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Lepodisiran — A Long-Duration Small Interfering RNA Targeting Lipoprotein(a)

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ABSTRACT

BACKGROUND

Elevated lipoprotein(a) concentrations are associated with atherosclerotic cardiovascular disease. The safety and efficacy of lepodisiran, an extended-duration, small interfering RNA targeting hepatic synthesis of lipoprotein(a), are unknown.

METHODS

We randomly assigned participants in a 1:2:2:2:2 ratio to receive lepodisiran at a dose of 16 mg, 96 mg, or 400 mg at baseline and again at day 180, lepodisiran at a dose of 400 mg at baseline and placebo at day 180, or placebo at baseline and at day 180, all administered by subcutaneous injection. Data from the two groups that received lepodisiran at a dose of 400 mg at baseline were pooled for the primary analysis. The primary end point was the time-averaged percent change from baseline in the serum lipoprotein(a) concentration (lepodisiran difference from placebo [i.e., placebo-adjusted]) during the period from day 60 to day 180.

RESULTS

A total of 320 participants underwent randomization; the median baseline lipoprotein(a) concentration was 253.9 nmol per liter. The placebo-adjusted time-averaged percent change from baseline in the serum lipoprotein(a) concentration from day 60 to day 180 was −40.8 percentage points (95% confidence interval [CI], −55.8 to −20.6) in the 16-mg lepodisiran group, −75.2 percentage points (95% CI, −80.4 to −68.5) in the 96-mg group, and −93.9 percentage points (95% CI, −95.1 to −92.5) in the pooled 400-mg groups. The corresponding change from day 30 to day 360 was −41.2 percentage points (95% CI, −55.4 to −22.4), −77.2 percentage points (95% CI, −81.8 to −71.5), −88.5 percentage points (95% CI, −90.8 to −85.6), and −94.8 percentage points (95% CI, −95.9 to −93.4) in the 16-mg, 96-mg, 400-mg–placebo, and 400-mg–400-mg dose groups, respectively. Serious adverse events, none of which were deemed by investigators to be related to lepodisiran or placebo, occurred in 35 participants. Dose-dependent, generally mild injection-site reactions occurred in up to 12% (8 of 69) of the participants in the highest lepodisiran dose group.

CONCLUSIONS

Lepodisiran reduced mean serum concentrations of lipoprotein(a) from 60 to 180 days after administration. (Funded by Eli Lilly; ALPACA ClinicalTrials.gov number, NCT05565742.)

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*A complete list of the investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

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CME

Serum concentrations of lipoprotein(a) higher than 125 nmol per liter are present in approximately 20 to 25% of the global population, affecting 1.4 to 2 billion people.[1-3] Mendelian randomization studies as well as epidemiologic studies have shown a strong association between elevated lipoprotein(a) concentrations and atherosclerotic cardiovascular disease, aortic stenosis, and death from any cause.[4-7] Traditional approaches to reduction in the risk of cardiovascular disease, including lifestyle alterations and statin therapy, have minimal effects on serum lipoprotein(a) concentrations.[1,3,8] Proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors slightly reduce lipoprotein(a) concentrations but have not been studied in dedicated prospective, randomized trials assessing cardiovascular outcomes among persons with elevated lipoprotein(a) concentrations.[9] No pharmacologic therapies have been approved by regulatory authorities, although plasma apheresis is approved in some countries.[10]

A Quick Take is available at NEJM.org

Lipoprotein(a) particles contain apolipoprotein B covalently bound to apolipoprotein(a). Concentrations of lipoprotein(a) in the circulation are determined largely by the *LPA* gene, which produces the messenger RNA (mRNA) responsible for synthesis of apolipoprotein(a), the rate-limiting step in production of lipoprotein(a).[11] Recent developments in RNA-interference techniques have allowed development of nucleic acid–based therapies that degrade the mRNA responsible for apolipoprotein(a) synthesis.[12-17] An oral drug (muvalaplin) that disrupts the association of apolipoprotein B with apolipoprotein(a) is also under development.[18,19] Lepodisiran is a noncanonical, tetraloop, Dicer-substrate small interfering RNA (siRNA) (i.e., a string of base pairs processed by the Dicer enzyme into a shorter, functional, siRNA) that inhibits hepatic production of apolipoprotein(a). In a phase 1 study, the highest studied dose of lepodisiran, 608 mg, reduced serum lipoprotein(a) concentrations by more than 90% for 337 days after a single injection.[15] The phase 2 trial reported here was designed to further assess the safety of lepodisiran in a population with higher lipoprotein(a) concentrations, determine the magnitude and duration of the reduction in lipoprotein(a) concentrations, and help inform the dose and dosing interval for a long-term phase 3 trial assessing cardiovascular outcomes that is currently under way (ClinicalTrials.gov number, NCT06292013).

