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

Declaration of interest

- Research contracts (Amgen, Sanofi, Pfizer, Regeneron, MSD)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Medicines Company, Amgen, Sanofi, Regeneron, Lilly, ACCEA, Novo Nordisk, Takeda, Boehringer Ingelheim, Astra Zeneca, MSD, Abbvie, Cerenis, Resverlogix, Cipla, Algorithm, Kowa)

Disclosures

Research grants:

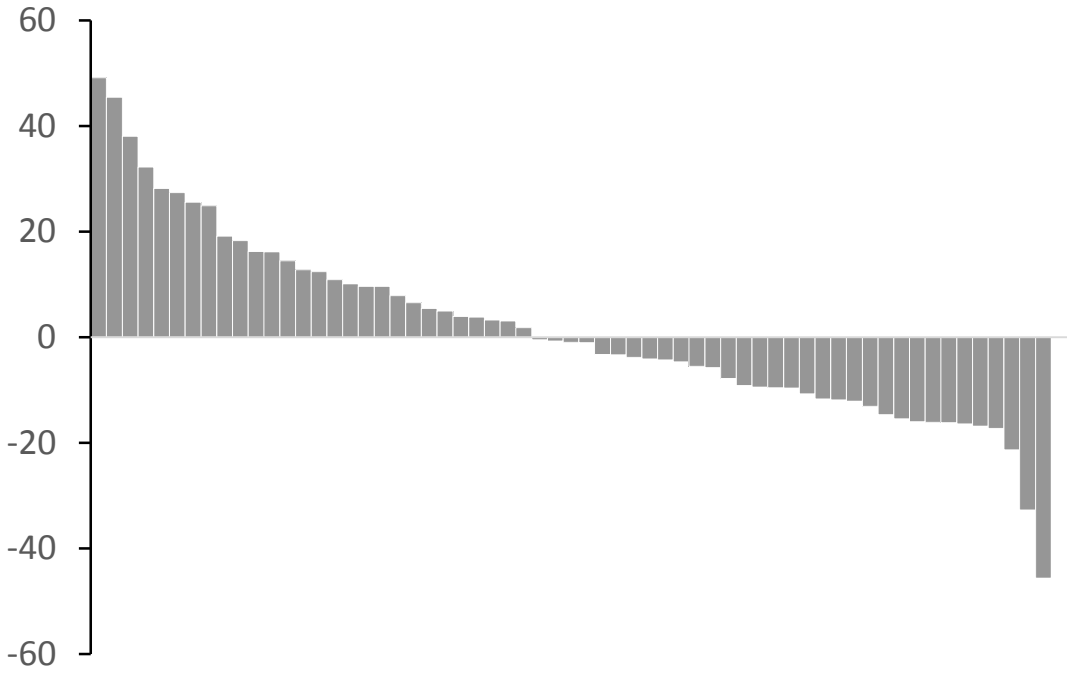
- Amgen, Sanofi, Regeneron, MSD, Pfizer

Consultancy:

