Amylyx Pharmaceuticals Announces Positive Topline Results from Phase 2 HELIOS Clinical Trial Demonstrating Sustained Improvements with AMX0035 in People Living with Wolfram Syndrome

October 17, 2024 at 9:00 AM EDT

- Improvement observed in pancreatic function, as measured by C-peptide response, following 24 weeks of treatment with AMX0035; worsening is typically expected with disease progression based on natural history studies of Wolfram syndrome

- Longer-term data for all participants who have completed Week 36 and Week 48 assessments showed sustained improvement over time

- Improvements or stabilization observed across all secondary endpoints, including measures of glycemic control, vision, and patient- and clinician-reported impressions of overall disease burden

- AMX0035 was generally well-tolerated in all participants

- Amylyx plans to meet with the FDA and other stakeholders to inform a Phase 3 program and expects to provide an update in 2025

- Topline data to be presented during a live webcast today at 1:30 p.m. ET

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Oct. 17, 2024-- Amylyx Pharmaceuticals, Inc. (NASDAQ: AMLX) ("Amylyx" or the "Company") today announced positive topline data from the Phase 2 open-label HELIOS clinical trial of AMX0035 (sodium phenylbutyrate [PB] and taurursodiol [TURSO, also known as ursodoxicoltaurine]) in 12 adults living with Wolfram syndrome. Wolfram syndrome is a rare, progressive, monogenic disease impacting approximately 3,000 people in the U.S. HELIOS showed improvement in pancreatic function, as measured by C-peptide response after 24 weeks of treatment with AMX0035, the study's primary efficacy endpoint, in contrast to the expected decrease in pancreatic function with disease progression. Similar overall improvements or stabilization were observed across all secondary endpoints, including hemoglobin A1c (HbA1c), time in target glucose range assessed by continuous glucose monitoring, and visual acuity. Patient- and physician-reported global impressions of change showed disease stability or improvement in all participants, meeting prespecified responder criteria.

In addition, longer-term data for all participants who completed Week 36 (n=10) and Week 48 (n=6) assessments showed sustained improvement over time. Data from HELIOS are being presented today at the International Society for Pediatric and Adolescent Diabetes (ISPAD) 50th Annual Congress and during a webcast held by the Company.

"The topline results of HELIOS indicate that AMX0035 has the potential to favorably change the trajectory of Wolfram syndrome, a progressive disease with no approved treatment options. These results build on the interim data presented in April of this year and show an improvement on multiple measures of pancreatic beta cell function, glycemic control, and vision," 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. "In addition, the participants who reached their Week 36 or Week 48 assessments demonstrated sustained improvement over baseline in C-peptide and HbA1c, which are objective laboratory measures of pancreatic function and glycemic control. These data are encouraging since Wolfram syndrome is a progressive disease."

The analysis performed includes Week 24 data for all 12 participants and data for all participants who completed their Week 36 (n=10) and Week 48 (n=6) assessments as of the data cutoff. 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 a surrogate marker of glycemic control, assessed using a mixed meal tolerance test (MMTT) at Week 24. Secondary and exploratory outcomes include the assessment of other diabetic measures and other domains affected by the disease.

HELIOS showed improvements in its primary endpoint of C-peptide response with a change from baseline to Week 24 at 120 minutes of +3.8 minutes*ng/mL (min*ng/mL) [standard error (SE): 19.3] in the Intent to Treat group (N=12) and +20.2 min*ng/mL [SE: 11.2] in the Per Protocol group (N=11). In addition, as outlined in the table below, participants receiving AMX0035 had improved glycemic control, as measured by markers of glucose metabolism; improved visual acuity in some participants, as measured by the Snellen chart; and improvement or stabilization of the disease, as measured by the Clinician Reported Global Impression of Change (CGIC) and Patient Reported Global Impression of Change (PGIC).

	Week 24 ITT (N=12)	**Week 24 Per Protocol† (N=11)**	**Week 36 (n=10)**	**Week 48 (n=6)**
C-Peptide Response (min*ng/mL) *mean change in AUC from baseline over 120 minutes††*	+3.8 (SE: 19.3)	+20.2 (SE: 11.2)	+30.7 (SE: 9.7)	+36.7 (SE: 19.6)
Hemoglobin A1c (%) *change from baseline*	-0.09 (SE: 0.14)	-0.16 (SE: 0.13)	-0.35 (SE: 0.18)	-0.30 (SE: 0.31)