Methods

Trial Organization and Oversight

In this randomized, placebo-controlled trial, we enrolled participants at 66 centers in Argentina, China, Denmark, Germany, Japan, Mexico, the Netherlands, Romania, Spain, and the United States from November 11, 2022, to April 17, 2023. The trial protocol, available with the full text of this article at NEJM.org, was approved by an ethics committee at each participating site. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.[20] All the participants provided written informed consent before any trial procedures began. Eli Lilly funded the trial and participated in the design and conduct of the trial, including data collection. An internal assessment committee at Eli Lilly reviewed unblinded safety and efficacy data, and all the results remained confidential until the date of the final database lock. At trial completion, the trial database was transferred to the Cleveland Clinic Coordinating Center for Clinical Research, where statisticians conducted data analyses for this report. The first author wrote the initial draft of the manuscript, which was reviewed and edited by the authors; the final version was reviewed and approved by all the authors. Employees of Eli Lilly reviewed the manuscript and suggested revisions; however, the final decision with respect to the content was reserved for the first author, who vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and the statistical analysis plan.

Trial Design and Participants

The trial enrolled adults 40 years of age or older who had a serum lipoprotein(a) concentration of at least 175 nmol per liter as measured by the Randox Laboratories assay at a central laboratory. Participants receiving lipid-modifying drugs including statins, PCSK9 inhibitors, and other drugs known to influence lipoprotein(a) concentrations were required to be receiving stable doses for at least 4 weeks before screening. Women of childbearing potential were excluded. Persons were excluded if they had had a cardiovascular event within the 3 months before screening or if they had moderate or severe heart failure, an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2 of body-surface area, or

hepatic enzyme levels greater than three times the upper limit of the normal range. Full inclusion and exclusion criteria are provided in the protocol.

Participants were randomly assigned, in a 1:2:2:2:2 ratio, to receive lepodisiran at a dose of 16 mg, 96 mg, or 400 mg at baseline and again at day 180, lepodisiran at a dose of 400 mg at baseline and placebo (0.9% sodium chloride) at day 180, or placebo at baseline and at day 180, all administered by subcutaneous injection. Randomization was stratified according to baseline lipoprotein(a) concentration (<275 nmol per liter vs. ≥275 nmol per liter) and the risk of cardiovascular events (high risk, as defined in the protocol, vs. not high risk). Investigators remained unaware of each participant's assigned group. An uninvolved third party was responsible for the preparation of lepodisiran and placebo. At scheduled visits (described in the protocol), participants were assessed for adverse events, a symptom-directed physical examination was performed, serum lipoprotein(a) concentrations were measured, and laboratory studies were performed.

END POINTS

The primary end point was the time-averaged percent change from baseline in the serum lipoprotein(a) concentration (lepodisiran difference from placebo [i.e., placebo-adjusted]) during the period from day 60 to day 180. Secondary end points included the placebo-adjusted time-averaged percent change from baseline in the lipoprotein(a) concentration during the periods from day 240 to day 360, day 30 to day 180, and day 30 to day 360. In other secondary end-point analyses, we evaluated the mean percent change in the concentrations of lipoprotein(a), apolipoprotein B, and high-sensitivity C-reactive protein from baseline to day 60, day 180, day 240, day 360, and day 540 and the percentage of participants with lipoprotein(a) concentrations of less than 125 nmol per liter and less than 75 nmol per liter.

STATISTICAL ANALYSIS

The primary efficacy and safety assessments were performed in the full analysis set, which included data from participants who received at least one dose of lepodisiran or placebo. Secondary end points were analyzed in the efficacy analysis set, which excluded data collected from participants after discontinuation of lepodisiran or placebo or initiation of medications known to affect lipoprotein(a). The primary efficacy end point was analyzed with the use of a mixed-effects model for repeated measures (MMRM) with a restricted maximum-likelihood approach. Values below the lower limit of quantification were imputed as the lower limit of quantification divided by 2. The model for the primary end point of the between-group difference in the percent change from baseline in the mean lipoprotein(a) concentration from day 60 to day 180 included the calculation log [lipoprotein(a) concentration] − log [baseline lipoprotein(a) concentration] as the dependent variable and the fixed class effects of treatment group, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline lipoprotein(a) concentration.

The MMRM for secondary efficacy end points included all postbaseline values through day 540 and fixed effects for the randomization strata. Missing values were assumed to be missing at random and were handled implicitly by the model. End points involving time-averaged measurements represent the area under the curve, constructed with the use of the trapezoidal method, which was applied according to the prespecified time window divided by the length of observation. Least-squares mean differences between lepodisiran and placebo were calculated from the MMRM. Standard errors and 95% confidence intervals were determined with the use of the delta method. No adjustment for multiple comparisons was planned.

We calculated that a sample size of 254 would provide sufficient safety data and give the trial more than 99% power to detect a difference of 70 percentage points between lepodisiran and placebo for the primary end point, assuming a standard deviation of 20 percentage points and a two-sided alpha level of 0.05. Full details regarding the statistical methods are provided in the statistical analysis plan available with the protocol.

