Lepodisiran: An Extended-Duration siRNA Targeting Lipoprotein(a)

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Disclosure

Consulting: Many pharmaceutical companies

Clinical Trials: AbbVie, Arrowhead, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Esperion, Medtronic, Novartis, and Silence Therapeutics.

Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor a tax deduction is received.

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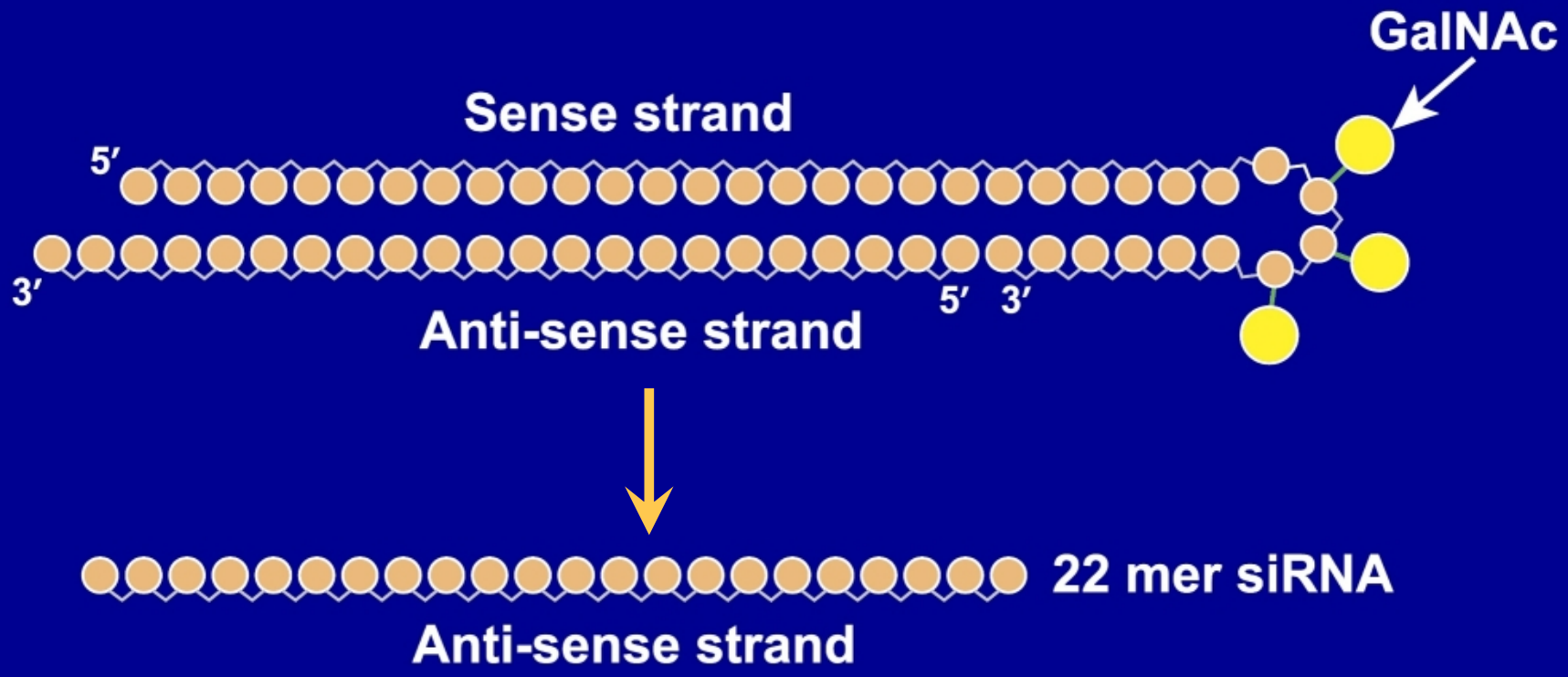
Background

