



ORION-1

Impact of a 1- or 2-dose starting regimen of inclisiran, a novel siRNA inhibitor to PCSK9 on time averaged LDL-C reductions over 1 year

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On behalf of the ORION-1 investigators

Disclosures

Research grants:

- Amgen, Sanofi, Regeneron, MSD, Pfizer

Consultancy:

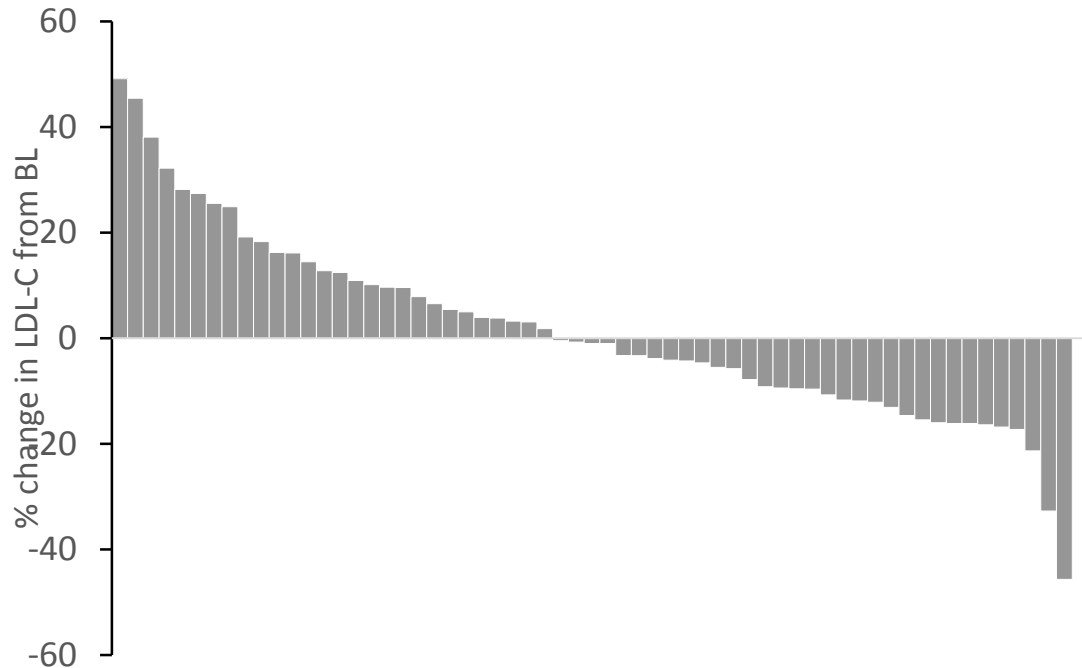
- Amgen, Sanofi, Regeneron, MSD, Pfizer, Astra Zeneca, Lilly, Medicines Company, Kowa, IONIS, Takeda, Novo Nordisk, Boehringer Ingelheim, Esperion, Cipla, Algorithm, Abbvie, Resverlogix, Cerenis

Background

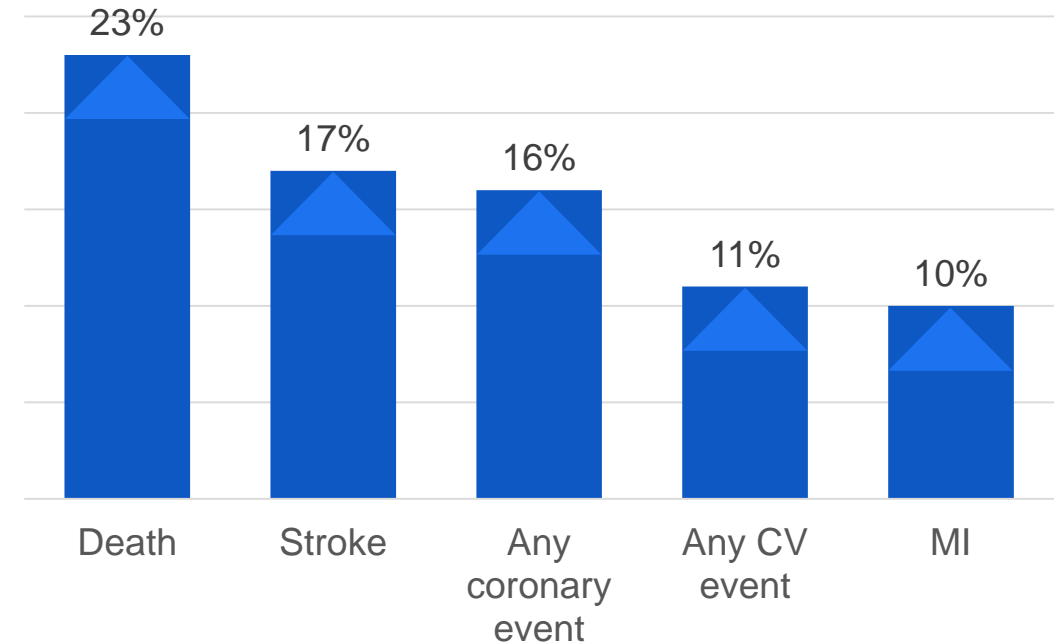
LDL-C variability common, associated with worse outcomes