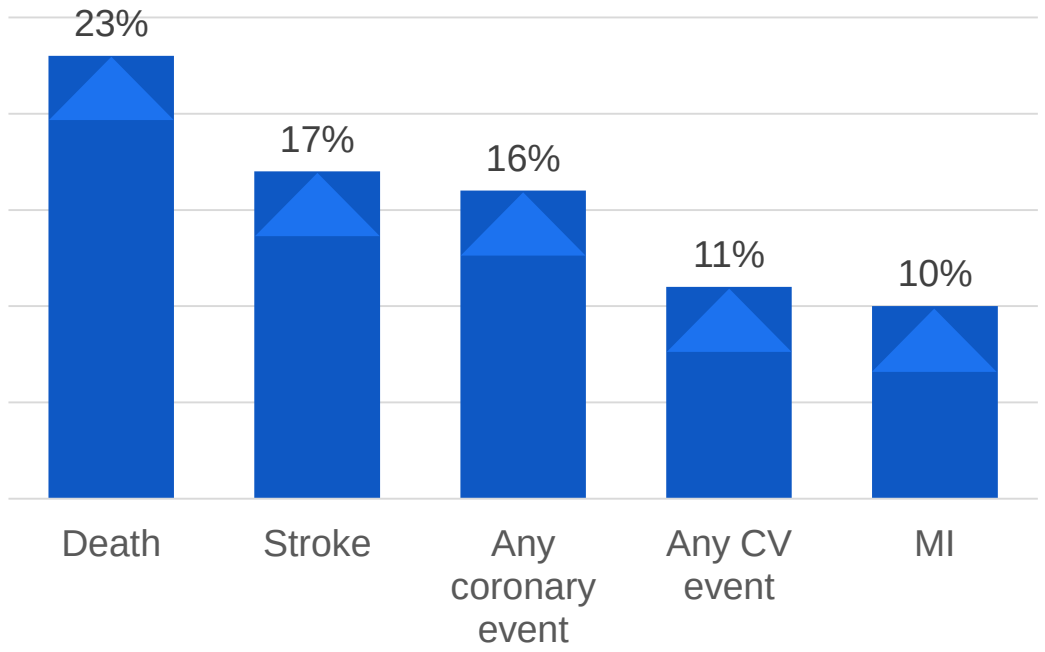
- Amgen, Sanofi, Regeneron, MSD, Pfizer, Astra Zeneca, Lilly, Medicines Company, Kowa, IONIS, Takeda, Novo Nordisk, Boehringer Ingelheim, Esperion, Cipla, Algorithm, Abbvie, Resverlogix, Cerenis

Background
LDL-C variability common, associated with worse outcomes

Six month percent change in LDL-C among statin users from starting level[1]



Increase in death, CV outcomes with each 1 standard deviation of LDL-C variability[2]



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

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Background
PCSK9 inhibition reduces LDL-C and ASCVD[1]

PCSK9 monoclonal antibody treatment requires 12-26 injections per year[1]

Adherence unlikely to show substantial improvement over statins[2]

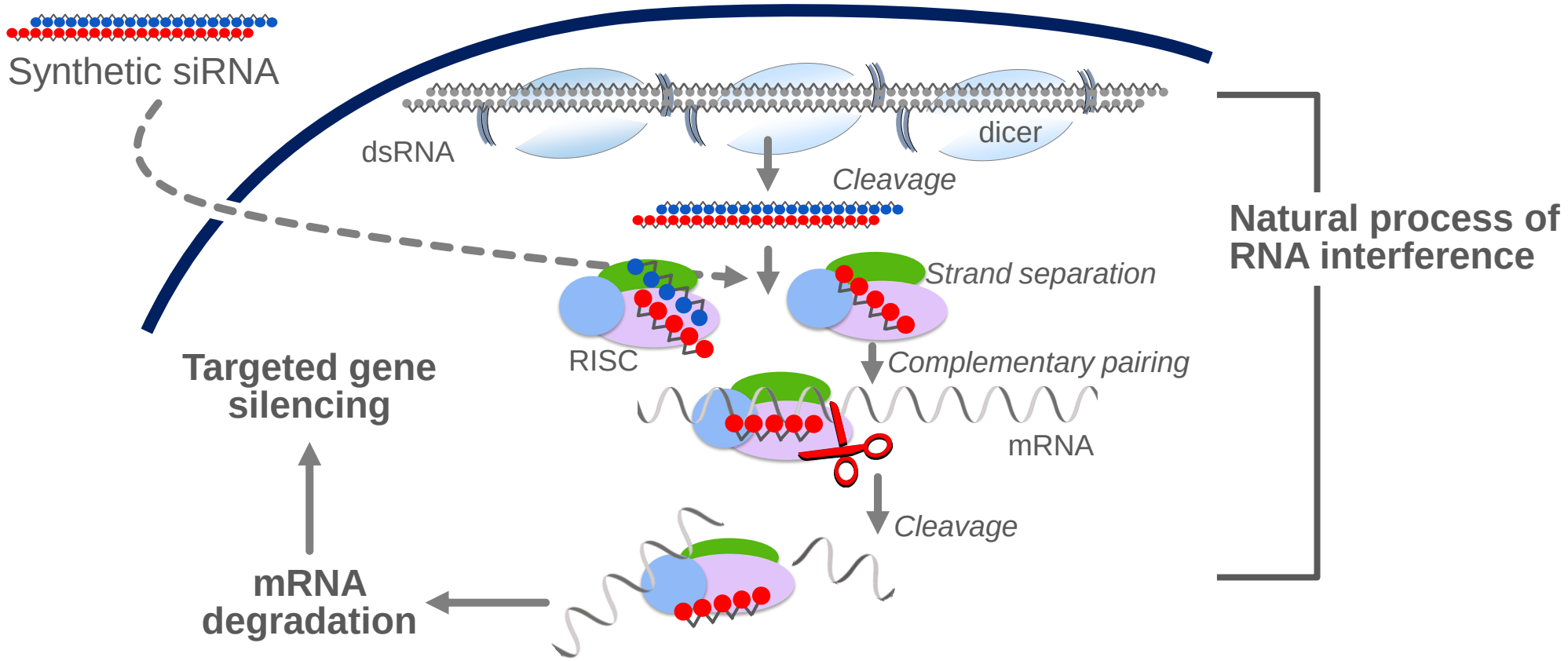
Limitations are most relevant in high risk patients needing lifelong therapy

