Amylyx Pharmaceuticals Announces Interim Data From Ongoing Phase 2 HELIOS Clinical Trial Demonstrating Improvements in Pancreatic Function and Glycemic Control with AMX0035 in People with Wolfram Syndrome

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- Interim analysis, including eight participants assessed at Week 24, demonstrated improvements in pancreatic function and glycemic control, as measured by C-peptide and other markers of glucose metabolism, rather than worsening typically expected with disease progression

- All eight participants met prespecified responder criteria demonstrating either improvement or stabilization of disease according to both the Patient Reported Global Impression of Change (PGIC) and the Clinician Reported Global Impression of Change (CGIC) scales

- Majority of participants reported some improvement in vision

- AMX0035 was generally well-tolerated in all participants

- Interim data to be presented during a webcast today at 1:30 p.m. Eastern Time

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Apr. 10, 2024-- Amylyx Pharmaceuticals, Inc. (NASDAQ: AMLX) ("Amylyx" or the "Company") today announced interim data from the ongoing Phase 2 HELIOS clinical trial of AMX0035 (sodium phenylbutyrate [PB] and taurursodiol [TURSO, also known as ursodoxicoltaurine]) in adults living with Wolfram syndrome, a rare, progressive genetic disease impacting approximately 3,000 people in the U.S. The interim data from eight participants who have completed 24 weeks of treatment demonstrated that AMX0035 had a clinically meaningful effect on key outcomes measuring the progression of diabetes, visual decline, and overall disease burden in adult participants living with Wolfram syndrome.

"I have been studying Wolfram syndrome and caring for people with the disease for more than 20 years. This community has an urgent unmet need for disease modifying treatments. Outcomes for people with Wolfram syndrome consistently worsen over time, so disease stabilization alone is clinically meaningful for both patients and their doctors. The interim results from HELIOS that demonstrate improvement across multiple organ systems impacted by this progressive disease are encouraging," said Fumihiko Urano, MD, PhD, Principal Investigator of the Phase 2 HELIOS clinical trial in Wolfram syndrome and the Samuel E. Schechter Professor of Medicine in the Division of Endocrinology, Metabolism & Lipid Research at Washington University School of Medicine in St. Louis.

HELIOS is an ongoing, open-label Phase 2 study in 12 participants designed to evaluate if AMX0035 slows progression of diabetic, visual, and other measures in people living with Wolfram syndrome and to evaluate safety and tolerability. The primary efficacy endpoint of the trial measures change from baseline in C-peptide, an established, objective laboratory measure of pancreatic beta cell function and glycemic control, assessed using a Mixed Meal Tolerance Test (MMTT). Secondary and exploratory outcomes include the measurement of other diabetic responses and other domains affected by the disease. The interim analysis performed is based on a data cutoff as of March 5, 2024, which includes all participants who completed their Week 24 assessments as of the cutoff (n=8).

In this interim analysis of eight participants treated with AMX0035, increases were observed on average in the primary outcome of total C-peptide response (C-peptide AUC change from baseline) including in the 90-minute response at Week 24 (+15.6 ng*min/mL, 95% CI: [1.3, 30.0]). In Wolfram syndrome, progressive decline would have been expected on this measure. Additionally, seven out of eight participants demonstrated at least a 30-minute shorter time to peak C-peptide response. In Wolfram syndrome, a progressive increase in time to peak C-peptide response, indicating slower pancreatic response, and reduced total C-peptide response would have been expected.

"The improvements in C-peptide, an objective laboratory measure, observed in our HELIOS trial are promising and differ from the normal course of Wolfram syndrome despite best supportive care," said Camille L. Bedrosian, MD, Chief Medical Officer of Amylyx. "The majority of people with Wolfram syndrome carry mutations in the *WFS1* gene, which encodes a protein that spans the membrane of the endoplasmic reticulum (ER) called wolframin. Loss of wolframin function leads to ER stress and impaired mitochondrial dynamics, which in turn leads to dysfunction and apoptosis of cells. Because of the clear link between *WFS1* mutations and ER stress, Wolfram syndrome is considered a prototypical ER stress disorder. AMX0035 is believed to target both ER stress and mitochondrial dysfunction. We believe today's interim results support the compelling science behind the mechanism of action of AMX0035 and its potential to help people living with Wolfram syndrome."

"The HELIOS trial began as a result of a multi-year collaboration with the Wolfram syndrome community and follows strong preclinical data with clear effects in cellular and animal models. We thank the Wolfram community, including those participating in HELIOS, their loved ones, and the clinical staff at Washington University School of Medicine in St. Louis, for their support of this important trial," said Justin Klee and Joshua Cohen, Co-CEOs of Amylyx. "We are planning to engage with regulatory authorities to align on the development path in Wolfram syndrome. We expect topline data for all 12 participants at Week 24 in the second half of this year."