RESULTS

PARTICIPANTS

A total of 320 participants underwent randomization, and 312 participants completed the trial with the last visit on October 17, 2024 (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The characteristics of the participants at baseline are reported in Table 1 and Table S1. The mean age was 62.7 years; 138 participants

Table 1. Demographic and Clinical Characteristics of Participants at Baseline.*

Characteristic	Placebo (N=69)	Lepodisiran 16 mg–16 mg (N=36)	Lepodisiran 96 mg–96 mg (N=74)	Lepodisiran 400 mg–Placebo (N=72)	Lepodisiran 400 mg–400 mg (N=69)
Age — yr	63.5±8.4	62.6±10.6	63.8±9.9	62.2±9.7	61.4±10.9
Sex — no. (%)					
Female	32 (46)	9 (25)	35 (47)	27 (38)	35 (51)
Male	37 (54)	27 (75)	39 (53)	45 (62)	34 (49)
Race or ethnic group — no. (%)†					
White	59 (86)	30 (83)	58 (78)	60 (83)	53 (77)
Black	0	1 (3)	2 (3)	2 (3)	2 (3)
Asian	10 (14)	3 (8)	13 (18)	8 (11)	13 (19)
Multiracial or mixed race	0	0	1 (1)	0	0
Hispanic or Latino	2 (3)	7 (19)	8 (11)	17 (24)	10 (14)
Body-mass index‡	27.8±4.8	28.3±4.9	27.8±4.6	28.4±3.8	27.8±5.6
Lipid-modifying medications — no. (%)					
Statins	50 (72)	25 (69)	55 (74)	56 (78)	50 (72)
Ezetimibe	23 (33)	13 (36)	24 (32)	25 (35)	20 (29)
PCSK9 inhibitors	7 (10)	1 (3)	3 (4)	7 (10)	1 (1)
Laboratory findings					
Median lipoprotein(a) (IQR) — nmol/liter	241.9 (202.9–301.7)	243.2 (203.4–313.3)	262.0 (213.0–325.3)	264.1 (201.1–331.1)	242.2 (199.7–329.9)
Median LDL cholesterol (IQR) — mg/dl§	76.2 (59.9–107.5)	78.7 (63.1–118.3)	79.3 (59.2–106.7)	78.5 (61.9–112.0)	81.7 (60.1–115.0)
Median HDL cholesterol (IQR) — mg/dl§	53.0 (45.2–64.0)	63.6 (45.1–70.6)	50.7 (41.0–62.3)	52.1 (43.0–59.1)	52.2 (41.0–69.0)
Median triglycerides (IQR) — mg/dl¶	100.0 (75.0–129.0)	100.6 (72.9–137.6)	102.0 (83.3–147.0)	94.1 (77.5–135.9)	104.0 (75.0–151.0)
Median apolipoprotein B (IQR) — mg/dl	75.0 (63.0– 93.0)	82.5 (67.0–94.5)	83.0 (67.0–101.0)	79.0 (65.5–91.0)	79.0 (69.0–97.0)
Median hsCRP (IQR) — mg/liter	0.8 (0.4–1.6)	0.6 (0.4–1.7)	0.8 (0.5–1.6)	0.9 (0.5–1.9)	0.7 (0.4–2.6)

* Plus–minus values are means ±SD. Shown are the characteristics of the participants in each group, with the first dose of lepodisiran or placebo received at baseline (lepodisiran at a dose of 16 mg, 96 mg, or 400 mg) and the second dose at day 180 (lepodisiran at a dose of 16 mg, 96 mg, or 400 mg or placebo). HDL denotes high-density lipoprotein, hsCRP high-sensitivity C-reactive protein, IQR interquartile range, LDL low-density lipoprotein, and PCSK9 proprotein convertase subtilisin–kexin type 9.
† Race and ethnic group were reported by the participant.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
¶ To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

(43%) were women, 219 (68%) met the criteria for being at high risk for a cardiovascular event, 153 (48%) had known coronary artery disease, and 99 (31%) had had a previous myocardial infarction. The median serum lipoprotein(a) concentration was 253.9 nmol per liter, the median low-density lipoprotein (LDL) cholesterol concentration was 79.3 mg per deciliter (2.05 mmol per liter), and the median apolipoprotein B concentration was 79.0 mg per deciliter. Concomitant medications included statins in 236 participants (74%), ezetimibe in 105 participants (33%), and PCSK9 inhibitors in 19 participants (6%). The characteristics of the participants were broadly similar across the groups.

PRIMARY EFFICACY ANALYSIS

Results for the primary and secondary end points are reported in Table 2 and Tables S2 through S5. For the primary end point, the placebo-adjusted

time-averaged percent change from baseline in the lipoprotein(a) concentration from day 60 to day 180 was −40.8 percentage points (95% confidence interval [CI], −55.8 to −20.6) in the 16-mg lepodisiran group and −75.2 percentage points (95% CI, −80.4 to −68.5) in the 96-mg group. The corresponding change in the pooled 400-mg group (the group that received lepodisiran at a dose of 400 mg at baseline and again at day 180 and the group that received lepodisiran at a dose of 400 mg at baseline and placebo at day 180) was −93.9 percentage points (95% CI, −95.1 to −92.5). The least-squares mean percent change in the lipoprotein(a) concentration from baseline through 540 days of follow-up in each group is shown in Figure 1A, and waterfall plots for the primary end point are shown in Figure 2.