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

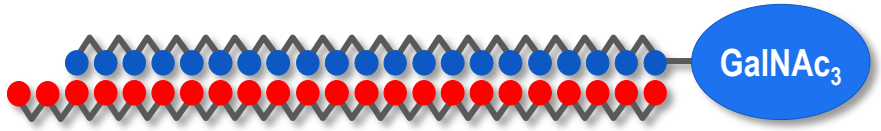
Background

RNAi is an intrinsic process for inhibiting mRNA

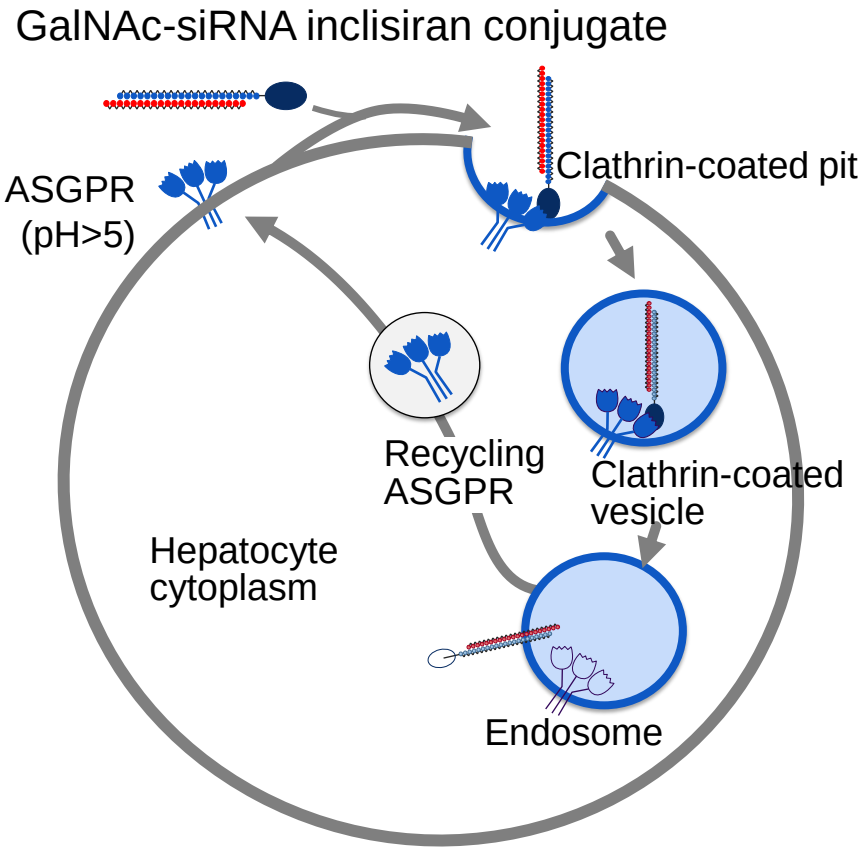


Background
GalNAc-siRNA conjugates facilitate rapid hepatic uptake

Asialoglycoprotein receptor (ASGPR)
- Highly expressed in hepatocytes only
- High rate of uptake