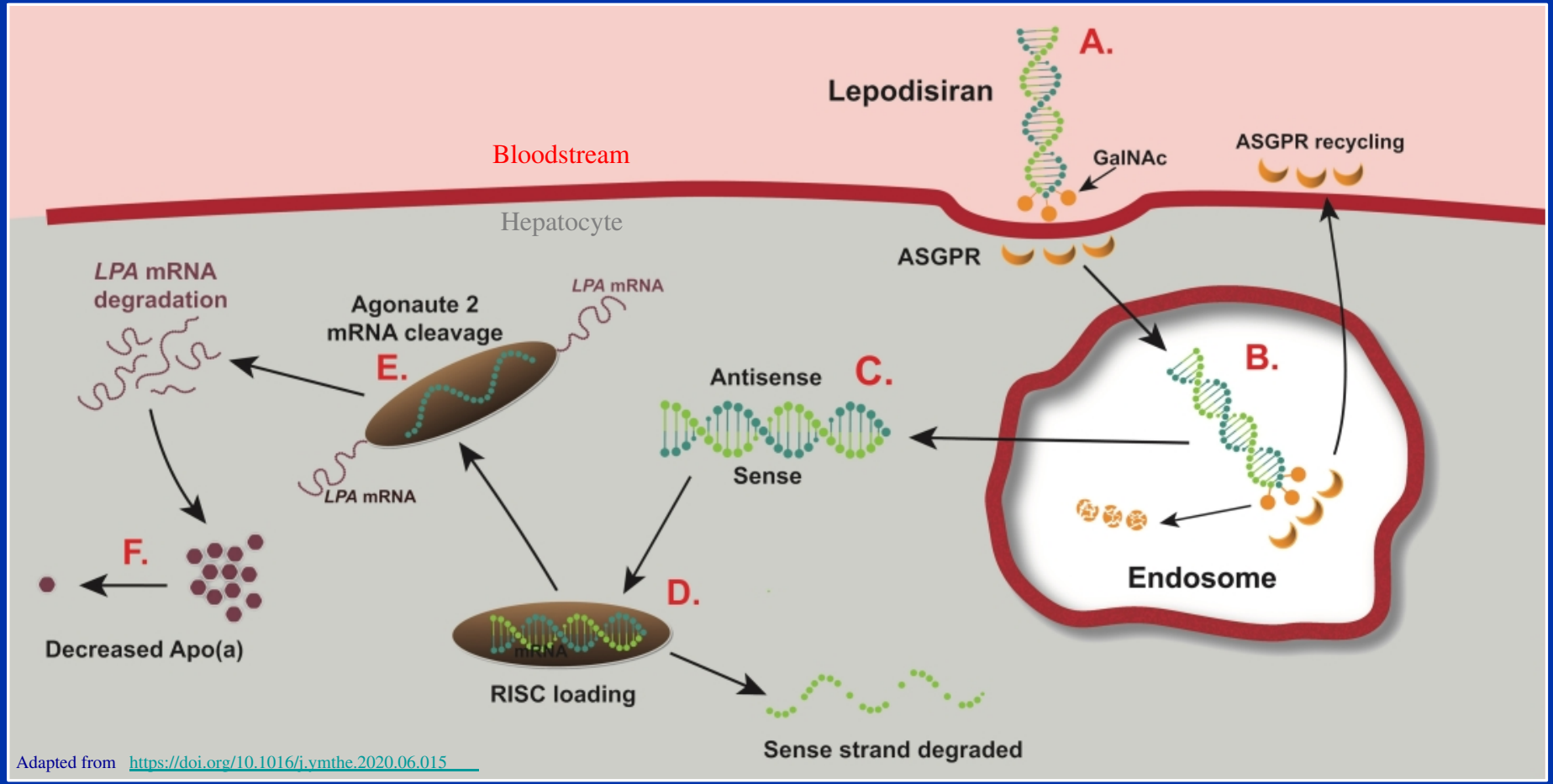
- Lipoprotein(a) is an important genetically-determined risk factor for cardiovascular disease with no pharmacological treatments currently approved by regulatory authorities.
- The *LPA* gene encodes apolipoprotein(a), an essential component required for hepatic synthesis of lipoprotein(a).
- Lepodisiran is an siRNA designed to degrade the mRNA coding for apolipoprotein(a) thereby reducing translation of the *LPA* gene.
- The current trial examined the safety and efficacy of this siRNA in participants followed for up to 48 weeks.