Six month percent change in LDL-C among statin users from starting level¹



Increase in death, CV outcomes with each 1 standard deviation of LDL-C variability²



1. Ray KK et al. N Engl J Med 2017; 376:1430-1440
2. Bangalore S et al. JACC 2015; 65: 1539-1548



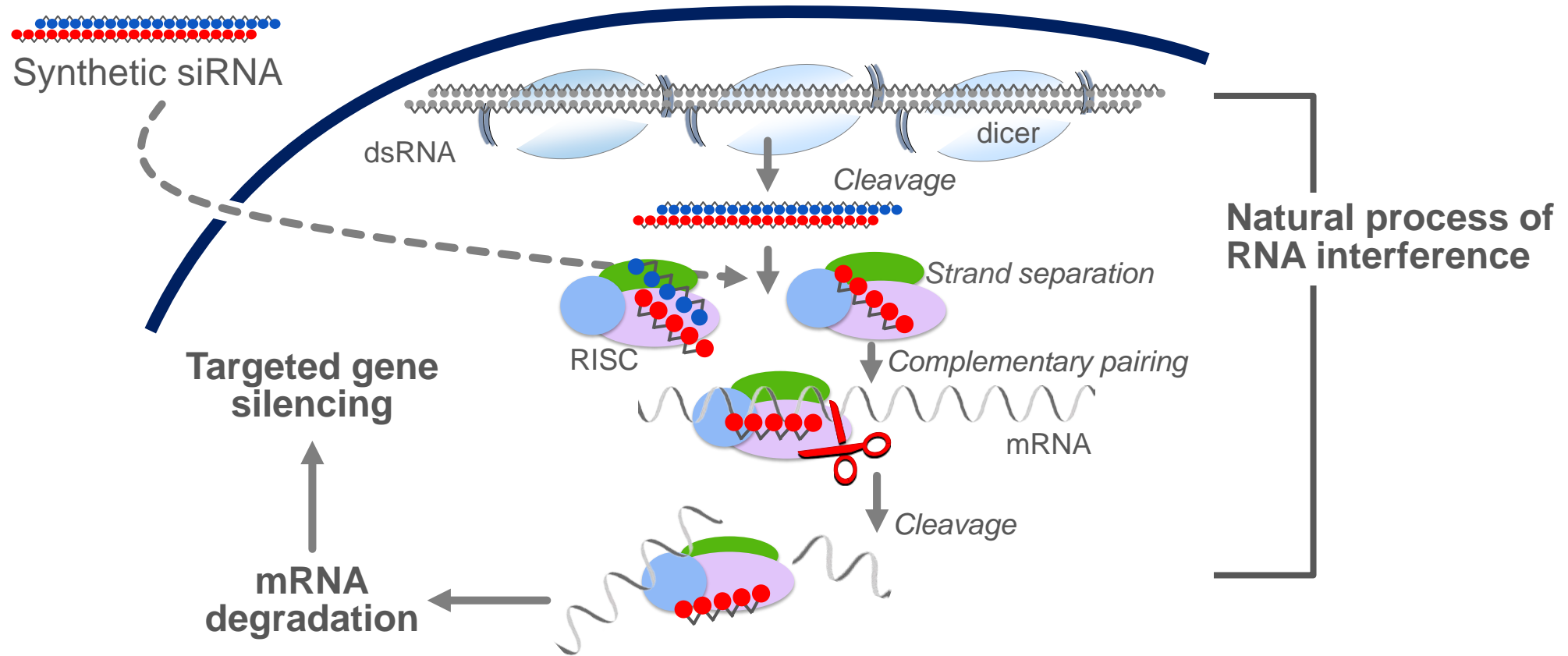
PCSK9 monoclonal antibody treatment requires 12-26 injections per year¹

Adherence unlikely to show substantial improvement over statins²

Limitations are most relevant in high risk patients needing lifelong therapy

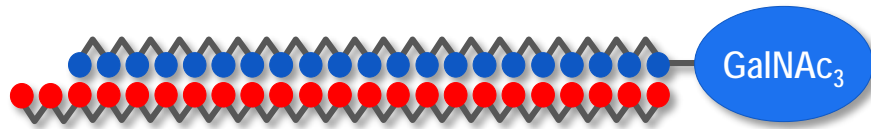
In the future can we do better?