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



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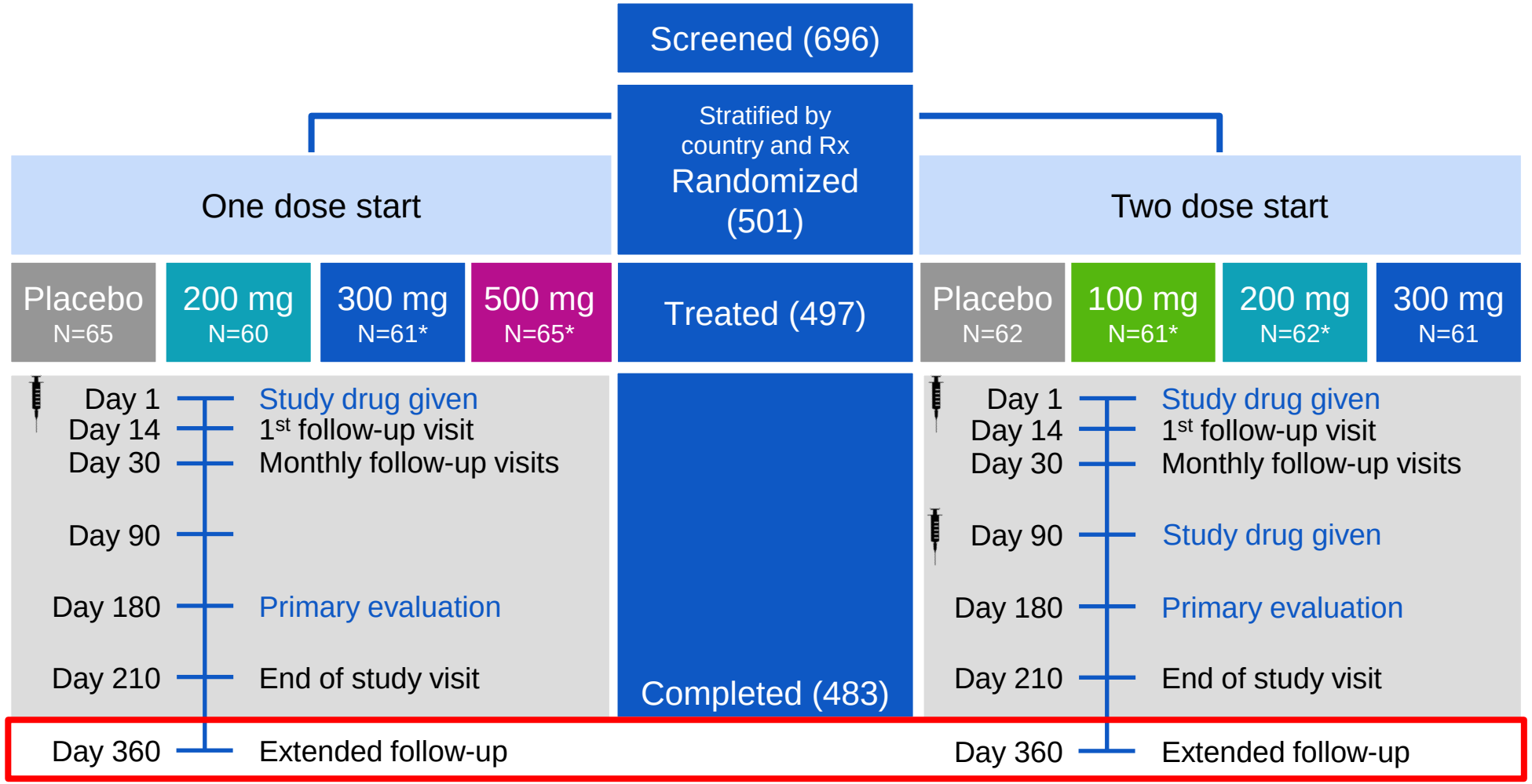
Methods
ORION 1 trial design



