Lilly's lepodisiran reduced levels of genetically inherited heart disease risk factor, lipoprotein(a), by nearly 94% from baseline at the highest tested dose in adults with elevated levels

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In Phase 2 ALPACA results, lepodisiran significantly reduced levels of genetically inherited cardiovascular risk factor, with some patients sustaining reductions for nearly 1.5 years

These data were presented at the American College of Cardiology 2025 Scientific Sessions and simultaneously published in the New England Journal of Medicine (NEJM)

INDIANAPOLIS, March 30, 2025 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced positive Phase 2 results for lepodisiran, an investigational small interfering RNA (siRNA) therapy designed to lower the production of lipoprotein(a) [Lp(a)], a genetically inherited risk factor for heart disease. In the Phase 2 ALPACA study, lepodisiran significantly reduced Lp(a) levels by an average of 93.9% over the 60 to 180-day period after treatment with the highest tested dose (400 mg), meeting the primary endpoint.[i] Participants who received the 16 mg and 96 mg lepodisiran doses experienced a 40.8% reduction and a 75.2% reduction in Lp(a) levels over the same time period, respectively.[i]

Lepodisiran also met additional secondary endpoints, showing reductions in Lp(a) levels following one or two administrations of each of the three tested doses across all timepoints assessed throughout the nearly 18-month-long study.[ii] Lepodisiran was administered twice at each dose (16 mg, 96 mg, or 400 mg), once at baseline and at day 180, with a separate group receiving 400 mg at baseline and placebo at day 180. The effect of additional doses of lepodisiran remains undetermined.

"Nearly a quarter of the world's population has elevated levels of Lp(a), putting them at a significantly higher risk of cardiovascular events such as heart attacks and strokes. Unfortunately, there are no approved cholesterol-lowering therapies specifically for this genetic risk factor, and lifestyle changes like diet and exercise do not provide meaningful reductions," said Steven Nissen, M.D., chief academic officer of the Heart, Vascular & Thoracic Institute at the Cleveland Clinic. "These significant and sustained Lp(a) reductions are encouraging and suggest that siRNA approaches like lepodisiran could potentially offer durable benefits with long-term dosing."

About 20% of Americans have high levels of Lp(a), which increases their risk of cardiovascular disease.[1,2] Elevated Lp(a) levels can double or even triple the risk of a heart attack and are associated with other cardiovascular issues such as stroke and heart valve narrowing (aortic valve stenosis).[3,4,5] Lepodisiran is an investigational siRNA therapy designed to reduce levels of Lp(a) by inhibiting the production of apolipoprotein(a) (apo[a]), a key component of Lp(a).

"Reducing the inherited cardiovascular risk for patients with high Lp(a) has long been a critically unmet need. These results offer hope for a long-term, durable treatment option," said Ruth Gimeno, group vice president, diabetes, obesity and cardiometabolic research at Lilly. "These data underscore Lilly's commitment to advancing genetic medicine to address one of the world's most pressing healthcare challenges. We will continue to evaluate the potential benefits of lepodisiran in the ongoing Phase 3 cardiovascular outcomes trial."

Results from additional secondary endpoints showed:

- Participants who received 400 mg of lepodisiran at both baseline and day 180 experienced a 94.8% reduction in average Lp(a) levels over the day 30 to 360 period, which remained 91.0% below baseline at day 360 (~1 year) and 74.2% below baseline at day 540 (~1.5 years).[ii]
- Lepodisiran also reduced apolipoprotein B (apoB) levels, a separate cholesterol biomarker. The highest dose (400 mg) of lepodisiran showed 14.1% and 13.7% ApoB reductions from baseline at day 60 and 180, respectively. A second 400 mg lepodisiran dose at day 180 sustained these apoB reductions through day 540.[ii]

Treatment-emergent adverse events (TEAEs) related to the study drug occurred in 1% (1/69) of the placebo group, 3% (1/36) of the 16 mg group, 12% (9/74) of the 96 mg group and 14% (20/141) of the pooled 400 mg group. There were no serious adverse events related to lepodisiran treatment. A single death occurred in the 16 mg dose group due to complications of chronic coronary disease. One participant in the placebo group was withdrawn from the study drug due to a TEAE; however, no participants receiving lepodisiran experienced a TEAE leading to withdrawal from treatment or the study.

The ACCLAIM-Lp(a) Phase 3 clinical development program, investigating the effect of lepodisiran on the reduction of cardiovascular events in adults with elevated Lp(a), is currently enrolling.

About ALPACA
ALPACA was a randomized, double-blind, placebo-controlled Phase 2 study designed to investigate the efficacy and safety of lepodisiran in adults with elevated Lp(a). A total of 320 participants were randomized to receive either placebo or one of three doses of lepodisiran (16 mg, 96 mg, or 400 mg) both at baseline and day 180. An additional group received 400 mg of lepodisiran at baseline and placebo at day 180. Results from the two groups receiving 400 mg of lepodisiran were pooled for the primary analysis. The primary endpoint was placebo-adjusted, time-averaged percent change in Lp(a) serum concentration from day 60 to 180.

About Lilly

Lilly is a medicine company turning science into healing to make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help tens of millions of people across the globe. Harnessing the power of biotechnology, chemistry and genetic medicine, our scientists are urgently advancing new discoveries to solve some of the world's most significant health challenges: redefining diabetes care; treating obesity and curtailing its most devastating long-term effects; advancing the fight against Alzheimer's disease; providing solutions to some of the most debilitating immune system disorders; and transforming the most difficult-to-treat cancers into manageable diseases. With each step toward a healthier world, we're motivated by one thing: making life better for millions more people. That includes delivering innovative clinical trials that reflect the diversity of our world and working to ensure our medicines are accessible and affordable. To learn more, visit Lilly.com and Lilly.com/news, or follow us on Facebook, Instagram, and LinkedIn. P-LLY

[i] Placebo-adjusted values based on the treatment-regimen estimand.

[ii] Placebo-adjusted values based on the efficacy estimand, which represents efficacy prior to discontinuation of study drug or initiation of medications known to affect lipoprotein(a).

Cautionary Statement Regarding Forward-Looking Statements
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about lepodisiran as a potential treatment for people with high risk for cardiovascular events and reflects Lilly's current beliefs and expectations. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of drug research, development, and commercialization. Among other things, there is no guarantee that planned or ongoing studies will be completed as planned, that future study results will be consistent with study results to date, that lepodisiran will prove to be a safe and effective treatment for the reduction of cardiovascular events associated with a reduction in Lp(a), that lepodisiran will receive regulatory approval, or that Lilly will execute its strategy as expected. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, see Lilly's Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

References

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Refer to: Stefanie Prodouz; stefanie.prodouz@lilly.com; 317-287-9899 (Media)
Michael Czapar; czapar_michael_c@lilly.com; 317-617-0983 (Investors)

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