Amylyx Pharmaceuticals Announces Topline Results From Global Phase 3 PHOENIX Trial of AMX0035 in ALS

March 8, 2024

- PHOENIX Study Did Not Meet Prespecified Primary or Secondary Endpoints

- Data From 664-Participant Study Reinforce That AMX0035 is Generally Safe and Well-Tolerated

- Within the Next Eight Weeks, Amylyx Will Continue to Engage With Regulatory Authorities and the ALS Community to Share Topline Data; Amylyx Will Share Plans for RELYVRIO/ALBRIOZA in ALS Which May Include Voluntarily Withdrawing RELYVRIO/ALBRIOZA From the Market

- At This Time, RELYVRIO/ALBRIOZA Will Continue to be Available for People Living With ALS; Amylyx Has Voluntarily Decided to Pause Promotion; Related Patient Support Services Will Remain in Place

- Studies With AMX0035 in Wolfram Syndrome (WS) and Progressive Supranuclear Palsy (PSP) to Continue Based on Data Supporting its Potential in These Diseases

- Amylyx to Host Investor Conference Call Today, March 8, at 8:00 a.m. ET

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Mar. 8, 2024-- Amylyx Pharmaceuticals, Inc. (NASDAQ: AMLX) ("Amylyx" or the "Company") today announced topline results from PHOENIX, a global, 48-week, randomized, placebo-controlled Phase 3 clinical trial of AMX0035 (sodium phenylbutyrate and taurursodiol [also known as ursodoxicoltaurine]; RELYVRIO® in the U.S., ALBRIOZA™ inCanada) in people living with amyotrophic lateral sclerosis (ALS). PHOENIX did not meet its primary endpoint of reaching statistical significance (p=0.667) as measured by change from baseline in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) total score at Week 48, nor was there statistical significance seen in secondary endpoints. Amylyx plans to present the data from PHOENIX at an upcoming medical meeting and will publish the results in a medical journal later this year.

Amylyx will continue to engage with regulatory authorities and the broader ALS community, including ALS specialists and other multidisciplinary experts, people living with ALS, and advocates, to discuss the results from PHOENIX within the next eight weeks and make informed decisions. Amylyx intends to share plans for RELYVRIO/ALBRIOZA in ALS, which may include voluntarily withdrawing RELYVRIO/ALBRIOZA from the market. At this time, RELYVRIO/ALBRIOZA and its related patient support program will continue to be available for people living with ALS. Amylyx has voluntarily decided to pause promotion of the medication during this time.

"We are surprised and deeply disappointed by the PHOENIX results following the positive data from the CENTAUR trial. Our main priority at the moment is sharing the information with people living with ALS and their treating physicians; this is part of our continued commitment to them and our mission. Over the next eight weeks, our team will continue to engage with regulatory authorities and the ALS community to discuss the results from PHOENIX. We will be led in our decisions by two key principles: doing what is right for people living with ALS, informed by regulatory authorities and the ALS community, and by what the science tells us. On behalf of the entire Amylyx team, we are grateful to the ALS community and for the dedication of trial participants, investigators, and study site teams. With data collected from 664 participants in PHOENIX, we are certain there will be important learnings that will help inform future ALS research. We are steadfast in our commitment to the ALS community and our mission, including with AMX0035 where it has shown potential in neurodegenerative diseases such as Wolfram syndrome and progressive supranuclear palsy, and with AMX0114, our investigational antisense oligonucleotide targeting calpain-2, in ALS," said Justin Klee and Joshua Cohen, Co-CEOs of Amylyx.

PHOENIX Study Results:

The Phase 3 PHOENIX study enrolled 664 adults living with ALS. Participants were randomized three-to-two to receive either AMX0035 or placebo, with both treatment groups receiving standard-of-care. Continuation of a stable dosing regimen of riluzole and/or edaravone was permitted.