Patients
High-risk CV patients, balanced by randomization

		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

Safety
No safety concerns in study with follow up to Day 360

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

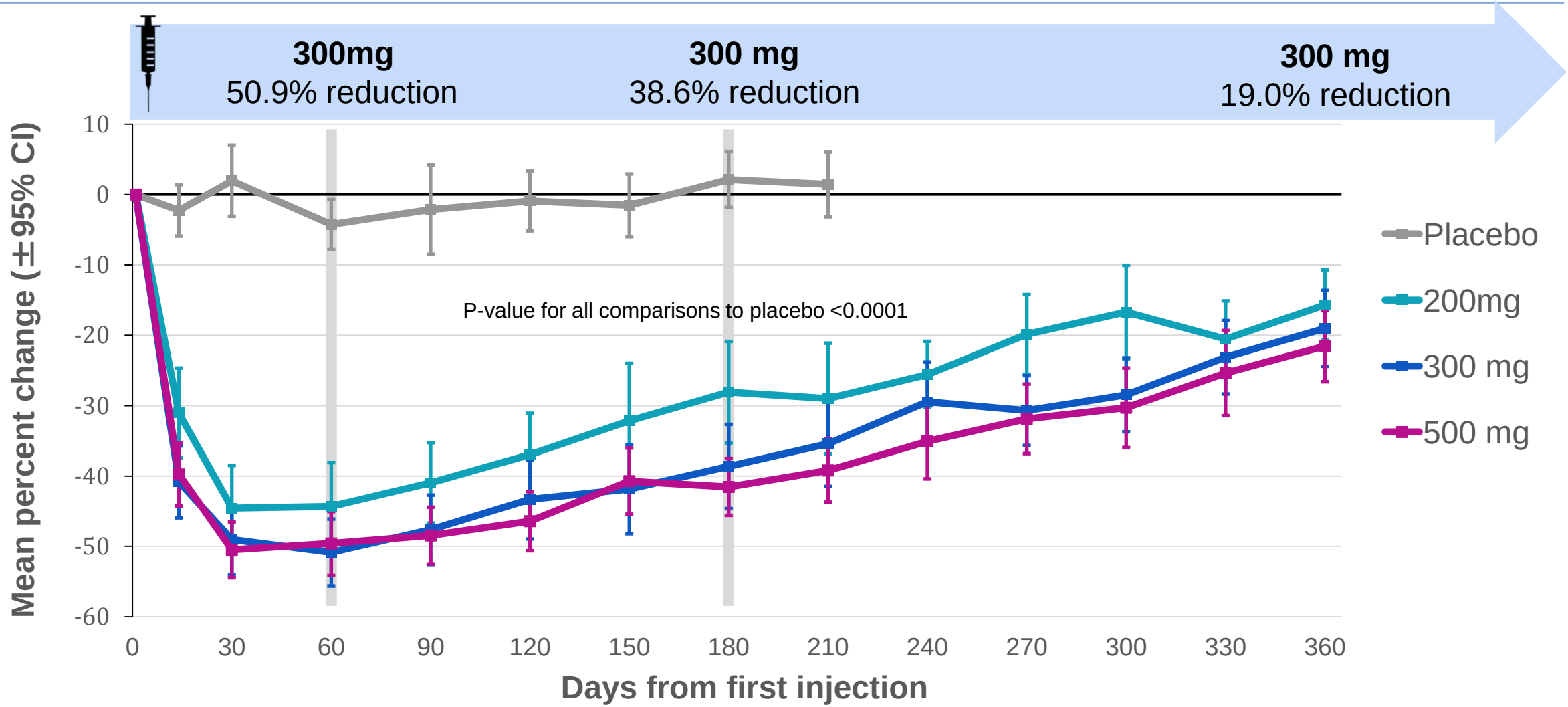
- Two previously reported deaths[1] >100 days, related to underlying disease

