A Single Ascending Dose Study of an siRNA Targeting Lipoprotein(a)

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for the APOLLO Study Investigators

Disclosure

Consulting: Many pharmaceutical companies

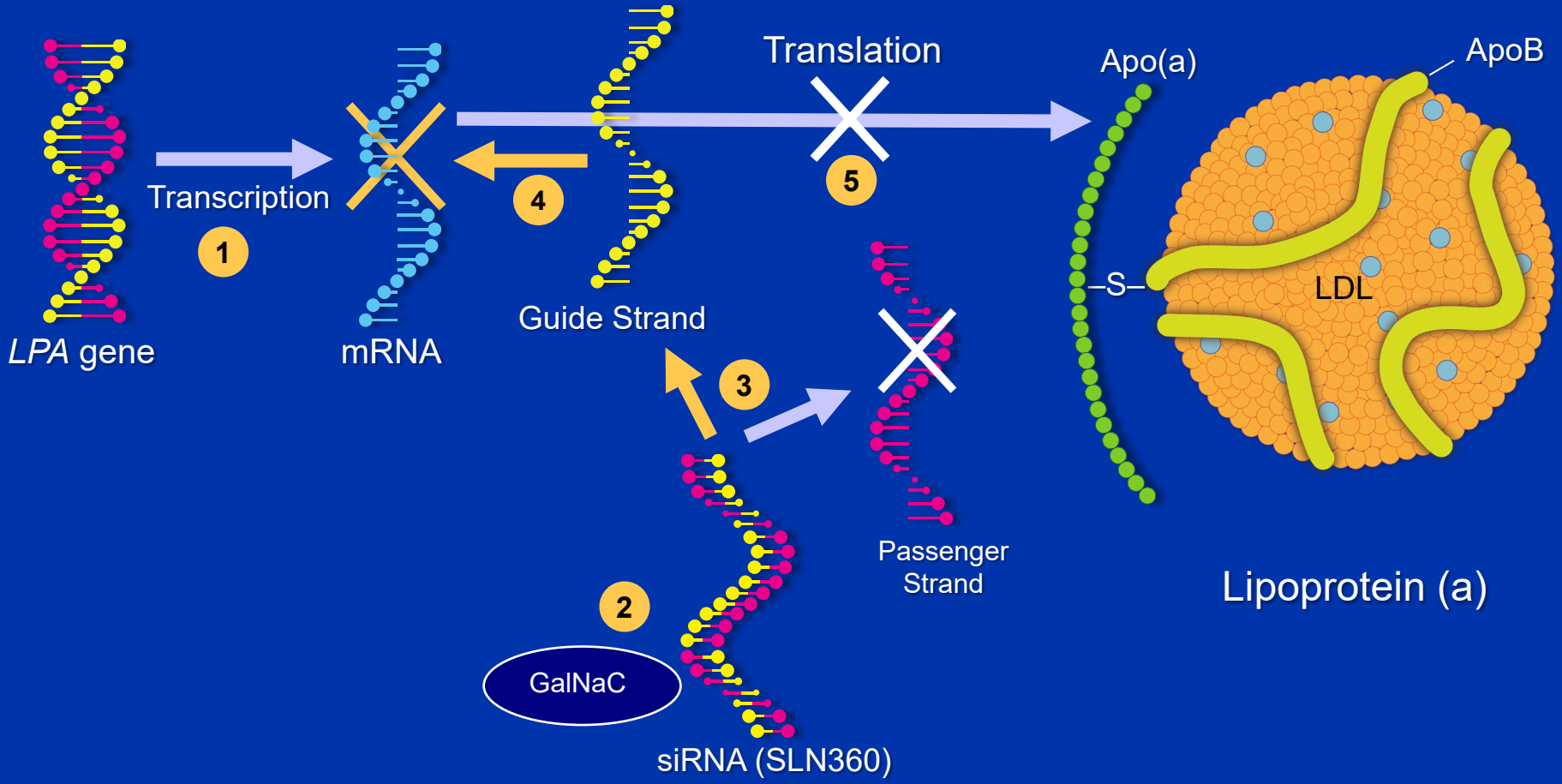
Clinical Trials: AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Esperion, Medtronic, Novartis, Silence Therapeutics, and Pfizer.

