Amylyx Pharmaceuticals Announces Pivotal Phase 3 LUCIDITY Trial Design for GLP-1 Receptor Antagonist (Avexitide) in Post-Bariatric Hypoglycemia

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- Pivotal Phase 3 LUCIDITY trial will evaluate FDA-agreed upon primary outcome of reduction in hypoglycemia events and designed to align as closely as possible with previous Phase 2 trial designs

- Amylyx expects first study participant dosed in LUCIDITY in Q1 2025 and topline results in 2026

- Avexitide has FDA Breakthrough Therapy Designation for the treatment of post-bariatric hypoglycemia and Orphan Drug Designation

- Amylyx to present the Phase 3 LUCIDITY trial design at the World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease on December 12-14

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Dec. 4, 2024-- Amylyx Pharmaceuticals, Inc. (Nasdaq: AMLX) ("Amylyx" or the "Company") today announced the design of its pivotal Phase 3 LUCIDITY clinical trial for avexitide, an investigational, first-in-class glucagon-like peptide-1 (GLP-1) receptor antagonist, for the treatment of post-bariatric hypoglycemia (PBH). LUCIDITY is designed to evaluate the FDA-agreed upon primary outcome of reduction in hypoglycemia events and to have similar inclusion and exclusion criteria to the previous Phase 2 trials of avexitide in PBH. Amylyx expects that the first study participant will be dosed in the first quarter of 2025, followed by expected completion of recruitment in 2025, and anticipates topline data in 2026.

"We are excited to advance avexitide into a Phase 3 clinical trial, marking a pivotal step toward bringing this investigational therapy to people living with PBH," said Joshua Cohen and Justin Klee, Co-CEOs of Amylyx. "The consistent data from five clinical trials of avexitide in PBH underscore avexitide's potential to be the first therapy approved for people living with PBH."

LUCIDITY will be a multicenter, randomized, double-blind, placebo-controlled Phase 3 clinical trial evaluating the efficacy and safety of avexitide in participants with PBH following Roux-en-Y gastric bypass (RYGB) surgery. The Phase 3 trial will be conducted at approximately 20 sites in the U.S. Approximately 75 participants will be randomized 3:2 to receive either 90 mg of avexitide subcutaneously once daily or placebo. The trial will include a three-week run-in period and a 16-week double-blind treatment period. Participants who complete the double-blind period of the planned study will be eligible to enter an open-label extension (OLE) period with a duration of 32 weeks. The primary efficacy objective of LUCIDITY will evaluate the reduction in the composite of Level 2 and Level 3 hypoglycemia events through Week 16. Safety and tolerability will also be evaluated.

"PBH is believed to result from an excessive GLP-1 response leading to persistent, recurrent, and debilitating hypoglycemia events that take a profound toll on someone's quality of life. Avexitide is designed to bind to the GLP-1 receptor and inhibit the effects of excessive GLP-1 in PBH, mitigating hypoglycemia by decreasing insulin secretion and stabilizing blood glucose levels. We are excited to evaluate avexitide, which has FDA Breakthrough Therapy and Orphan Drug Designations, in the Phase 3 LUCIDITY trial, following two Phase 2 clinical studies that demonstrated compelling clinical data supporting avexitide's ability to significantly reduce the rates of hypoglycemia events," said Camille L. Bedrosian, MD, Chief Medical Officer of Amylyx. "Our goal in Phase 3 is to align the trial design as closely as possible with the prior studies. Importantly, we believe LUCIDITY is well powered to detect a treatment effect. We look forward to continuing to collaborate with study investigators and the PBH community as we seek to initiate LUCIDITY and advance avexitide through the clinical development process."