SECONDARY EFFICACY ANALYSES

The placebo-adjusted percent change in the apolipoprotein B concentration from baseline to day 60, day 180, day 240, day 360, and day 540 is shown in Table 2, and the percent changes in the apolipoprotein B concentration over time in the placebo and lepodisiran groups are shown in Figure 1B. The placebo-adjusted time-averaged percent change from baseline in the lipoprotein(a) concentration during the period from day 30 to day 360 was −41.2 percentage points (95% CI, −55.4 to −22.4) in the 16-mg lepodisiran group, −77.2 percentage points (95% CI, −81.8 to −71.5) in the 96-mg group, and −94.8 percentage points (95% CI, −95.9 to −93.4) in the group that received lepodisiran at a dose of 400 mg at baseline and again at day 180. The corresponding change in the group that received lepodisiran at a dose of 400 mg at baseline and placebo at day 180 was −88.5 percentage points (95% CI, −90.8 to −85.6).

The placebo-adjusted time-averaged percent change in the lipoprotein(a) concentration from day 240 to day 360 was −38.9 percentage points (95% CI, −54.9 to −17.2) in the 16-mg group, −77.4 percentage points (95% CI, −82.4 to −71.1) in the 96-mg group, and −95.0 percentage points (95% CI, −96.1 to −93.6) in the group that received lepodisiran at a dose of 400 mg at baseline and again at day 180. The corresponding change in the group that received lepodisiran at a dose of 400 mg at baseline and placebo at day 180 was −76.8 percentage points (95% CI, −81.9 to −70.2).

Results for the placebo-adjusted time-averaged percent change in the lipoprotein(a) concentration from day 30 to day 180 and in the mean percent changes from baseline to day 60, day 180, day 240, day 360, and day 540 (secondary end points) are shown in Table 2. The placebo-adjusted differences in lipoprotein(a) concentration from baseline to days 60 through 540 are shown in Table S4. The placebo-adjusted percent change in the high-sensitivity C-reactive protein concentration from baseline to day 60, day 180, day 240, day 360, and day 540 and the percentage of participants with a lipoprotein(a) concentration of less than 125 nmol per liter or less than 75 nmol per liter at days 60 through 540 (other secondary end points) are shown in Tables S3 and S5, respectively. The placebo-adjusted percent change in total cholesterol, LDL cholesterol, high-density lipoprotein cholesterol, and triglycerides (exploratory end points) are shown in Table S6. Percent changes in LDL cholesterol over time are shown in Figure S2.

SAFETY

Adverse events are reported in Table 3. Adverse events that emerged during treatment occurred in 236 participants (74%) and were deemed by investigators to be related to lepodisiran or placebo in 31 participants (10%); one event in a participant in the placebo group (<1%) resulted in discontinuation of the regimen. Injection-site reactions, which were generally mild, transient, and dose-dependent, were reported in 1% of participants after receipt of placebo and in 0 to 12% of participants after receipt of lepodisiran; the reactions typically consisted of localized pain, erythema, or pruritus (Table S7). A total of 45 serious adverse events were reported in 35 participants (11%); none of these were deemed by investigators to be related to lepodisiran or placebo. A complete list of serious adverse events is shown in Table S8. One death due to complications of chronic coronary disease occurred in the 16-mg group. Elevations in liver-enzyme levels to greater than 3 times the upper limit of the normal range without an increase in the bilirubin level occurred in 7 of the 251 participants who received lepodisiran (3%), and all the levels returned to baseline without intervention.

DISCUSSION

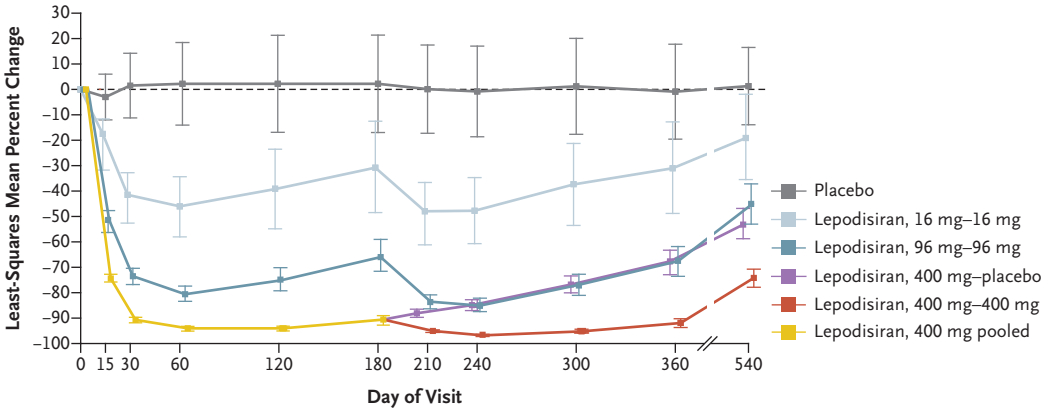
In this trial involving participants with a median lipoprotein(a) concentration of 253.9 nmol per liter, a single injection of the highest dose of

Table 2. Changes in Serum Lipoprotein(a) and Apolipoprotein B Concentrations.