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

Background

- Lipoprotein(a) is an important risk factor for ASCVD and aortic stenosis with no treatments approved by regulatory authorities.
- The *LPA* gene encodes for apolipoprotein(a), a dominant, rate-limiting component in the hepatic synthesis of Lp(a).
- An siRNA is a double-stranded RNA designed to degrade a specific mRNA to suppress the translation of a target gene.
- The Phase 1 APOLLO trial examined the tolerability and Lp(a) lowering effects of SLN360 (Silence Therapeutics, London, UK) an siRNA targeting mRNA specific for the *LPA* gene.

Mechanism of Action of SLN360 in Lowering Lp(a)

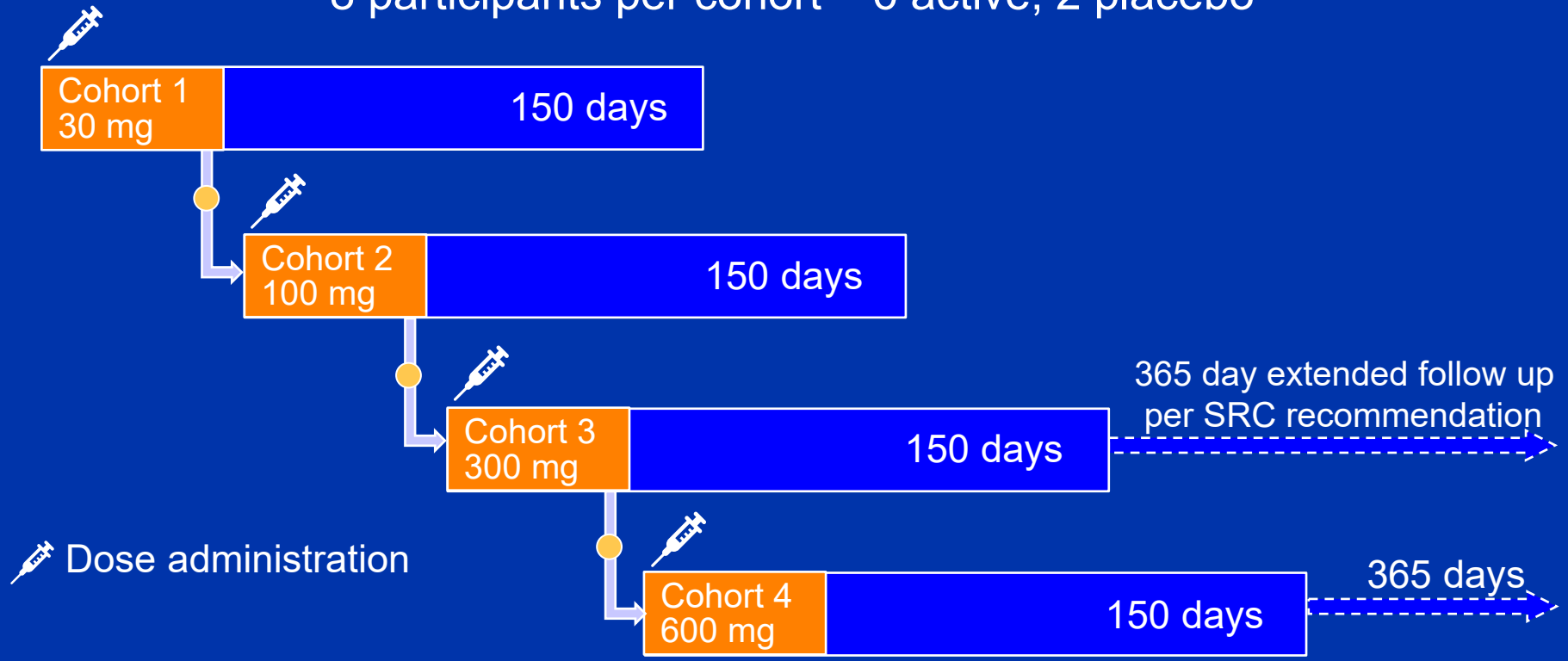


Study Design

- Adults ≥18 years in age without known ASCVD and an Lp(a) concentration ≥150 nmol/L.
- Single dose cohorts randomized to SLN360 (30 mg, 100 mg, 300 mg or 600 mg) or placebo given subcutaneously.
- Participants monitored in a Clinical Research Unit for 24 hours following dose administration.
- Visits at 7, 14, 30, 45, 60, 90 and 150 days following administration.