Lepodisiran: A Dicer-Substrate Tetraloop siRNA



Nucleotides chemically modified for resistance to degradation by ribonucleases

Mechanism for Lepodisiran Reduction of Lipoprotein(a)



Adapted from https://doi.org/10.1016/j.ymthe.2020.06.015

Study Procedures

- 48 participants enrolled, 18-65 years in age, without known cardiovascular disease and Lp(a) concentration ≥75 nmol/L.
- Participants admitted to a Clinical Research Unit 1 day prior to dosing and monitored for 3 days after drug administration.
- Six participants randomized to a single doses of lepodisiran (4 mg,12 mg, 32 mg, 96 mg, 304 mg, or 608 mg) or placebo administered subcutaneously.
- Visits and laboratory studies up to 48 weeks following dosing.

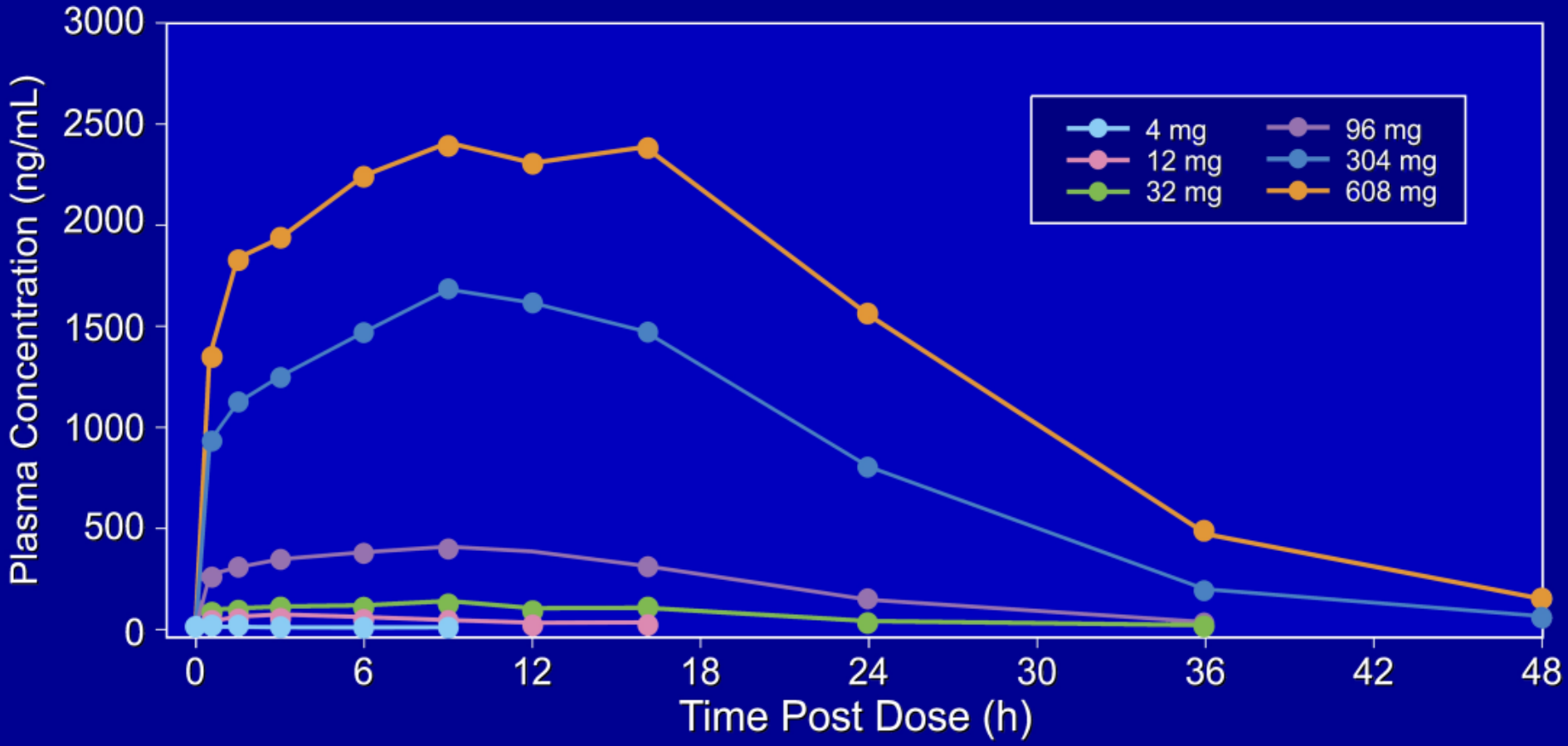
Primary Safety and Efficacy Outcomes

- Safety:
  - Treatment emergent adverse events and injection site reactions
  - Safety laboratory parameters
- Lepodisiran plasma concentrations through 48 hours
- Effects on lipoprotein(a) serum concentrations through 337 days (48 weeks).