1. Sabatine MS et al. N Engl J Med 2017; 376:1713-1722
2. Hines D et al. ACC 2017 abstract #1203-313



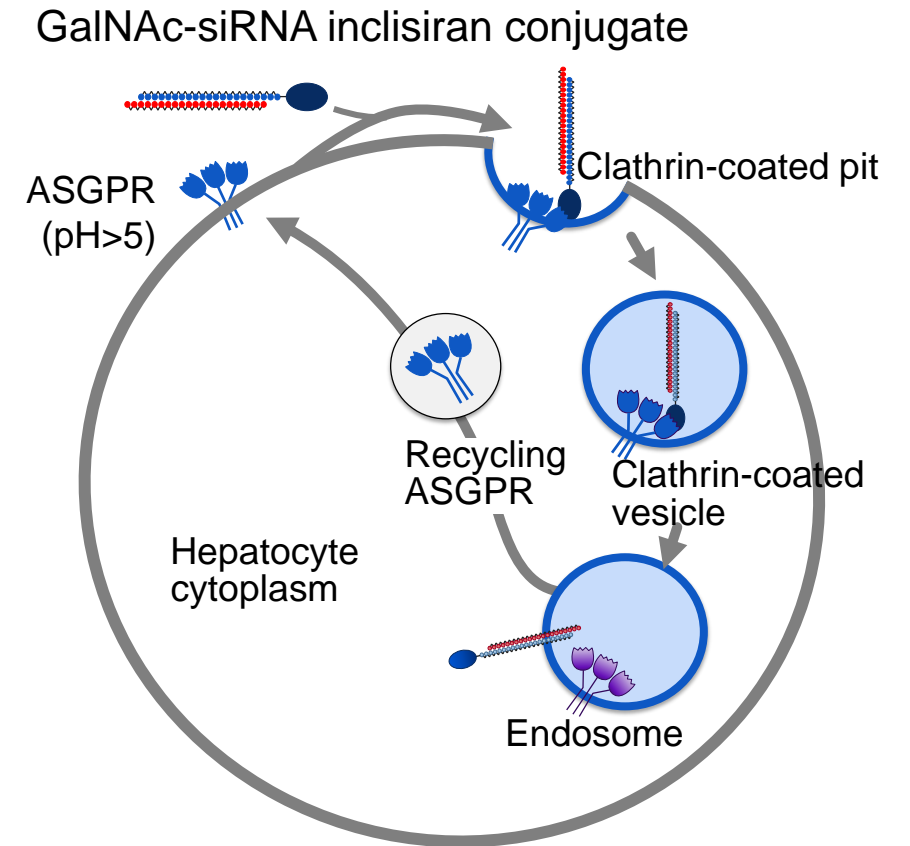
Asialoglycoprotein receptor (ASGPR)