- **PHOENIX did not meet the primary endpoint:** There was no significant difference observed between participants treated with AMX0035 and placebo in ALSFRS-R total score change from baseline at Week 48 (p=0.667). No significant difference was observed in the subset of participants who met the CENTAUR trial criteria. There were also no significant differences observed across secondary endpoints.
- **Consistent safety and tolerability profile:** AMX0035 was well-tolerated in PHOENIX. There were no new safety signals, reinforcing the favorable and manageable safety profile observed with AMX0035 to date.

- European participants who completed the 48-week randomized phase had the option to enroll in an open label extension of the trial of up to two years in duration, which remains ongoing.

Science of AMX0035:

AMX0035, a specially formulated oral fixed-dose combination of PB and TURSO, has been shown in numerous preclinical studies to have a robust, synergistic effect in targeting two different destructive neurodegenerative disease pathways by mitigating endoplasmic reticulum stress and the associated unfolded protein response and mitochondrial dysfunction thereby reducing neuronal cell death. Additionally, AMX0035 has been shown to also reduce markers associated with neurodegenerative diseases in clinical trials, including a reduction of tau, a key protein aggregate shared across several neurodegenerative diseases, and YKL-40, a marker of neuroinflammation.

Update on Ongoing AMX0035 Studies:

The global, randomized, double-blind, placebo-controlled Phase 3 ORION clinical study of AMX0035 in PSP remains ongoing. The first participant was dosed in December 2023, and the Company is planning for an interim analysis. Topline results continue to be anticipated in 2025 or 2026.

Data from the ongoing 12-participant, single site, open-label Phase 2 HELIOS clinical study are demonstrating evidence of clinical activity of AMX0035 in Wolfram syndrome. This study is fully recruited, and the Company plans to present preliminary data in the second quarter of 2024.

Investor Conference Call Information

Amylyx' management team will host a live conference call and webcast today, March 8, 2024, at 8:00 a.m. ET to discuss the results of the PHOENIX trial. To participate in the conference call, please dial +1 (877) 870-4263 (U.S.), +1 (855) 669-9657 (Canada), or +1 (412) 317-0790 (International) at least 10 minutes prior to the start time and ask to be joined into the Amylyx Pharmaceuticals call. All interested parties are invited to access a live broadcast of the call via a webcast, which will be available on the "Events and Presentations" page in the "Investors" section of the Company's website at investors.amylyx.com/news-events/events. An archived webcast will be available on the Company's website approximately two hours after the conference call and will be available for replay for 90 days following the call.

About the PHOENIX Trial

PHOENIX was a 48-week, randomized, placebo-controlled, global Phase 3 clinical trial further evaluating the safety and efficacy of AMX0035 (sodium phenylbutyrate and taurursodiol) for the treatment of ALS. The primary efficacy outcome of the trial was change from baseline in ALS Functional Rating Scale-Revised (ALSFRS-R) total score at 48 weeks. Secondary endpoints include quality of life patient-reported outcome assessments, overall survival, and respiratory function as measured by slow vital capacity (SVC). Safety and tolerability were also assessed.

European participants who completed the 48-week trial had the option to enroll in an open-label extension (OLE) phase. During this phase, all participants receive AMX0035, and continued safety and efficacy measures will be assessed.

About the CENTAUR Trial

CENTAUR was a multicenter Phase 2 clinical trial in 137 participants with ALS encompassing a 6-month randomized, placebo-controlled phase and an open-label long-term follow-up phase. The trial met its primary efficacy endpoint of reducing functional decline as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R).

Overall, reported rates of adverse events and discontinuations were similar between AMX0035 and placebo groups during the 24-week randomized phase; however, gastrointestinal events occurred with greater frequency (≥2%) in the AMX0035 group. Detailed data from CENTAUR is published in the New England Journal of Medicine (NEJM) and Muscle & Nerve.

The CENTAUR trial was funded, in part, by the ALS ACT grant and the ALS Ice Bucket Challenge, and was supported by The ALS Association, ALS Finding a Cure (a program of The Leandro P. Rizzuto Foundation), the Northeast ALS Consortium, and the Sean M. Healey & AMG Center for ALS at Mass General.