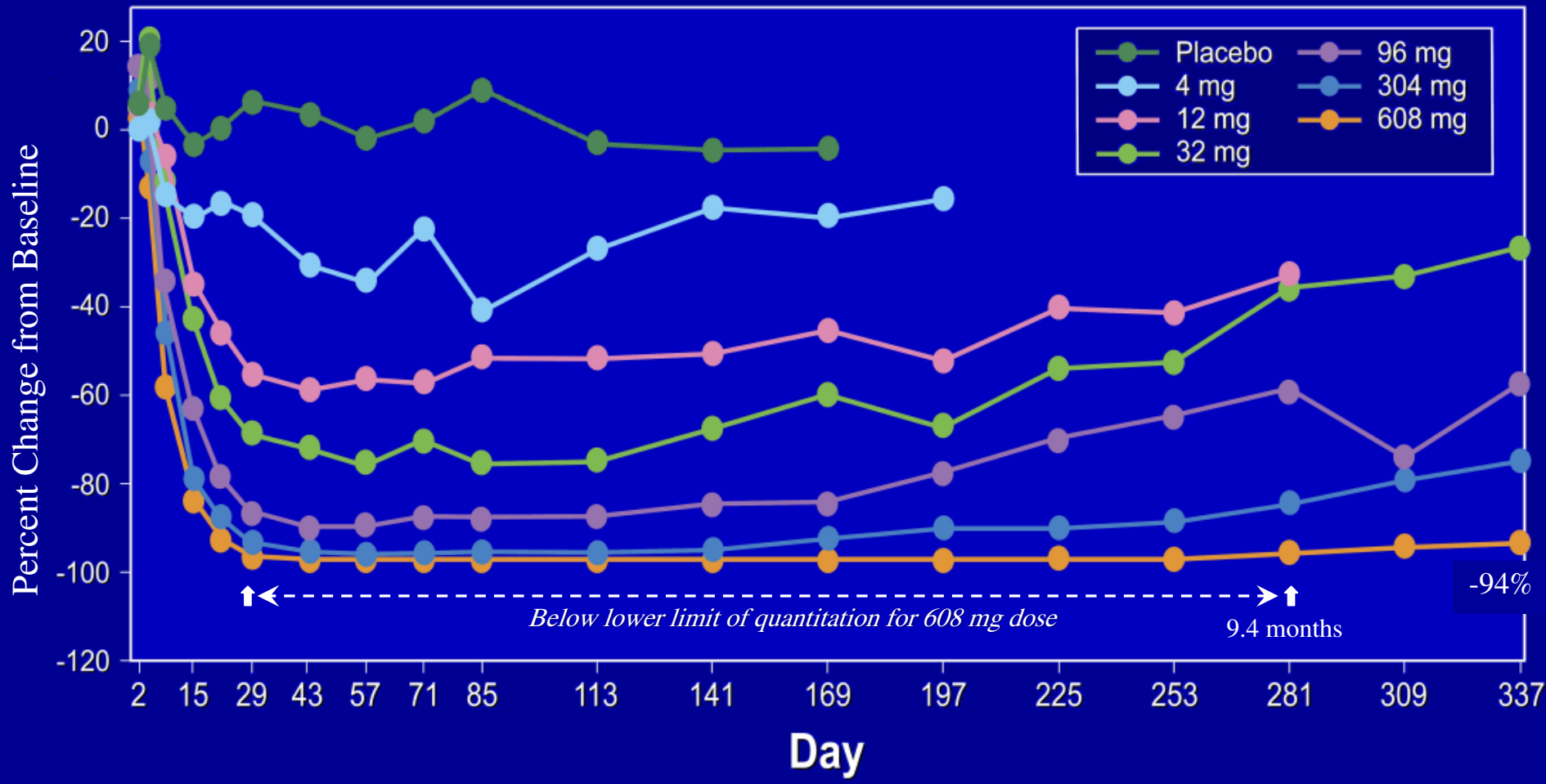
Selected Baseline Characteristics of Participants