- Highly expressed in hepatocytes only
- High rate of uptake



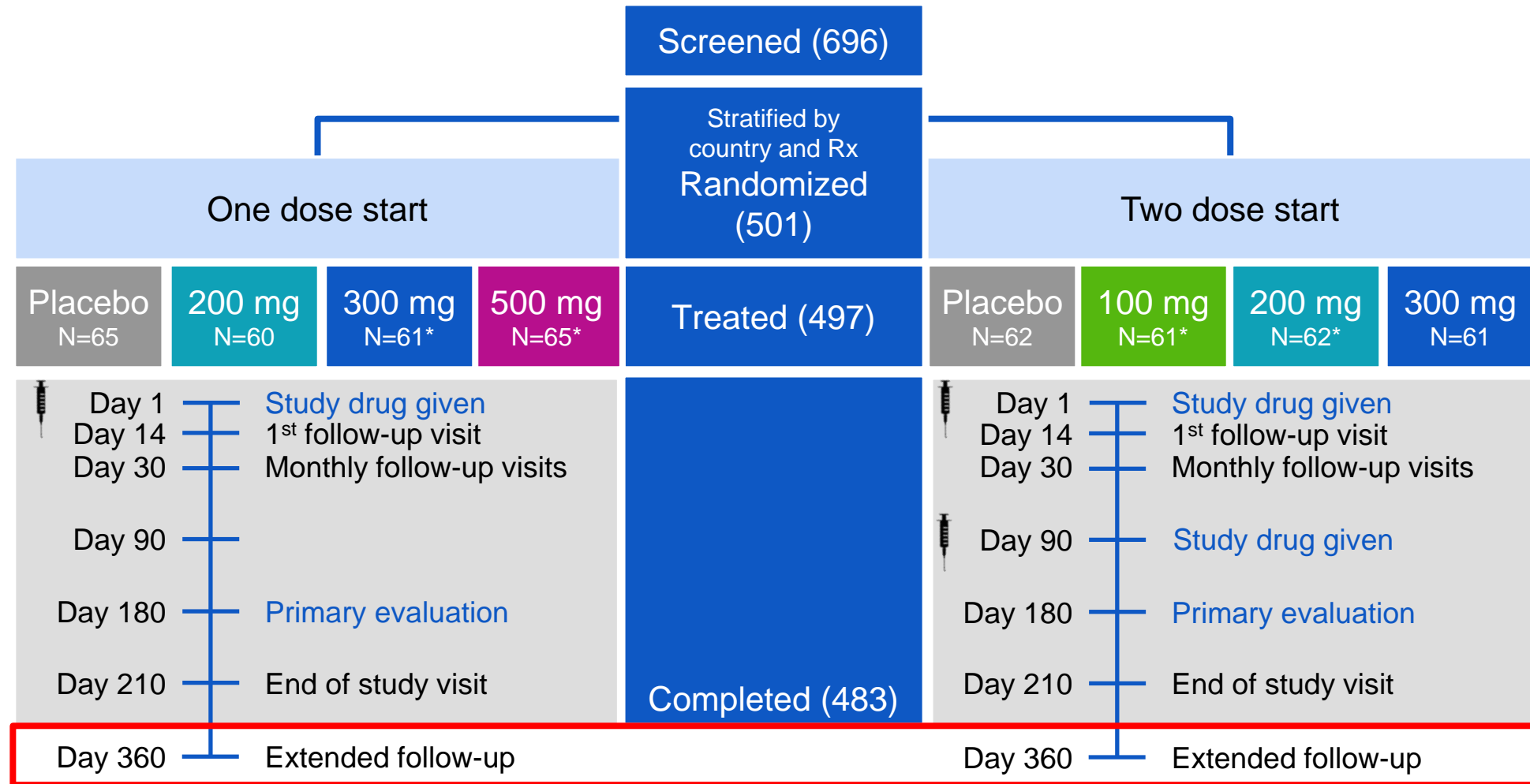
Inclisiran

- siRNA conjugated to N-acetylgalactosamine
- Subcutaneous administration
- Targeted delivery to hepatocytes



Methods

ORION 1 trial design





		One dose starting regimen		Two dose starting regimen	
		Placebo	Inclisiran	Placebo	Inclisiran
		N=65	N=186	N=62	N=184
Age	Mean years	62	63	63	64
Male sex	%	64.6	67.7	53.2	66.3
Prior ASCVD	%	69.2	67.9	74.2	68.3
Statin Rx	%	70.3	74.4	77.0	70.2
LDL-C	Mean mg/dL	128.5	125.9	125.2	133.0
Non-HDL-C	Mean mg/dL	157.8	156.5	157.1	165.6