LUCIDITY was informed by data from five clinical trials of avexitide in people with PBH showing consistent, dose-dependent effects across studies. The five clinical trials include a Phase 1 trial, a single ascending dose trial, a multiple ascending dose trial, and two Phase 2 trials:

- In the Phase 2 (PREVENT), 28-day, randomized, placebo-controlled crossover trial (N=18), results showed a significant reduction in rates of Level 2 and 3 hypoglycemia events in participants with PBH after RYGB surgery following treatment with 30 mg twice daily and 60 mg once daily of avexitide compared with placebo. PREVENT's primary endpoint was met with statistical significance, showing both avexitide dosing regimens improved the lowest glucose level (nadir) after a meal as measured during formal mixed meal tolerance testing (MMTT). Mean plasma glucose nadir was increased by 21% (p=0.001) and 26% (p=0.0002) following avexitide 30 mg twice daily and 60 mg once daily dosing, respectively, compared to placebo.
- In the Phase 2b, 28-day, open-label, investigator-initiated, crossover trial (N=16), 90 mg once daily and 45 mg twice daily of avexitide met its primary endpoint and significantly reduced rates of hypoglycemia events in participants following RYGB surgery and other upper-gastrointestinal surgeries. Participants in the Phase 2b trial receiving 90 mg once daily of avexitide, the dose Amylyx plans to evaluate in LUCIDITY, saw a statistically significant 53% reduction in Level 2 hypoglycemia events (p=0.004) and a statistically significant 66% reduction in Level 3 hypoglycemia events (p=0.0003).

Avexitide was generally well tolerated, with a favorable safety profile replicated across the clinical trials.

Amylyx will present the trial design at the World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease (WCIRDC) in Los Angeles on December 12-14, 2024. Following the conclusion of the poster presentation on December 12, the poster will be made available on the "Publications" page of the Amylyx website.

About Avexitide

Avexitide is an investigational, first-in-class glucagon-like peptide-1 (GLP-1) receptor antagonist that has been evaluated in five clinical trials for post-bariatric hypoglycemia (PBH) and has also been studied in congenital hyperinsulinism (HI). The U.S. Food and Drug Administration (FDA) has granted avexitide Breakthrough Therapy Designation for both indications, Rare Pediatric Disease Designation in congenital HI, and Orphan Drug Designation for the treatment of hyperinsulinemic hypoglycemia (which includes PBH and congenital HI). Avexitide is designed to bind to the GLP-1 receptor on pancreatic islet beta cells and inhibit the effect of GLP-1 to mitigate hypoglycemia by decreasing insulin secretion and stabilizing blood glucose levels. In PBH, excessive GLP-1 can lead to the hypersecretion of insulin and subsequent debilitating hypoglycemia events. In two Phase 2 PBH trials, avexitide demonstrated highly statistically significant reductions in hypoglycemia events. These events can lead to autonomic and neuroglycopenic symptoms that can have a devastating impact on daily living.

About Post-Bariatric Hypoglycemia (PBH)

Symptomatic post-bariatric hypoglycemia (PBH) is a condition that affects approximately 8% of people who have undergone bariatric surgery, or approximately 160,000 people, in the U.S. PBH is thought to be caused by an excessive glucagon-like peptide-1 (GLP-1) response leading to hypoglycemia and impaired quality of life. PBH can cause debilitating hypoglycemia events associated with inadequate supply of glucose to the brain, known as neuroglycopenia. Clinical manifestations can include impaired cognition, loss of consciousness, and seizures. PBH is also associated with a high degree of disability that can result in major disruptions to independent living. There are no approved therapies for PBH.

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 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, the potential of avexitide as a treatment for PBH; expectations regarding the timing of initiation of a Phase 3 trial of avexitide in PBH and the timing of results from the trial; and expectations regarding the potential for the results of a Phase 3 trial to support approval of avexitide; the Company's expectations regarding its financial performance; and expectations regarding the Company's cash runway and longer-term strategy. Any forward-looking statements in this press release and related comments in the Company's earnings 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 success, cost, and timing of Amylyx' program development activities; Amylyx' ability to execute on its regulatory development plans and expectations regarding the timing of results from its planned data announcements and initiation of clinical studies; the risk that early-stage results may not reflect later-stage results; Amylyx' ability to fund operations, and the impact that global macroeconomic uncertainty, geopolitical instability, and public health events will have on Amylyx' operations, as well as 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 earnings 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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