Efficacy and Safety of Lepodisiran: An Extended Duration Short-Interfering RNA Targeting Lipoprotein (a)

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Abstract Content:

Background: Observational and Mendelian randomization studies have associated elevated serum levels of lipoprotein(a) [Lp(a)] with major adverse cardiovascular events including myocardial infarction, stroke, cardiovascular death and an increased risk of developing calcific aortic stenosis. Although several promising therapies are currently in development, no Lp(a)-lowering agents have been approved by regulatory authorities. Lp(a) is an LDL-like lipoprotein particle that consists of an apolipoprotein-B100 covalently bound to apolipoprotein(a) [apo(a)]. The LPA gene encodes for apo(a), and inhibiting LPA mRNA expression via short-interfering RNA (siRNA) technology reduces apo(a) production and lowers circulating levels of Lp(a).

Lepodisiran is an LPA-specific siRNA conjugated to N-acetyl-galactosamine that concentrates lepodisiran in hepatocytes to potently and durably reduce hepatic LPA mRNA levels and thereby reduce circulating Lp(a) levels.

Objectives: To assess safety, tolerability, pharmacokinetics (PK), and effects on Lp(a) serum concentrations after administration of single doses of lepodisiran, an extended duration siRNA directed at hepatic synthesis of apo(a), an essential component necessary for assembly of Lp(a) particles.

Design, Setting, Participants: A single ascending dose trial of lepodisiran was conducted at 5 clinical research sites in the US and Singapore. The study enrolled 48 adults without cardiovascular disease and Lp(a) serum concentrations ≥75 nmol/L or 30 mg/dL.

Interventions: Participants were randomized to receive placebo (n=12) or single doses (n=6) of 4, 12, 32, 96, 304 or 608 mg of lepodisiran administered subcutaneously.

Outcomes Measures: Participants were followed until study completion up to 48 weeks. The primary outcome was safety and tolerability. Secondary outcomes included PK of lepodisiran and the change in Lp(a) serum concentrations following administration to a maximum of 337 days (48 weeks).

Results: Forty-eight participants were enrolled, mean (SD) age 46.8 (11.6) years, 35% female; 46 completed the trial. A single serious adverse event was reported (fall from bicycle). Peak plasma concentrations of lepodisiran were achieved within 8 hours and undetectable by 48 hours. Median [IQR]) baseline Lp(a) concentrations in nmol/L were 111 (78,134), 78 (50,152), 97 (86,107), 120 (110,188), 167 (124,189), 96 (72,132), and 130 (87,151) for the placebo, 4, 12, 32, 96, 304 and 608 mg treatment groups, respectively. The effect of lepodisiran on concentrations of Lp(a) from baseline to 337 days (48 weeks) will be available for simultaneous publication and presentation at the AHA Scientific Sessions.

Conclusions: In this phase 1 study of 48 participants with elevated Lp(a) levels, lepodisiran was well tolerated and produced dose-dependent reductions in serum Lp(a) concentrations. The full study results will be presented.