End Point	Lepodisiran 16 mg–16 mg (N=36)	Lepodisiran 96 mg–96 mg (N=74)	Lepodisiran 400 mg–Placebo (N=72)	Lepodisiran 400 mg–400 mg (N=69)
		percentage points (95% confidence interval)		
Primary End Point				
Placebo-adjusted time-averaged percent change from baseline in serum lipoprotein(a) concentration, from day 60 to day 180*	−40.8 (−55.8 to −20.6)	−75.2 (−80.4 to −68.5)	−93.9 (−95.1 to −92.5)†	
Secondary End Points				
Placebo-adjusted time-averaged percent change from baseline in serum lipoprotein(a) concentration				
Day 30 to day 180	−41.6 (−55.6 to −23.2)	−75.6 (−80.5 to −69.5)	−93.8 (−94.9 to −92.5)†	
Day 30 to day 360	−41.2 (−55.4 to −22.4)	−77.2 (−81.8 to −71.5)	−88.5 (−90.8 to −85.6)	−94.8 (−95.9 to −93.4)
Day 240 to day 360	−38.9 (−54.9 to −17.2)	−77.4 (−82.4 to −71.1)	−76.8 (−81.9 to −70.2)	−95.0 (−96.1 to −93.6)
Placebo-adjusted percent change from baseline in lipoprotein(a) concentration‡				
Day 60	−47.4 (−59.9 to −30.9)	−80.9 (−84.7 to −76.1)	−95.5 (−96.3 to −94.5)†	
Day 180	−31.9 (−50.6 to −6.2)	−66.0 (−73.8 to −55.9)	−90.7 (−92.6 to −88.3)†	
Day 240	−47.3 (−61.3 to −28.3)	−84.7 (−88.1 to −80.3)	−84.7 (−87.9 to −80.8)	−96.8 (−97.4 to −95.9)
Day 360	−30.2 (−49.4 to −3.6)	−67.4 (−74.9 to −57.6)	−67.8 (−74.8 to −59.0)	−91.0 (−92.9 to −88.5)
Day 540	−19.7 (−37.8 to 3.7)	−45.8 (−56.0 to −33.2)	−53.4 (−61.7 to −43.3)	−74.2 (−78.8 to −68.5)
Placebo-adjusted percent change from baseline in apolipoprotein B concentration				
Day 60	−10.4 (-17.5 to -2.6)	−11.9 (−17.7 to −5.8)	−14.1 (−19.0 to −8.8)†	
Day 180	−8.2 (−16.2 to 0.6)	−10.7 (−17.1 to −3.8)	−13.7 (−19.3 to −7.9)†	
Day 240	−9.2 (−16.7 to −1.2)	−15.4 (−21.1 to −9.3)	−10.6 (−16.3 to −4.4)	−15.5 (−21.0 to −9.6)
Day 360	−7.0 (−14.9 to 1.7)	−12.0 (−18.1 to −5.3)	−8.6 (−14.9 to −1.9)	−14.1 (−20.0 to −7.8)
Day 540	−2.8 (−10.7 to 5.8)	−4.7 (−11.1 to 2.1)	−5.0 (−11.2 to 1.7)	−12.9 (−18.6 to −6.8)

* The time-averaged percent change in the lipoprotein(a) concentration (lepodisiran difference from placebo [i.e., placebo-adjusted]) was derived from a mixed-effects model for repeated measures including visits at day 60, day 120, and day 180. The model included baseline lipoprotein(a) concentration, treatment group, visit, and treatment-by-visit interaction.
† These data are from the pooled groups of participants who received lepodisiran at a dose of 400 mg at baseline.
‡ The difference in the percent change from baseline to day 60, day 180, day 240, day 360, and day 540 was derived as the value at each time point minus the baseline value, divided by the baseline value, and multiplied by 100. Absolute changes and changes from baseline (not reported as difference from placebo) are provided in the Supplementary Appendix.

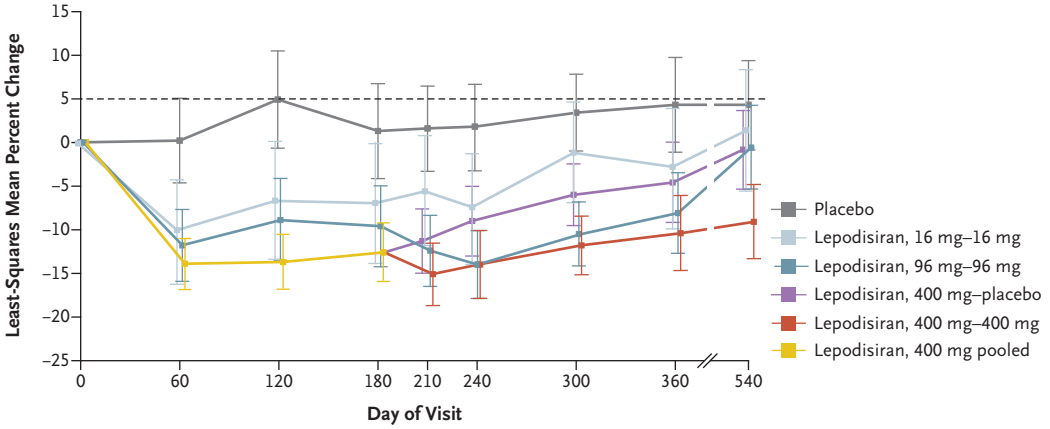
A Change in Lipoprotein(a) Concentration