Study Schematic: Single Ascending Dose Study

8 participants per cohort – 6 active, 2 placebo



- Safety Review Committee (SRC) reviewed data for a minimum of 4 participants on SLN360

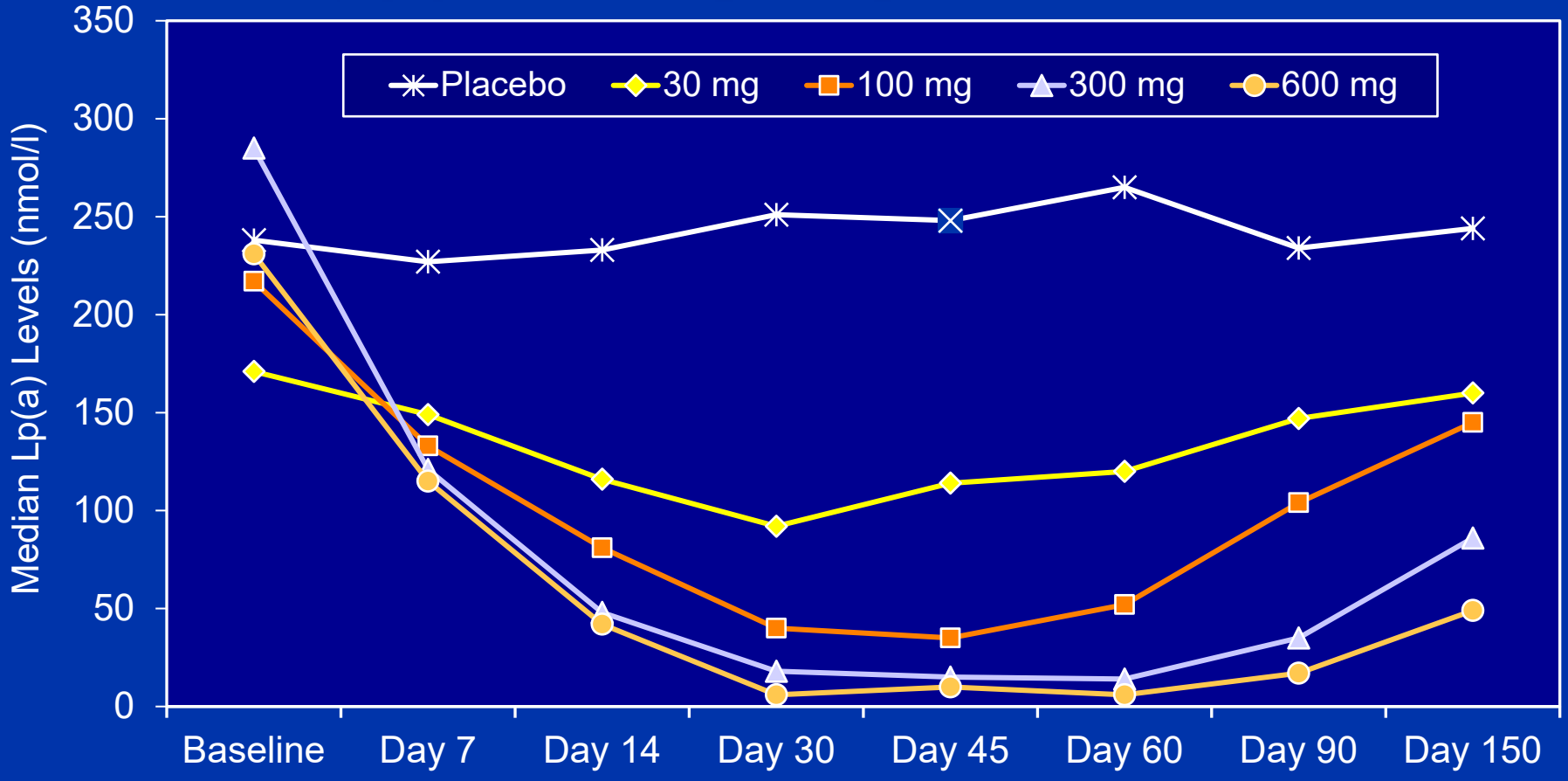
Outcomes

- *Safety:*
  - Vital signs, physical examination, ECG, lab chemistries
  - Treatment emergent adverse events – AE's of special interest and any dose-limiting toxicity.
- *Efficacy:*
  - Primary: Effect on lipoprotein(a) concentration from baseline to 150 days.
  - Effects on LDL-C, apoB, oxidized LDL, inflammatory markers, plasminogen and pharmacokinetics.