Apo-B	Mean mg/dL	102.4	103.2	104.6	107.7
Lipoprotein(a)	Median nmol/L	27.0	34.0	50.5	40.0
PCSK9	Mean ng/mL	404.7	428.7	431.3	416.2



Similar overall adverse event profile and incidence for inclisiran and placebo

No LFT elevations considered related to investigational drug

- Similar incidence of transient transaminase increases in randomized groups

No difference in incidence of myalgias or CPK enzyme elevation

- One clinically relevant case of myonecrosis on placebo

No deaths related to drug administration

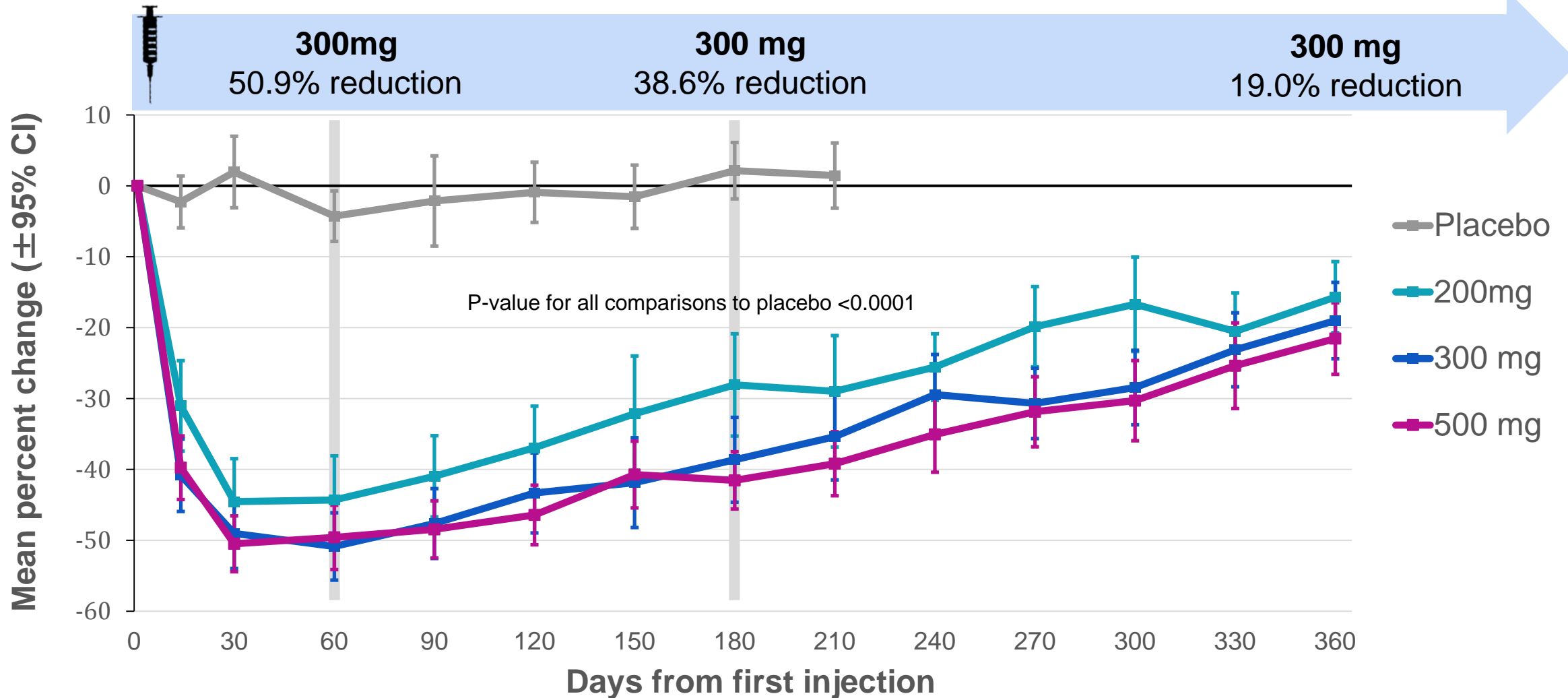
- Two previously reported deaths¹ >100 days, related to underlying disease