No. of Participants

Placebo	69	69	68	68	67	66	64	64	64	64	60
Lepodisiran, 16 mg–16 mg	36	36	36	35	36	35	33	33	33	33	32
Lepodisiran, 96 mg–96 mg	74	73	73	73	72	72	67	67	69	68	65
Lepodisiran, 400 mg–placebo	72	71	71	69	70	69	65	66	64	64	62
Lepodisiran, 400 mg–400 mg	69	69	67	68	68	63	61	63	63	63	61

B Change in Apolipoprotein B Concentration



No. of Participants

Placebo	69	68	67	66	64	64	64	64	60
Lepodisiran, 16 mg–16 mg	36	35	36	35	33	33	33	33	31
Lepodisiran, 96 mg–96 mg	74	73	72	72	67	67	69	68	65
Lepodisiran, 400 mg–placebo	71	69	70	69	65	66	64	64	62
Lepodisiran, 400 mg–400 mg	69	67	68	63	61	62	63	63	61

Figure 1. Percent Change from Baseline in Lipoprotein(a) and Apolipoprotein B Concentrations.

Shown are the results for the participants in each group, with the first dose of lepodisiran or placebo received at baseline (lepodisiran at a dose of 16 mg, 96 mg, or 400 mg) and the second dose at day 180 (lepodisiran at a dose of 16 mg, 96 mg, or 400 mg or placebo); the data for the participants in the two groups that received 400 mg of lepodisiran at baseline are shown pooled for the first 180 days. The markers represent least-squares (LS) mean percent changes at each time point, and the I bars indicate 95% confidence intervals. Panel A shows the LS mean percent change in the lipoprotein(a) concentration from baseline through 540 days in the efficacy analysis set, which included data from participants who received at least one dose of lepodisiran or placebo, with the exclusion of data collected from participants after discontinuation of lepodisiran or placebo or initiation of medications known to affect lipoprotein(a). The model for the LS mean percent change includes baseline lipoprotein(a) concentration, treatment group, visit, treatment-by-visit interaction, and the presence or absence of a high risk of cardiovascular events. Panel B shows the LS mean percent change in the apolipoprotein B concentration from baseline through 540 days in the efficacy analysis set. The model for the LS mean percent change includes the baseline apolipoprotein B concentration, treatment group, visit, treatment-by-visit interaction, the risk of cardiovascular events (high risk vs. not high risk), and baseline lipoprotein(a) concentration strata (<275 nmol per liter vs. ≥275 nmol per liter).

lepodisiran administered in this trial, 400 mg, resulted in a placebo-adjusted time-averaged percent reduction from baseline of 93.9 percentage points in the serum concentration of lipoprotein(a) from day 60 to day 180 (the primary end point). Waterfall plots showed consistent effects for the primary end point with the 400-mg dose. After a second 400-mg dose was administered at day 180, the placebo-adjusted time-averaged percent change from baseline in the serum concentration of lipoprotein(a) from day 30 to day 360 was −94.8 percentage points and remained 91.0 percentage points below the baseline concentration at day 360 and 74.2 percentage points below the baseline concentration at day 540. A favorable safety profile was observed, with no serious adverse events