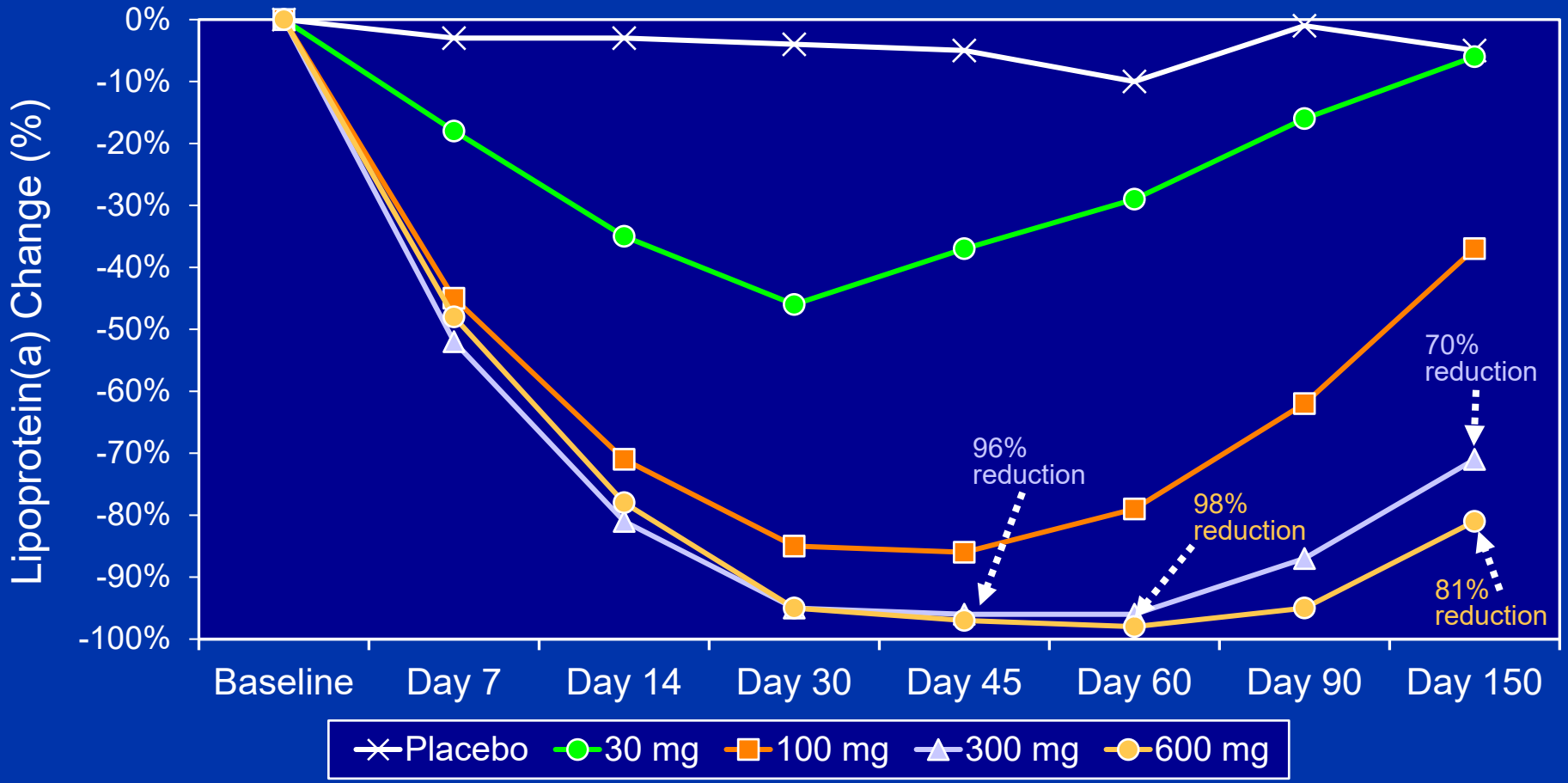
Baseline Characteristics

	All Participants (n=32)	Placebo (n=8)	30 mg (n=6)	100 mg (n=6)	300 mg (n=6)	600 mg (n=6)
Age (years)	**49.6**	52.9	45.5	46.3	58.7	43.7
Male (%)	**47**	25	67	67	33	50