1: Patient A: History of CHD, MI and PCI died of a fatal MI on Day 104 of the study. (500mg x1 dose)

Patient B: Developed complications of aortic aneurysm surgery including an aorto-esophageal fistula requiring esophagectomy, leading to infection of the prosthesis, sepsis, and stroke, culminating in death on Day 198 of the study. Patient also had AF, chronic renal failure, emphysema, HT and obesity. (200mg x2 doses)

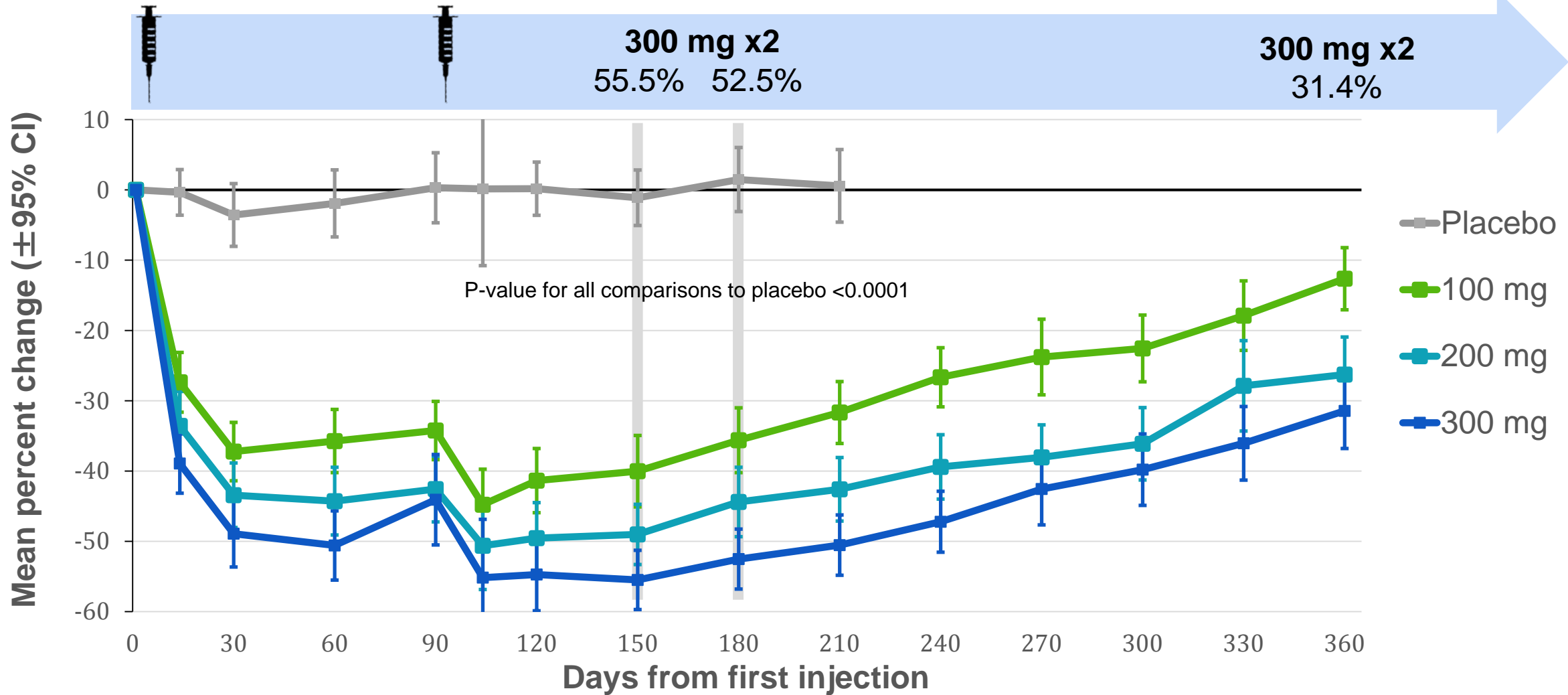
Efficacy: One dose starting regimen

Robust, sustained LDL-C reductions – 300 mg optimal



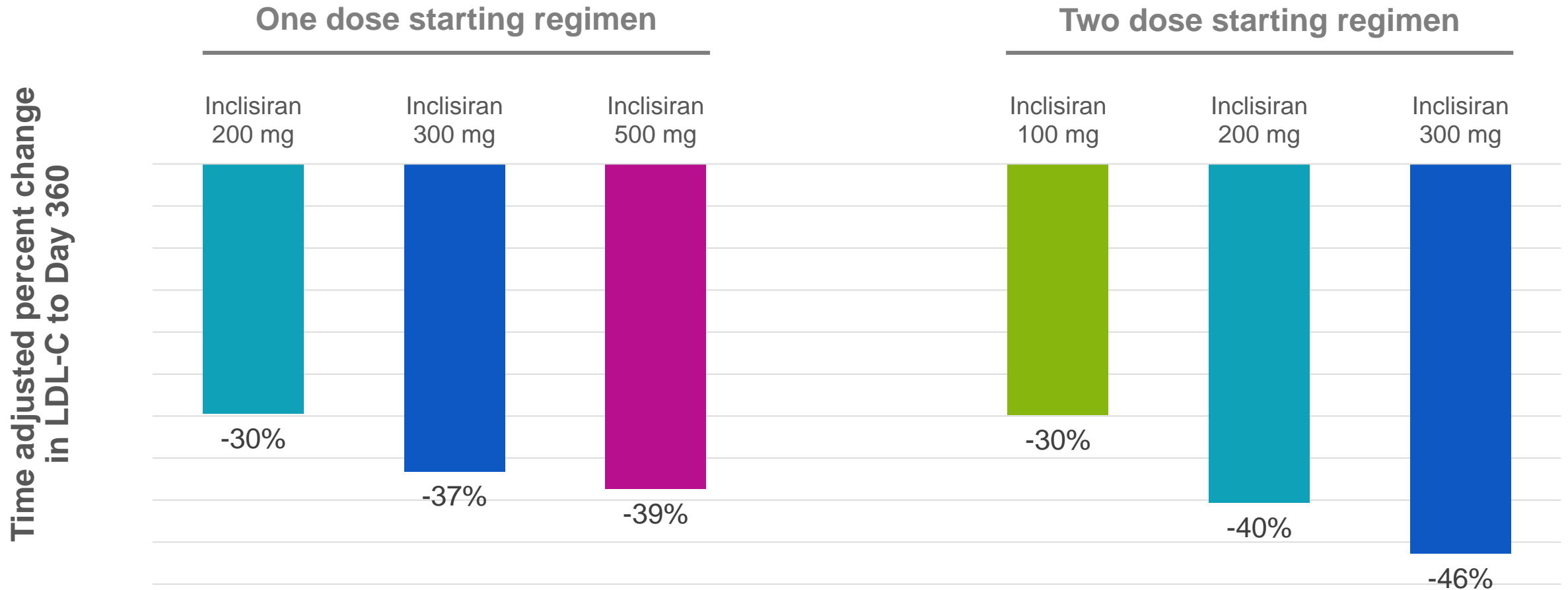
Efficacy: Two dose starting regimen

Robust, sustained LDL-C reductions – optimal start regimen



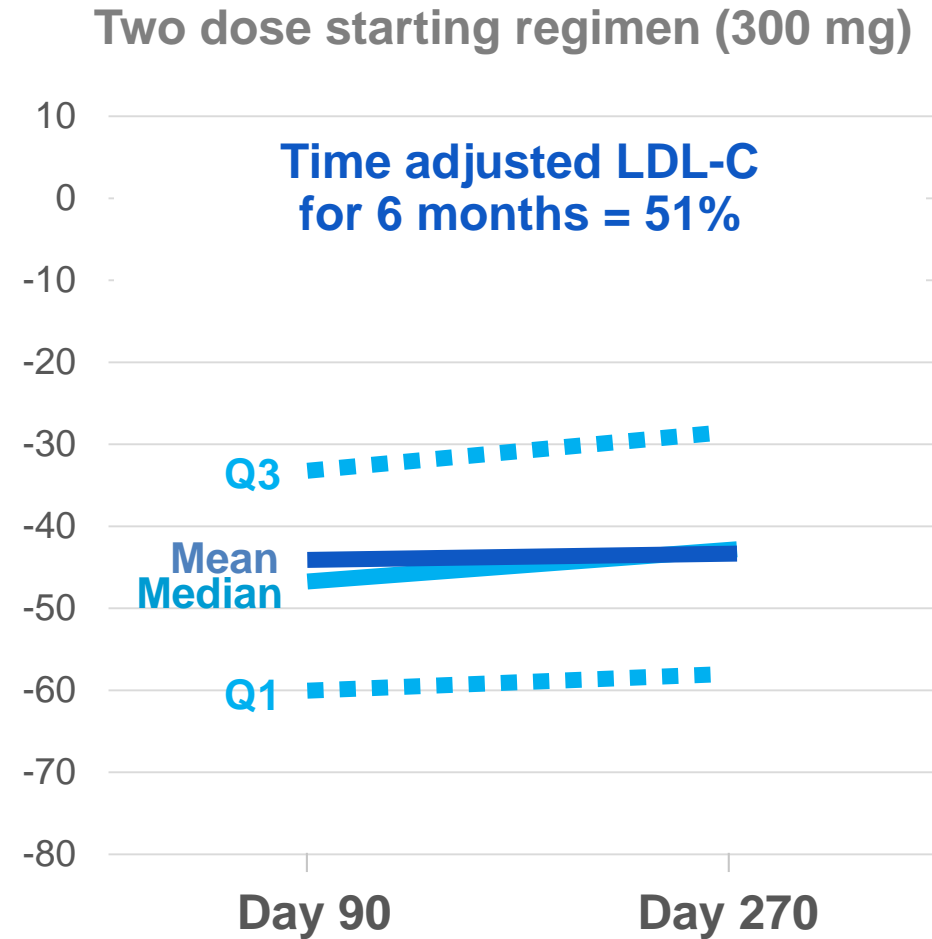
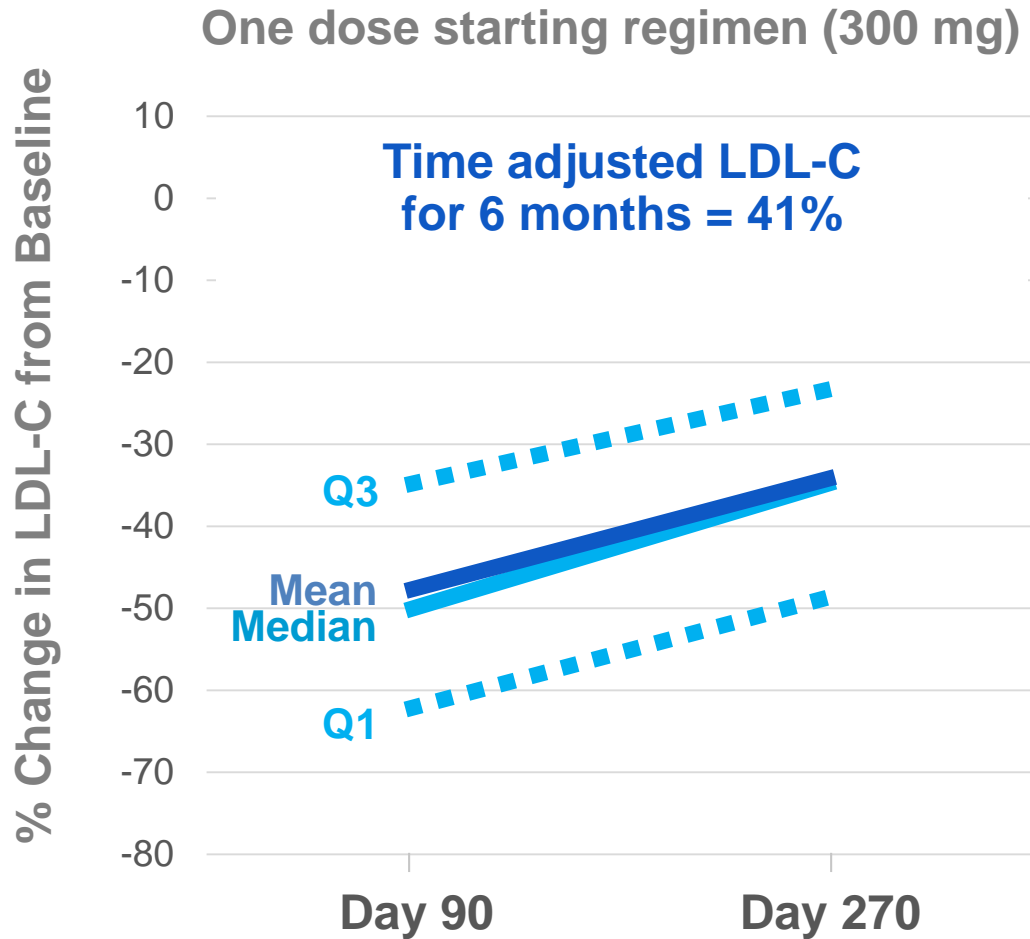
Sustained LDL-C lowering effects over time