The following includes additional key data from the interim analysis:

- Hemoglobin A1C (HbA1c) is a measure of glycosylated hemoglobin which serves as a metric of how well sugar levels are being controlled in the blood. HbA1c was reduced by 0.26% (SE: 0.15%) on average after 24-weeks of AMX0035 treatment with six out of eight participants showing improvement in their HbA1c. Many studies have associated reduced HbA1c with better clinical outcomes.
- All participants had continuous glucose monitoring in the study allowing for a rigorous measurement of the time in target

glucose range. The absolute time in target glucose range improved on average by +7.1% (SE: 4.7%). Five out of eight participants had improvements in the time in target glucose range. Increased time in target glucose range is associated with better diabetic outcomes.

- Visual acuity was measured by the Snellen chart. Wolfram syndrome results in progressive optic nerve atrophy leading to relentless loss of both visual acuity and color vision, and eventually blindness. On average in HELIOS, visual acuity improved +0.05 -LogMAR (SE: 0.09) with five out of eight participants demonstrating some improvement in vision. Of those who improved, one participant changed from legally blind to legally sighted. Optical coherence tomography outcomes have not yet been assessed and will be included in final data analysis from HELIOS.
- All participants (8 out of 8) showed disease stability or improvement at Week 24, as measured by The Clinician Report Global Impression of Change (CGIC) and Patient Reported Global Impression of Change (PGIC). Improvement was noted by the CGIC in 62.5% of cases (5 out of 8) and by the PGIC for 75% of cases (6 out of 8) with the remainder reporting disease stability on both the CGIC and PGIC. These outcome measures are designed to report if the overall burden of disease has improved, stayed the same, or worsened from the clinician's or patient's perspective.
- The safety profile of AMX0035 in HELIOS was consistent with prior safety data. AMX0035 was generally well-tolerated. The majority of adverse events (AEs) were mild or moderate, and there were no serious AEs related to AMX0035 treatment. The most common AE was diarrhea.

In September 2022, researchers from Washington University School of Medicine in St. Louis, including Dr. Urano, in collaboration with Amylyx, published positive preclinical data on AMX0035 in beta cell, neuronal cell and mouse models of Wolfram syndrome in the peer-reviewed Journal of Clinical Investigation Insight. Amylyx announced that the FDA granted orphan drug designation to AMX0035 for the treatment of Wolfram syndrome in November 2020.

HELIOS Interim Data in Wolfram Syndrome Virtual Webcast Details

Amylyx will host a virtual webcast with Dr. Fumihiko Urano, Principal Investigator of the Phase 2 HELIOS clinical trial in Wolfram syndrome and the Samuel E. Schechter Professor of Medicine in the Division of Endocrinology, Metabolism & Lipid Research at Washington University School of Medicine in St. Louis, to discuss interim HELIOS data today, April 10, 2024, at 1:30 p.m. ET. A live webcast of the presentation can be accessed under "Events and Presentations" in the Investor section of the Company's website, https://investors.amylyx.com/news-events/events, and will be available for replay for 90 days following the event.

About AMX0035

AMX0035 is an oral, fixed-dose combination of sodium phenylbutyrate (PB) and taurursodiol (TURSO; also known as ursodoxicoltaurine outside of the U.S.). AMX0035 was designed to slow or mitigate neurodegeneration by targeting endoplasmic reticulum (ER) stress and mitochondrial dysfunction, two connected central pathways that lead to cell death and neurodegeneration. Preclinical studies have provided evidence that AMX0035 may reduce cell death and improve cellular function, also supporting the synergistic effect of AMX0035 compared to individual compounds. AMX0035 is being studied as a potential treatment in neurodegenerative diseases, including Wolfram syndrome and progressive supranuclear palsy (PSP).

About the HELIOS Trial

The HELIOS trial (NCT05676034) is a 12-participant, open-label 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.

About Wolfram Syndrome

Wolfram syndrome is an autosomal recessive neurodegenerative disease characterized by childhood-onset diabetes, optic nerve atrophy, and neurodegeneration. Common manifestations of Wolfram syndrome include diabetes mellitus, optic nerve atrophy, central diabetes insipidus, sensorineural deafness, neurogenic bladder, and progressive neurologic difficulties. Literature suggests approximately 3,000 people are living with Wolfram syndrome in the United States.[1] Genetic and experimental evidence suggests that endoplasmic reticulum (ER) dysfunction is a critical pathogenic component of Wolfram syndrome. The prognosis of Wolfram syndrome is poor, and many people with the disease die prematurely with severe neurological disabilities.

1. Fraser FC and T Gunn. *J Med Genet*.1977;14(3): 190-193.

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. 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 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 ongoing evaluation of AMX0035 in Wolfram syndrome, including that early-stage results may not reflect later-stage results and the timing for expected topline data in the HELIOS study; and the potential for AMX0035 to help people living with Wolfram syndrome. Any forward-looking statements in this press release 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 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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