Mean BMI, kg/m^2	**27**	25	26	29	29	27
Median Lp(a), nmol/L	**224**	238	171	217	285	231
Mean LDL-C, mg/dL	**108**	99	113	121	100	108
Mean ApoB, mg/dL	**85**	81	83	94	89	81

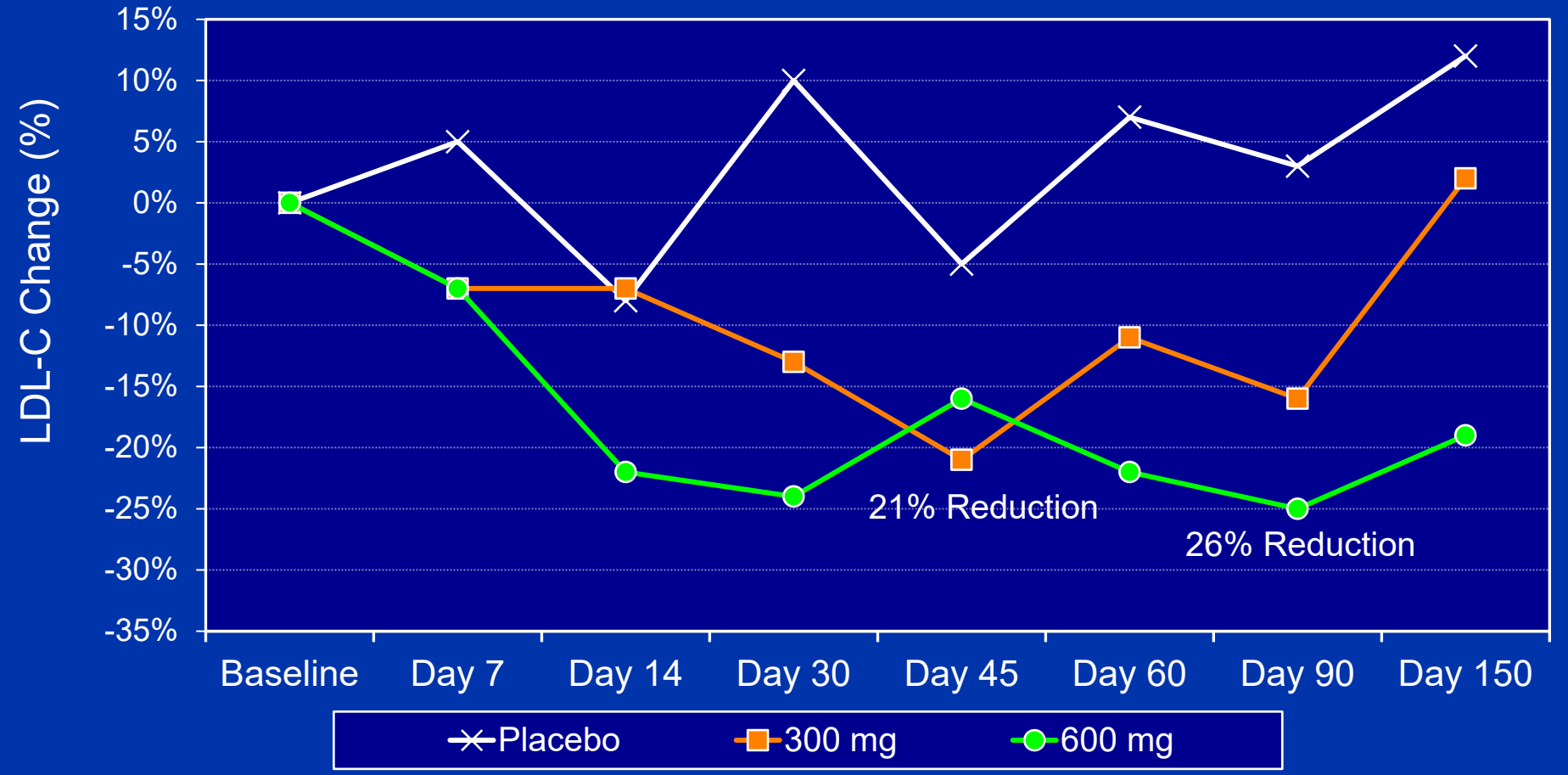
Median Lp(a) following Single Doses of SLN360