	Placebo (n=12)	4 mg (n=6)	12 mg (n=6)	32 mg (n=6)	96 mg (n=6)	304 mg (n=6)	608 mg N=6
Age (years)	50.3	40.5	44.3	50.7	47.8	51.8	38.5
Male (%)	50	83	50	50	50	66	83
Median Lp(a), nmol/L	111	78	97	120	167	96	130
Mean LDL-C, mg/dL	143	108	148	110	118	142	135
Mean ApoB, mg/dL	90	117	93	97	114	108	116
hsCRP, mg/L	1.3	3.5	1.3	2.0	1.4	1.7	0.8

Lepodisiran Plasma Concentrations in the First 48 Hours



Median Percent Reduction in Lipoprotein(a) over Time



Treatment Emergent Adverse Events & Lab Abnormalities

	Placebo (n=12)	4 mg (n=6)	12 mg (n=6)	32 mg (n=6)	96 mg (n=6)	304 mg (n=6)	608 mg (n=6)
Treatment emergent adverse events in 3 or more participants, n (%)							
COVID-19	1	0	1	0	2	1	1
Headache	1	0	1	0	1	1	2
Rhinorrhea	0	0	2	0	0	1	0
ECG Patch Erythema	0	0	1	0	1	1	0
Laboratory abnormalities							
CK > 5 x ULN	0	2	0	0	0	0	1
hsCRP > 5 mg/L	7	1	2	3	2	5	1

Investigator-Reported Injection Site Reactions

	Placebo (n=12)	4 mg (n=6)	12 mg (n=6)	32 mg (n=6)	96 mg (n=6)	304 mg (n=6)	608 [a] (n=6)	608 [b] (n=6)
Participants reporting an event	2	0	3	2	2	3	3	4
Individual events reported								
Erythema	1	0	0	1	1	2	0	1
Induration	0	0	0	0	0	0	0	0
Pain	2	0	3	1	2	2	3	4
Pruritus	0	0	0	0	0	0	0	0
Edema	0	0	0	0	0	1	0	0

The 608 mg dose was administered as two injections of 304 mg, [a]first injection, [b]second injection.

Limitations

- This was a small, first-in-human Phase 1 trial enrolling 48 participants without known cardiovascular disease.
- Safety cannot be comprehensively assessed in a trial of this size and duration.
- The minimum entry criteria for lipoprotein(a) was moderate (75 nmol/L).
- Single doses administered, although a Phase 2 multi-dose trial is underway.

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Lepodisiran, an Extended-Duration Short Interfering RNA Targeting Lipoprotein(a)

A Randomized Dose-Ascending Clinical Trial

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IMPORTANCE Epidemiological and genetic data have implicated lipoprotein(a) as a potentially modifiable risk factor for atherosclerotic disease and aortic stenosis, but there are no approved pharmacological treatments.

OBJECTIVES To assess the safety, tolerability, pharmacokinetics, and effects of lepodisiran on lipoprotein(a) concentrations after single doses of the drug; lepodisiran is a short interfering RNA directed at hepatic synthesis of apolipoprotein(a), an essential component necessary for assembly of lipoprotein(a) particles.

Conclusions

- Subcutaneous injection of lepodisiran, an siRNA targeting mRNA for the *LPA* gene substantially lowered lipoprotein(a).
- After the 608 mg dose, serum concentrations of lipoprotein(a) fell below the lower limit of quantitation from days 29 to 281 and remained >94% below baseline for 337 days (48 weeks) .
- There were no major safety issues, although low-grade, transient, injection site reactions occurred.
- These findings support further development of this therapy.

A Final Thought

Elevation of lipoprotein(a) is a common risk factor responsible for considerable cardiovascular morbidity and mortality with no pharmacological therapies approved by regulatory authorities. Nucleic acid therapeutics offer a highly promising approach to treat this previously untreatable disorder. Cardiovascular outcomes trials will determine whether these therapies can reduce the incidence of MACE. Stay tuned.