disease, the primary end point of safety and tolerability was met (NeurologyLive). Treatment with AMX0035 for 24 weeks was found to be associated with a higher incidence of gastrointestinal events when compared with placebo. In the AMX0035 treatment group, 36 patients (67%) reported treatment-emergent adverse events (TEAEs), compared with 26 patients (59%) in the placebo group. The greatest proportion of TEAEs in the treatment group were gastrointestinal events, primarily diarrhea, occurring in 20 (39%) patients, compared with 6 (14%) patients in the placebo group. In the AMX0035 treatment group, 10 out of 51 participants (19.6%) discontinued the study, and in the placebo group, 2 out of 44 participants (4.5%) discontinued.

Drug interactions: AMX0035 has 568 known drug interactions (Drugs.com). Examples of major drug interactions include aluminum-containing antacids, bile acid-binding resins (such as choestyramine, colestipol, and colesevelam), cyclosporine, probenecid, vorinostat, romidepsin, panobinostat, belinostat, and others (Drugs.com; WebMD.com).

AMX0035 has 4 disease interactions: liver disease, kidney disease, neurotoxicity, and biliary disorders (Drugs.com). The use of sodium phenylbutyrate may cause fluid retention in patients with congestive heart failure, renal dysfunction, or sodium retention with edema. Sodium phenylbutyrate is metabolized primarily by the liver and kidney; thus, caution should be exercised in patients with liver/kidney disease. Sodium phenylbutyrate is a prodrug and is metabolized to the active phenylacetate, which when administered intravenously, has been associated with exacerbation of preexisting neuropathy. Care should be exercised when sodium phenylbutyrate is used in patients at risk for neurotoxicity.

AMX0035 has 3 interactions with food/drinks: high-fat/calorie meals, nicotine, and caffeine (Drugs.com). Co-administration of sodium phenylbutyrate with a high-fat/high-calorie meal may reduce the rate and

extent of absorption of sodium phenylbutyrate. Taurursodiol may alter the blood levels and effects of caffeine and nicotine.

In human liver cell culture, TUDCA and UDCA reduced cell death induced by alcohol when administered at the same time (Henzel et al., 2004). However, when TUDCA or UDCA was administered before ethanol insult, damage to liver cells was exacerbated. The mechanisms driving these opposing effects are unclear. It is also unknown whether these effects extend to humans.

Sources and dosing:

AMX0035 (marketed as Relyvrio™, Amylyx Pharmaceuticals, Inc) was approved for the treatment of ALS in September 2022. In ALS patients, the recommended dosage for the first 3 weeks is 1 packet (3 g of sodium phenylbutyrate and 1 g of taurursodiol) daily (Relyvrio.com). After 3 weeks, the dosage increases to 1 packet twice daily. A packet is emptied into a cup of room temperature water (8 oz) and stirred well. The medication can be taken before a snack or meal. Due to the negative topline data from the pivotal phase 3 trial (PHOENIX) in ALS, Amylyx Pharmaceuticals announced discontinuation and removal of AMX0035 (Relyvrio) from the market in the US and Canada (NeurologyLive, April 4, 2024). AMX0035 will no longer be available for new patients with ALS, but those already on therapy in the US and Canada who wish to stay on treatment can be transitioned to a free drug program.

AMX0035 is also under clinical development by Amylyx Pharmaceuticals Inc. for the treatment of Alzheimer's disease, progressive supranuclear palsy, and Wolfram syndrome (Amylyx pipeline).

Research underway:

There are currently 4 ongoing clinical trials testing AMX0035. The open-label extension study of the phase 3b trial in ALS (PHOENIX) will evaluate the safety and tolerability of AMX0035 over 108 weeks (NCT05619783). This phase 3b study is scheduled to be completed in August 2026. A pharmacokinetic and pharmacodynamic study of AMX0035 is being carried out in 14 patients with ALS; this study had an expected study completion of September 2023 (NCT04987671). A phase 2 trial (HELIOS trial) is testing the safety and efficacy of AMX0035 in 12 adult patients with Wolfram Syndrome (NCT05676034). It is an open-label trial and AMX0035 will be administered for 48 weeks (once daily for first 3 weeks and twice daily for the remainder of the study if tolerated by participant). This study is scheduled to be completed in December 2024. A phase 3 study (ORION trial) is evaluating the safety and efficacy of AMX0035 treatment in 600 people with progressive supranuclear palsy, a sporadic, rare, and adult-onset

neurodegenerative disorder that affects walking, balance, eye movement, swallowing, and speech (NCT06122662). It is a 52-week double-blind placebo-controlled trial that is followed by an optional 52-week open-label extension phase. This phase 3 study is scheduled to be completed in May 2027.

Search terms:

Pubmed, Google: AMX0035, AMX-0035, Relyvrio

Websites visited for AMX0035, AMX-0035, Relyvrio:

- Clinicaltrials.gov
- NIH RePORTER (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca (TUDCA; PB)
- Cafepharma
- Pharmapro.com (0)