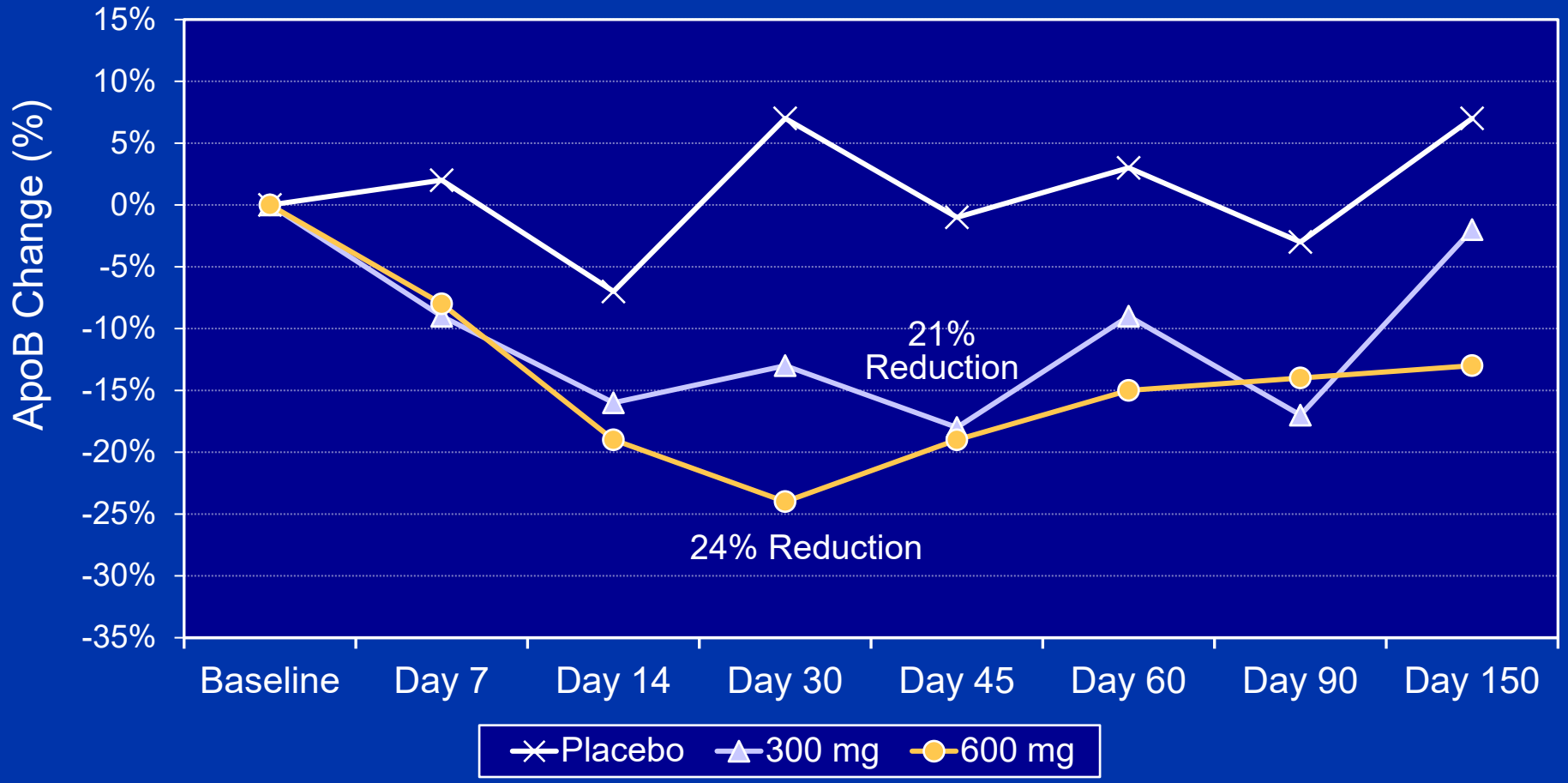
Median Percent Lowering of Lipoprotein(a)