About AMX0114

AMX0114 is an antisense oligonucleotide designed to target the gene encoding calpain-2, a key contributor to the axonal (Wallerian) degeneration pathway. Axonal degeneration has been recognized as an important early contributor to the clinical presentation and pathogenesis of ALS and other neurodegenerative diseases. Calpain-2 has been implicated in the pathogenesis of ALS based on findings of elevated levels of calpain-2 and its cleavage products in postmortem ALS tissue, therapeutic benefit of calpain-2 modulation in animal models of ALS, and the role of calpain-2 in cleaving neurofilament, a broadly researched biomarker in ALS. Preclinical studies completed to date have shown that AMX0114 achieves potent, dose-dependent, and durable knockdown of CAPN2 mRNA expression and calpain-2 protein levels in human motor neurons. Moreover, in preclinical efficacy studies, treatment with AMX0114 reduced extracellular neurofilament light chain levels following neurotoxic insult in iPSC-derived human motor neurons, and improved survival of iPSC-derived human motor neurons harboring ALS-linked, pathogenic TDP-43 mutations.

About ALS

Amyotrophic lateral sclerosis (ALS, also known as motor neuron disease) is a relentlessly progressive and fatal neurodegenerative disorder caused by motor neuron death in the brain and spinal cord. Motor neuron loss in ALS leads to deteriorating muscle function, the inability to move and speak, respiratory paralysis, and eventually, death. More than 90% of people with ALS have sporadic disease, showing no clear family history. ALS affects around 30,000 people in the U.S., and more than 30,000 people are estimated to be living with ALS in Europe (European Union and United Kingdom). People living with ALS have a median survival of approximately two years from diagnosis.

About HELIOS

The HELIOS trial (NCT05676034) is a 12-participant, open-label proof of biology, Phase 2 trial designed to study the effect of AMX0035 on safety and tolerability, and various measures of endocrinological, neurological, and ophthalmologic function in adult participants living with Wolfram syndrome (WS).

About Wolfram Syndrome

Wolfram syndrome (WS) is an autosomal recessive neurodegenerative disease characterized by childhood-onset diabetes, optic nerve atrophy, and neurodegeneration. Common manifestations of WS include diabetes mellitus, optic nerve atrophy, central diabetes insipidus, sensorineural deafness, neurogenic bladder, and progressive neurologic difficulties. Genetic and experimental evidence suggest that endoplasmic reticulum (ER) dysfunction is a critical pathogenic component of WS. The prognosis of WS is poor, and many people with the disease die prematurely with severe neurological disabilities.

About the ORION Trial

The Phase 3 ORION trial (NCT06122662) is a global, randomized, double-blind, placebo-controlled Phase 3 clinical trial designed to assess the efficacy, safety, and tolerability of AMX0035 compared to placebo in people living with progressive supranuclear palsy (PSP). The ORION Phase 3 trial was designed and planned in collaboration with key global academic leaders, people living with PSP and their caregivers, and industry advocacy organizations.

About PSP

Progressive supranuclear palsy (PSP) is a sporadic, rare and adult-onset neurodegenerative disorder that affects walking and balance, eye movement, swallowing, and speech. People living with PSP have a life expectancy of six to eight years after initial diagnosis, and its epidemiology is similar to that of amyotrophic lateral sclerosis (ALS). PSP typically begins in late-middle age and rapidly progresses over time. The disease affects approximately seven in 100,000 people worldwide, and there are currently no disease-modifying therapies approved for the treatment of PSP.

PSP is characterized by abnormal tau inclusions and is consequently also known as a tauopathy. Similar to other neurodegenerative diseases, pathophysiologic changes underlying PSP are multifactorial with several genetic and environmental factors likely contributing to tau dysfunction and aggregation.

Multiple pathways, including genetic mutations, endoplasmic reticulum (ER) stress and the activation of unfolded protein response, mitochondrial dysfunction, and neuroinflammation have been implicated as contributors to tau dysfunction and aggregation.