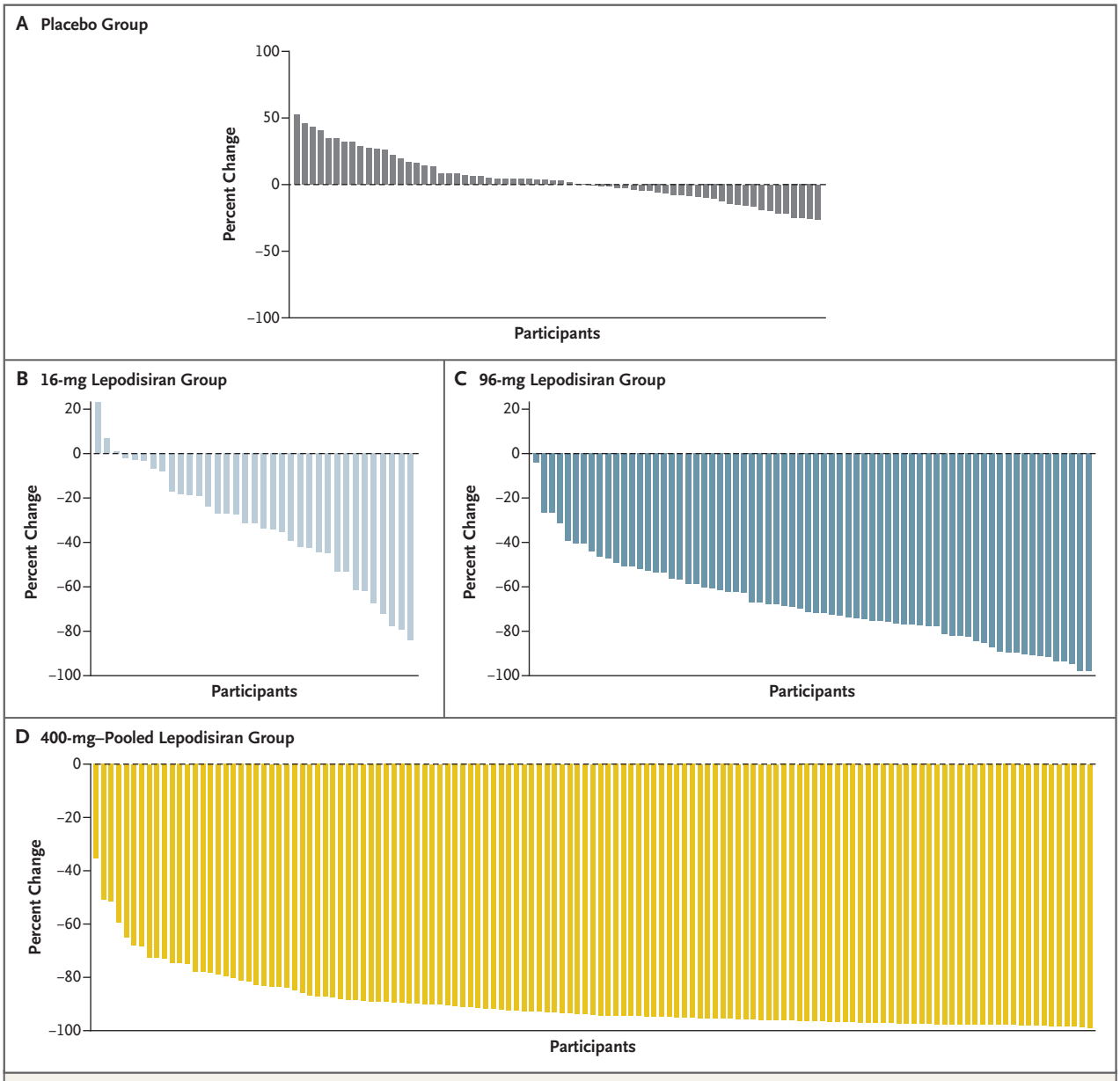


Figure 2. Distribution of the Percent Change in the Lipoprotein(a) Concentration from Baseline (Primary End Point).

The vertical bars show the time-averaged percent change from baseline in the lipoprotein(a) concentration with lepodisiran and placebo during the period from day 60 to day 180 in individual participants in each group. The percent changes were calculated with the use of the trapezoidal method.

Table 3. Adverse Events and Safety-Related Laboratory Findings.*

Adverse Events	Placebo (N=69)	Lepodisiran 16 mg–16 mg (N=36)	Lepodisiran 96 mg–96 mg (N=74)	Lepodisiran 400 mg–Placebo (N=72)	Lepodisiran 400 mg–400 mg (N=69)
	number of participants (percent)				
Adverse events that emerged during treatment	58 (84)	19 (53)	50 (68)	55 (76)	54 (78)
Related to trial regimen	1 (1)	1 (3)	9 (12)	8 (11)	12 (17)
Led to discontinuation of regimen	1 (1)	0	0	0	0
Led to withdrawal from the trial	0	0	0	0	0
Most common adverse events that emerged during treatment					
Nasopharyngitis	6 (9)	2 (6)	6 (8)	10 (14)	5 (7)
Injection-site reactions	1 (1)	0	6 (8)	6 (8)	8 (12)
Covid-19	7 (10)	2 (6)	1 (1)	4 (6)	5 (7)
Influenza	2 (3)	4 (11)	7 (9)	4 (6)	2 (3)
Arthralgia	2 (3)	1 (3)	2 (3)	6 (8)	3 (4)
Upper respiratory tract infection	0	0	5 (7)	6 (8)	3 (4)
Urinary tract infection	3 (4)	1 (3)	3 (4)	2 (3)	4 (6)
Headache	4 (6)	0	2 (3)	3 (4)	3 (4)
Back pain	4 (6)	0	1 (1)	3 (4)	2 (3)
Cough	1 (1)	0	4 (5)	2 (3)	2 (3)
Serious adverse events	6 (9)	1 (3)	9 (12)	8 (11)	11 (16)
Death†	0	1 (3)	0	0	0
Serious adverse events in any participant‡					
Unstable angina	0	0	1 (1)	1 (1)	0
Cellulitis	0	0	1 (1)	0	1 (1)
Transient ischemic attack	0	0	1 (1)	0	1 (1)
Osteoarthritis	1 (1)	0	1 (1)	0	0
Safety-related laboratory findings					
Alanine aminotransferase >3×ULN	0	1 (3)	2 (3)	0	4 (6)
Aspartate aminotransferase >3×ULN	0	0	2 (3)	0	1 (1)

* Data shown are from the safety population, which included the 320 participants who received at least one dose of lepodisiran or placebo during 540 days of follow-up. Covid-19 denotes coronavirus disease 2019 and ULN upper limit of the normal range.
† The participant was hospitalized for heart failure related to chronic coronary disease; the cause of death was recorded as chronic cardiomyopathy.
‡ A complete list of serious adverse events that emerged during treatment is shown in Table S8 in the Supplementary Appendix.

related to lepodisiran reported. Generally mild, dose-dependent injection-site reactions occurred in 0 to 12% of the participants.