Absolute Time in Target Glucose Range (%) *change from baseline*	+5.2 (SE: 3.6)	+5.7 (SE: 3.9)	+12.3 (SE: 4.0)	+5.8 (SE: 8.9)
Mean Exogenous Insulin Dose (units/kg/2 weeks) *change from baseline*	-0.01	-0.01	0.01	0.02
Visual Acuity (LogMAR) *change from baseline*	-0.04 (SE: 0.06)	-0.04 (SE: 0.06)	Not Collected at this Time Point	-0.11 (SE: 0.12)
Clinician Report Global Impression of Change (CGIC) *% meeting responder criteria*†††	100%	100%	100%	100%
Patient Reported Global Impression of Change (PGIC) *% meeting responder criteria*†††	100%	100%	100%	100%

† Upon genetic review, one participant did not meet the inclusion/exclusion criteria for HELIOS. This participant was found to have an autosomal recessive mutation confirmed to be pathogenic on just one of the two alleles and variant of uncertain significance on the other allele. This participant was within normal range for C-peptide, glycemic measures, and vision suggesting lack of typical Wolfram syndrome phenotype. Data presented with and without this participant who reached Week 24 (Intent to Treat and Per Protocol, respectively).

†† In non-diabetic individuals, C-peptide peaks after a meal at approximately ~30 minutes; in Wolfram syndrome, peak is slower but generally was at or before 120 minutes in HELIOS. Area under the curve (AUC) over 120 minutes after meal challenge reflects beta cell response to a meal. Amylyx is currently planning to focus on 120-minute AUC as the C-peptide measure for future studies.

††† HELIOS defines a “responder” on both the CGIC and PGIC as no change or improvement given the progressive nature of Wolfram syndrome.

The safety profile of AMX0035 in HELIOS was consistent with prior safety data. AMX0035 was generally well-tolerated. All adverse events (AEs) were mild or moderate, and there were no serious AEs related to AMX0035 treatment. The most common AE was diarrhea.

“These outcomes indicate that treatment with AMX0035 may result in meaningful improvements across multiple measures of disease progression,” said Camille L. Bedrosian, MD, Chief Medical Officer of Amylyx. “Wolfram syndrome is a progressive disease that is expected to consistently worsen over time, despite best supportive care, because of the underlying endoplasmic reticulum stress and mitochondrial dysfunction that occurs due to mutations in the *WSF1* gene. AMX0035 is believed to target both of these critical pathways. In addition, we are encouraged by the sustained improvement observed in all participants who completed Week 36 or Week 48 assessments, and we thank the Wolfram syndrome community for their continued collaboration and support in researching the potential of AMX0035. We continue to engage with stakeholders and plan to meet with the FDA to inform a Phase 3 program.”

The FDA and the European Commission granted Orphan Drug Designation to AMX0035 for the treatment of Wolfram syndrome in November 2020 and August 2024, respectively.

HELIOS Interim Data in Wolfram Syndrome Virtual Webcast Details
Amylyx will host a virtual webcast with management and Fumihiko Urano, MD, PhD, Principal Investigator of the HELIOS clinical trial 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 topline HELIOS data today, October 17, 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 the HELIOS Trial
HELIOS (NCT05676034) is a 12-participant, single-site, single-arm, 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. Participants in HELIOS receive AMX0035 for up to 96 weeks followed by a four-week safety follow-up. Primary and secondary outcomes are assessed at Week 24 and at longer-term time points.

In September 2022, researchers from Washington University School of Medicine in St. Louis, including Dr. Urano, in collaboration with Amylyx, published preclinical data on AMX0035 in beta cell, neuronal cell, and mouse models of Wolfram syndrome in the peer-reviewed *Journal of Clinical Investigation Insight*.

About Wolfram Syndrome
Wolfram syndrome is a rare, monogenic 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. 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.

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. We believe that our proprietary combination of PB and TURSO and their complementary mechanisms of action will allow us to synergistically target abnormal cell death to better prevent neurodegeneration than treatment targeted at either mechanism of action alone. AMX0035 is being studied as a potential treatment for Wolfram syndrome and progressive supranuclear palsy, two neurodegenerative diseases.

About Amylyx Pharmaceuticals
Amylyx is committed to the discovery and development of new treatment options for communities with high unmet needs, including people living with serious and fatal neurodegenerative diseases and endocrine conditions. Since its founding, Amylyx has been guided by science to address unanswered questions, keeping communities at the heart and center of all decisions. Amylyx is headquartered in Cambridge, Massachusetts. For more information, visit amylyx.com and follow us on LinkedIn and X. 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: the potential clinical benefit for AMX0035 to help people living with Wolfram syndrome; and interactions with regulatory authorities. 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’ Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, 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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