About AMX0035 / RELYVRIO® / ALBRIOZA™

AMX0035 is an oral, fixed-dose combination of sodium phenylbutyrate and taurursodiol (known as ursodoxicoltaurine outside of the U.S.). It is approved as RELYVRIO® to treat amyotrophic lateral sclerosis (ALS) in adults in the U.S. and approved with conditions as ALBRIOZA™ for the treatment of ALS in Canada. AMX0035 is being studied for the potential treatment of other neurodegenerative diseases, and Amylyx is exploring its treatment in other populations and regions. The formulation of RELYVRIO, ALBRIOZA, and AMX0035 is identical.

RELYVRIO® (sodium phenylbutyrate and taurursodiol) Safety Information for United States

WARNINGS AND PRECAUTIONS

Risk in Patients with Enterohepatic Circulation Disorders, Pancreatic Disorders, or Intestinal Disorders

RELYVRIO contains taurursodiol, which is a bile acid. In patients with disorders that interfere with bile acid circulation, there may be an increased risk for worsening diarrhea, and patients should be monitored appropriately for this adverse reaction. Pancreatic insufficiency, intestinal malabsorption, or intestinal diseases that may alter the concentration of bile acids may also lead to decreased absorption of either of the components of RELYVRIO. Because different enterohepatic circulation, pancreatic, and intestinal disorders have varying degrees of severity, consider consulting with a specialist. Patients with disorders of enterohepatic circulation (e.g., biliary infection, active cholecystitis), severe pancreatic disorders (e.g., pancreatitis), and intestinal disorders that may alter concentrations of bile acids (e.g., ileal resection, regional ileitis) were excluded from the study; therefore, there is no clinical experience in these conditions.

Use in Patients Sensitive to High Sodium Intake

RELYVRIO has a high salt content. Each initial daily dosage of 1 packet contains 464 mg of sodium; each maintenance dosage of 2 packets daily contains 928 mg of sodium. In patients sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of RELYVRIO and monitor appropriately.

ADVERSE REACTIONS

The most common adverse reactions (at least 15% and at least 5% greater than placebo) with RELYVRIO were diarrhea, abdominal pain, nausea, and upper respiratory tract infection. Gastrointestinal-related adverse reactions occurred throughout the study but were more frequent during the first 3 weeks of treatment.

Please click here for RELYVRIO Full U.S. Prescribing Information.

About Amylyx Pharmaceuticals

Amylyx Pharmaceuticals, Inc. is committed to supporting and creating more moments for the neurodegenerative disease community through the discovery and development of innovative new treatments. Amylyx is headquartered in Cambridge, Massachusetts and has operations in Canada, EMEA, and Japan. For more information, visit amylyx.com and follow us on LinkedIn and X, (formerly Twitter). For investors, please visit investors.amylyx.com.

Forward-Looking Statements

Statements contained in this press release and related comments in our earnings conference call regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, Amylyx’ expectations regarding: interactions with regulatory authorities; the continued availability of RELYVRIO/ALBRIOZA for people living with ALS while such interactions are ongoing; the pausing of promotion of RELYVRIO/ALBRIOZA; pathways for continued access for patients if RELYVRIO/ALBRIOZA are withdrawn from the market; the possibility for Amylyx to voluntarily withdraw RELYVRIO/ALBRIOZA from the market; the continued evaluation of AMX0035 in other neurodegenerative diseases, including the timing for expected data readouts in the ORION and HELIOS studies; and the evidence of biological activity of AMX0035 in Wolfram syndrome. Any forward-looking statements in this press release and related comments in the Company's conference call are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. Risks that contribute to the uncertain nature of the forward-looking statements include the risks and uncertainties set forth in Amylyx’ United States Securities and Exchange Commission (SEC) filings, including Amylyx’ Annual Report on Form 10-K for the year ended December 31, 2023, and subsequent filings with the SEC. All forward-looking statements contained in this press release and related comments in our conference call speak only as of the date on which they were made. Amylyx undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

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