The long duration of action of siRNA drugs such as lepodisiran represents a challenging conundrum for development programs. The phase 1 study of lepodisiran showed that a single dose had substantial lipoprotein(a)-lowering effects lasting a year in healthy participants who had lipoprotein(a) levels of 75 nmol per liter or higher.[15] This prolonged duration of action necessitated an extended observation period in the phase 2 trial to assess the durability of the first and second doses in participants with lipoprotein(a) levels of 175 nmol per liter or higher. To expedite development, a trial assessing cardiovascular outcomes with lepodisiran (NCT06292013) was initiated on the recommendation of the internal assessment committee, with the initial dosing frequency determined on the basis of the data that were avail-

able when the last participant completed day 180. It was planned that the final phase 2 data through 540 days of follow-up would be used to inform the dosing frequency for the phase 3 trial beyond the first year, through a protocol amendment, if necessary.

After a single 400-mg dose of lepodisiran, we observed a placebo-adjusted time-averaged percent reduction of 88.5 percentage points in the serum concentration of lipoprotein(a) from day 30 to day 360. The prolonged effect of lepodisiran may allow for infrequent administration in the ongoing phase 3 trial. This extended duration of the reduction in the lipoprotein(a) concentration has not been shown in phase 2 trials of other nucleic acid–based treatments. Each nucleic acid–based therapy requires a different dose to maximally reduce lipoprotein(a) concentrations, and each one has a different duration of action.[12-17] The mechanism of action of nucleic acid–based therapies is responsible for their inherently long duration of action. Contemporary siRNA therapeutics are conjugated with *N*-acetylgalactosamine, which binds to asialoglycoprotein receptors on the surface of hepatocytes. After endocytosis, the RNA is cleaved into separate strands, and the antisense strand is incorporated into an RNA-induced silencing complex (RISC) where it degrades mRNA for the target protein. The RNA nucleotides are chemically modified to resist degradation.[21] Lepodisiran is a noncanonical, tetraloop, Dicer-substrate RNA. Dicer cleavage and delivery into the RISC may reduce immunogenicity and increase effectiveness.[22]

Development of therapies designed to reduce lipoprotein(a) serum concentrations has intensified during the past several years. In the absence of effective therapeutic options, the global health burden of elevated lipoprotein(a) concentrations makes development of these therapies an important research priority. In addition to lepodisiran, two other lipoprotein(a)-lowering drugs, pelacarsen, an antisense oligonucleotide, and olpasiran, a siRNA, are currently being studied in phase 3 trials with cardiovascular outcomes. These trials will determine whether lowering lipoprotein(a) concentrations results in a reduction in the incidence of major adverse cardiovascular events. How much lipoprotein(a) reduction is necessary to produce clinical benefits remains uncertain and has been debated.[23-25] Data derived from the U.K. Biobank suggests a linear relationship between serum concentrations of lipoprotein(a) and cardiovascular outcomes down to very low levels, a pattern similar to that seen with LDL-cholesterol concentrations.[26] Modeling based on epidemiologic and mendelian randomization studies shows varying results, with predictions of the amount of reduction that would be needed to reduce major cardiovascular events by approximately 22% that range from 85 to 250 nmol per liter.[23-25]

A secondary end point, the placebo-adjusted change in apolipoprotein B serum concentrations with lepodisiran, showed dose-dependent maximal reductions ranging from 2.8 percentage points in the 16-mg group at day 540 to 15.5 percentage points at day 240 in the group that received two 400-mg doses of lepodisiran. Since lipoprotein(a) particles consist of apolipoprotein(a)-bound apolipoprotein B, reducing lipoprotein(a) concentrations leads to a decrease in measured apolipoprotein B concentrations. Reductions in apolipoprotein B concentrations have been consistently associated with reductions in the risk of major adverse cardiovascular events. Whether reductions in apolipoprotein B concentrations with nucleic acid–based therapies for lipoprotein(a) reduction contribute to a clinical benefit remains uncertain.

The trial has certain limitations. First, although the trial population was in many respects representative of the affected population (Table S9) and included more than 40% women, there were few Black participants. Because elevated lipoprotein(a) concentrations are more common in Black persons than in White persons, further study in this population will be necessary. Second, only two doses of lepodisiran were administered in the trial. The effect of additional doses is not known.

A single injection of the highest dose of lepodisiran administered in this trial, 400 mg, resulted in a placebo-adjusted time-averaged percent reduction from baseline of 93.9 percentage points in the serum concentration of lipoprotein(a) during the period from day 60 to day 180 and of 88.5 percentage points from day 30 to day 360. After a second 400-mg dose at day 180, the placebo-adjusted time-averaged percent reduction from day 30 to day 360 was 94.8 percentage points.

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