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



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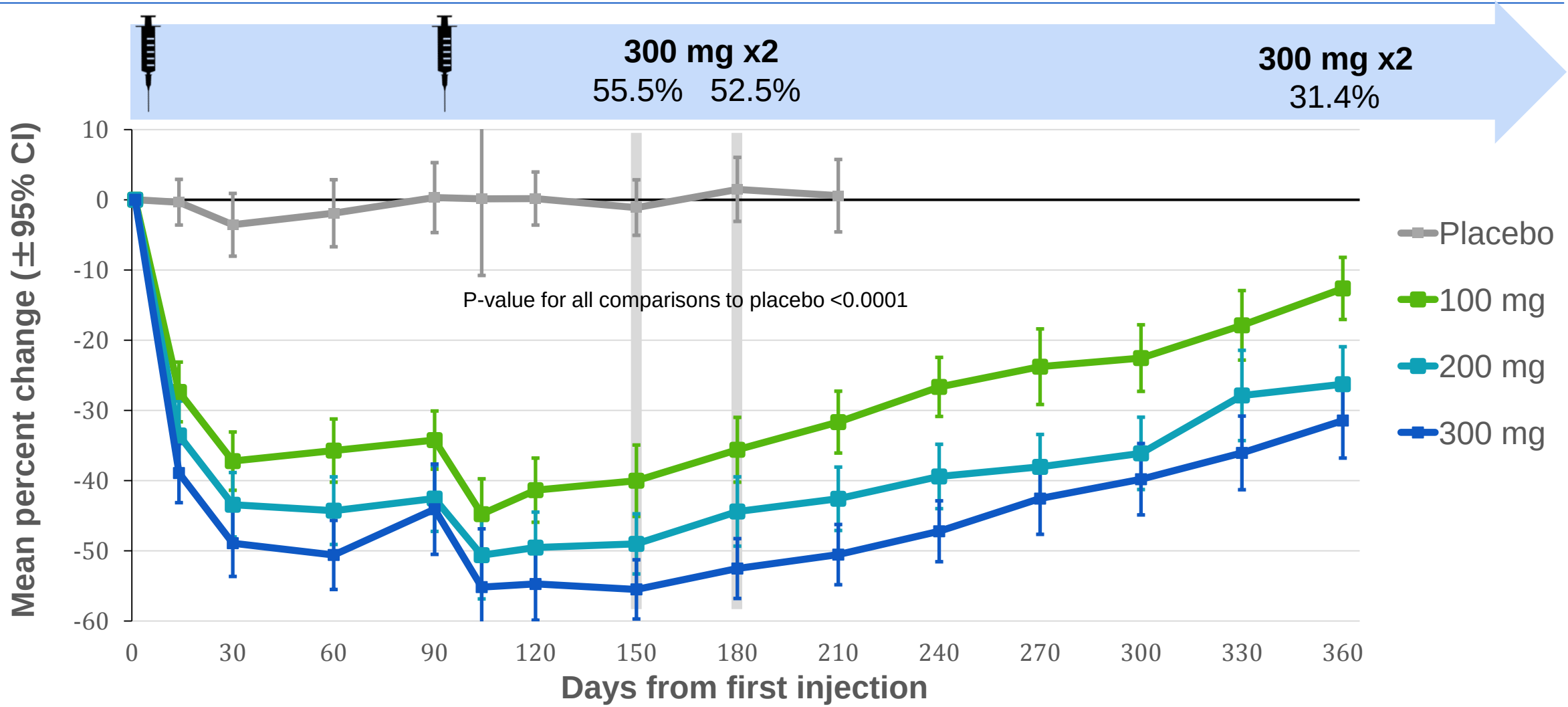
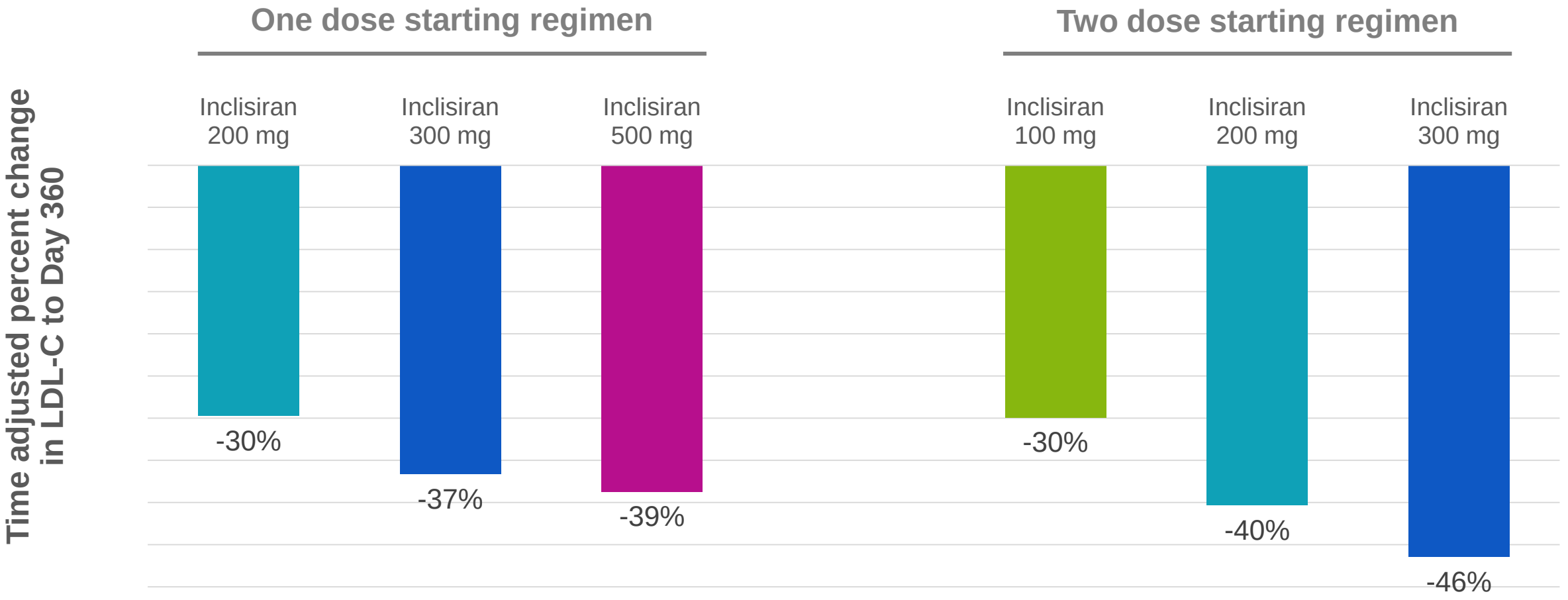
Efficacy: Two dose starting regimen