Mean Percent Reduction in LDL-C for Two Highest Doses



Mean Percent Reduction in ApoB for Two Highest Doses



Safety: Treatment Emergent Adverse Events

	All (n=32)	Placebo (n=8)	30 mg (n=6)	100 mg (n=6)	300 mg (n=6)	600 mg (n=6)
Treatment emergent adverse events occurring in more than 3 participants, n (%)						
Headache	9 (28)	1 (13)	2 (33)	1 (17)	0 (0)	5 (83)
Diarrhea	3 (9)	1 (13)	1 (17)	0 (0)	0 (0)	1 (17)
Arthralgia	3 (9)	0 (0)	1 (17)	0 (0)	1 (17)	1 (17)
Neutrophil count increased	3 (9)	0 (0)	0 (0)	0 (0)	0 (0)	3 (50)
C-reactive protein increased	4 (32)	0 (0)	0 (0)	0 (0)	0 (0)	4 (67)
Serious Adverse Events, n (%)	1 (3)	0 (0)	1 (17)*	0 (0)	0 (0)	0 (0)

* A single participant experienced 2 SAE episodes, unrelated to SLN360

Effect on Liver Enzymes and Injection Site Reactions

	All (n=32)	Placebo (n=8)	30 mg (n=6)	100 mg (n=6)	300 mg (n=6)	600 mg (n=6)
Liver Enzymes, n (%)						
ALT > 3x ULN	1(3)*	0 (0)	1 (17)^	0 (0)	0 (0)	0 (0)
AST > 3x ULN	1(3)*	0 (0)	1 (17)^	0 (0)	0 (0)	0 (0)
ALP† >2x ULN	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
*Injection site reactions, n (%)						
Grade 1	18 (56)	1 (13)	5 (83)	6 (100)	4 (67)	2 (33)
Grade 2	5 (16)	0 (0)	0 (0)	0 (0)	1 (17)	4 (67)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*Graded using the Common Terminology Criteria for Adverse Events †Alkaline phosphatase ^Same individual, single time point

Limitations

- This was a small, first-in-man Phase 1 trial enrolling only 32 participants.
- Safety cannot be comprehensively assessed in a trial of this size and duration.
- A population without known cardiovascular disease was selected for study.
- Single doses administered - effects of multiple doses uncertain, although a multidose study is underway.

JAMA | Original Investigation

Single Ascending Dose Study of a Short Interfering RNA Targeting Lipoprotein(a) Production in Individuals With Elevated Plasma Levels

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IMPORTANCE Lipoprotein(a) (Lp[a]) is an important risk factor for atherothrombotic cardiovascular disease and aortic stenosis, for which there are no treatments approved by regulatory authorities.

OBJECTIVES To assess adverse events and tolerability of a short interfering RNA (siRNA) designed to reduce hepatic production of apolipoprotein(a) and to assess associated changes in plasma concentrations of Lp(a) at different doses.

DESIGN, SETTING, AND PARTICIPANTS A single ascending dose study of SLN360, an siRNA targeting apolipoprotein(a) synthesis conducted at 5 clinical research unit sites located in the

+ Visual Abstract
+ Editorial
+ Supplemental content

Conclusions

- Subcutaneous injection of an siRNA (SLN360) targeting mRNA for the *LPA* gene lowered lipoprotein(a) up to 98%.
- >70% and >80% reductions in Lp(a) persisted for 150 days after the 300 mg and 600 mg doses.
- The highest doses reduced LDL-C and ApoB by 20-30%.
- There were no major safety issues, although low-grade, transient, dose-dependent injection site reactions occurred.
- These findings support further development of this therapy.

A Final Thought

Historically, elevated lipoprotein(a) has been considered an untreatable abnormality. The development of therapies targeting mRNA has made possible significant lowering of Lp(a). Whether these reductions can impact on the incidence of ASCVD events or prevent progression of aortic stenosis remains to be determined, but optimism is warranted.