Time-averaged reduction from Day 1 to Day 360



Inclisiran dose 300mg sc Day 1, 90, 270 and 6-monthly

Sustained >50% reduction in LDL-C for 6-months

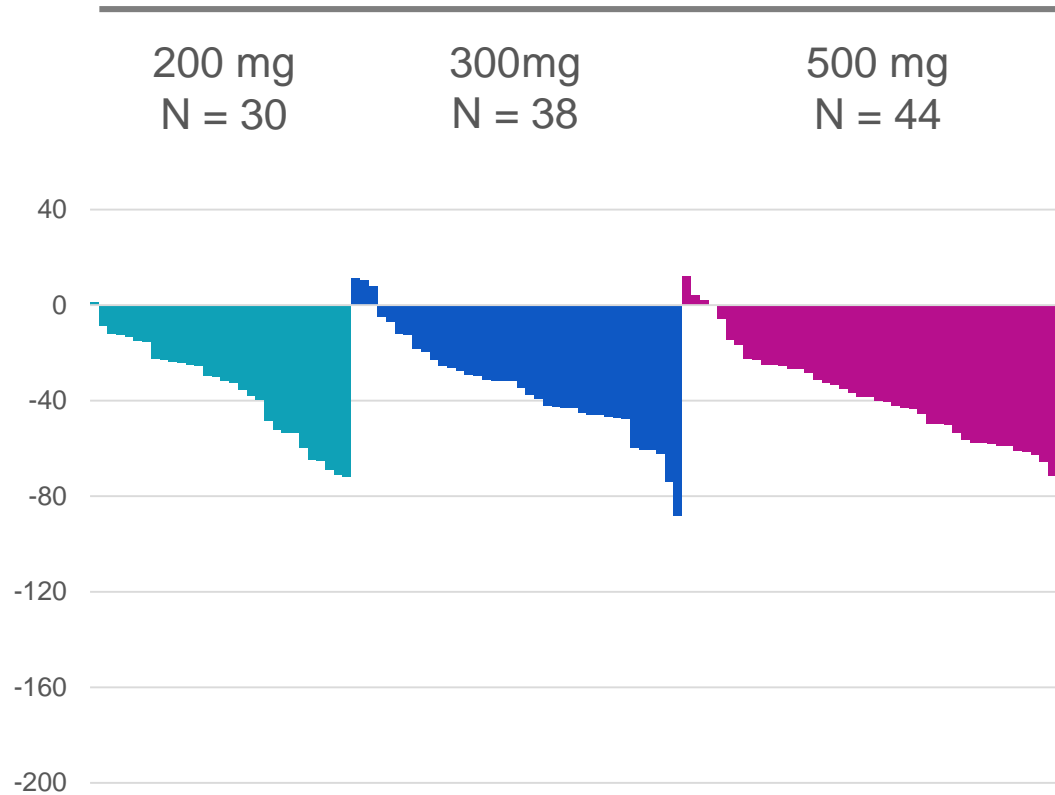


Efficacy: Day 360 LDL-C reduction in mg/dL

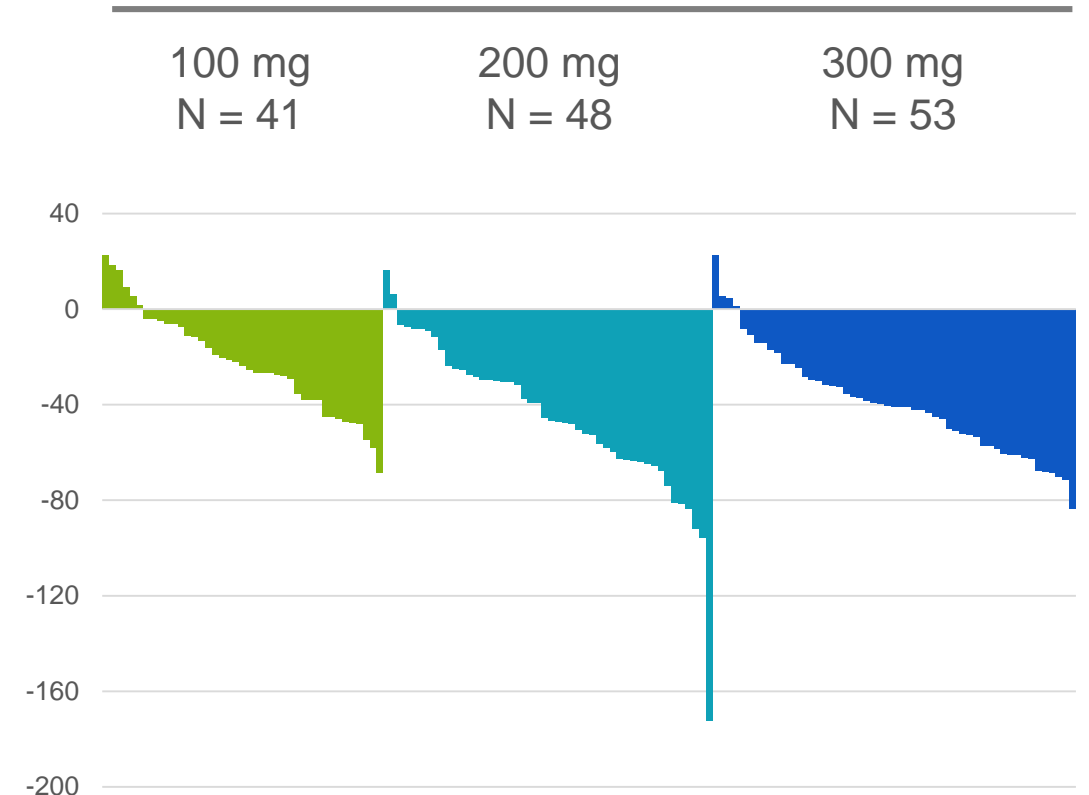
Individual patient responses



One dose starting regimen (N = 112)



Two dose starting regimen (N = 142)



Conclusions

Robust LDL-C↓ with 6 monthly inclisiran dosing



Safety

- By day 360, patients are predictably returning towards baseline
- No safety signals at 1 year (>250 patient-years of observation)

Dose and dose frequency

- 300 mg given s.c. at Day 1 and Day 90 represents the optimal starting dose
- 300 mg given s.c. at Day 270 then every 180 days is the maintenance dose

This dosing schedule provides robust and consistent LDL-C lowering

- 46% time-averaged reduction over 12 months
- 51% time-averaged reduction over 6-monthly dosing interval
- Minimal within-patient variability in LDL-C reduction over time

Implications

Inclisiran has moved into Phase III



LDL-C lowering trials underway

- 3,000 subjects with ASCVD/ risk equivalents (ORION-10, -11)
- 400 subjects with HeFH (ORION-9)
- 60 subjects with HoFH (ORION-5)

Parallel cardiovascular outcomes trial in preparation

- 15,000 subjects with high risk ASCVD (ORION-4)