Robust, sustained LDL-C reductions – optimal start regimen



Sustained LDL-C lowering effects over time

Time-averaged reduction from Day 1 to Day 360



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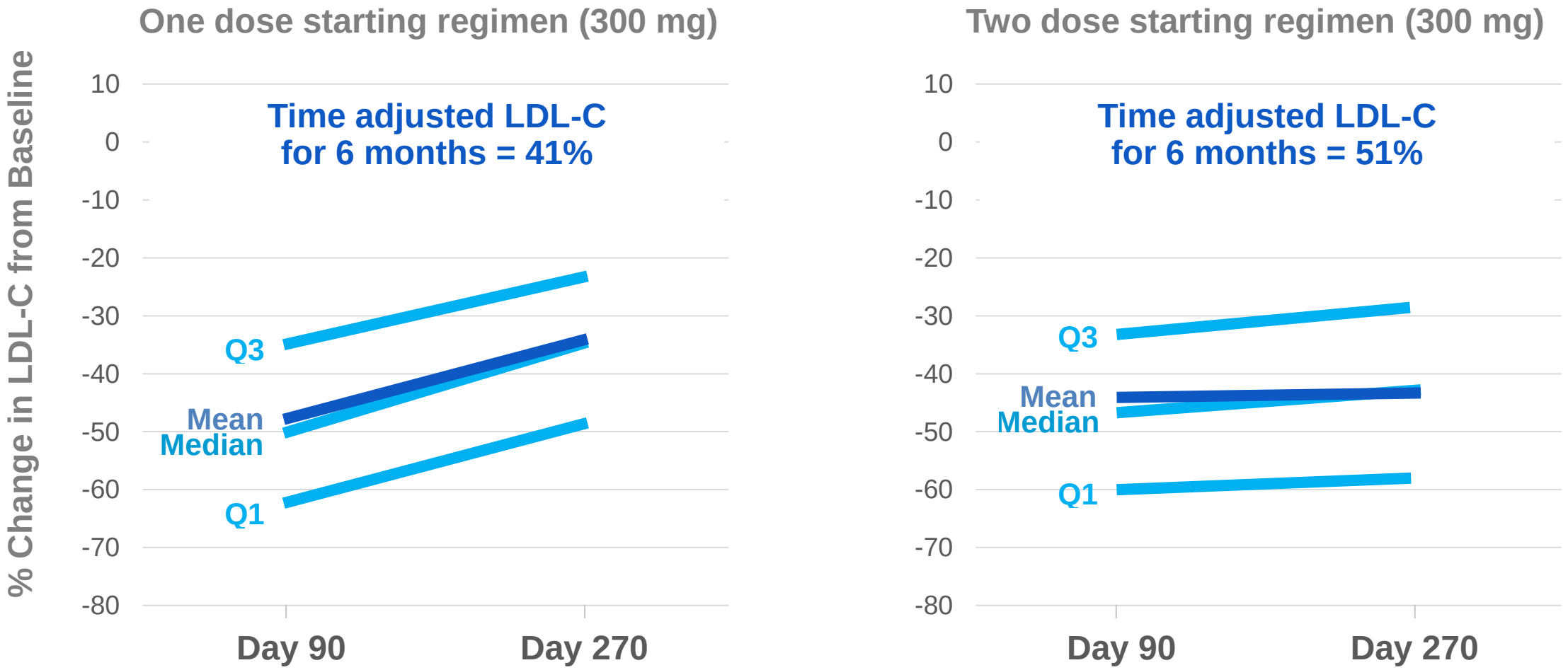
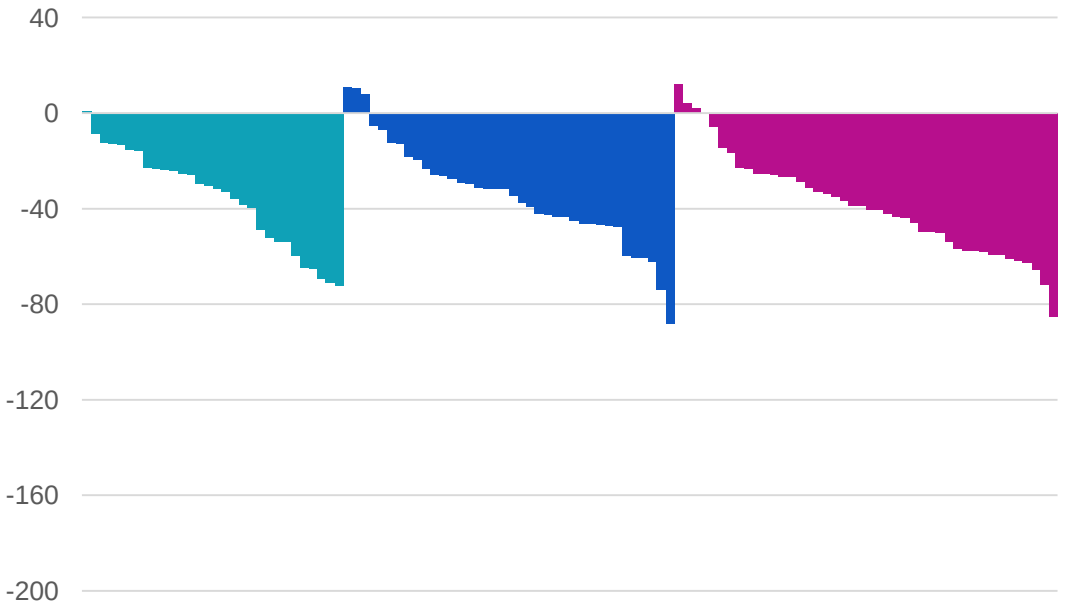
Inclisiran dose 300mg sc Day 1, 90, 270 and 6-monthly
Sustained >50% reduction in LDL-C for 6-months



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

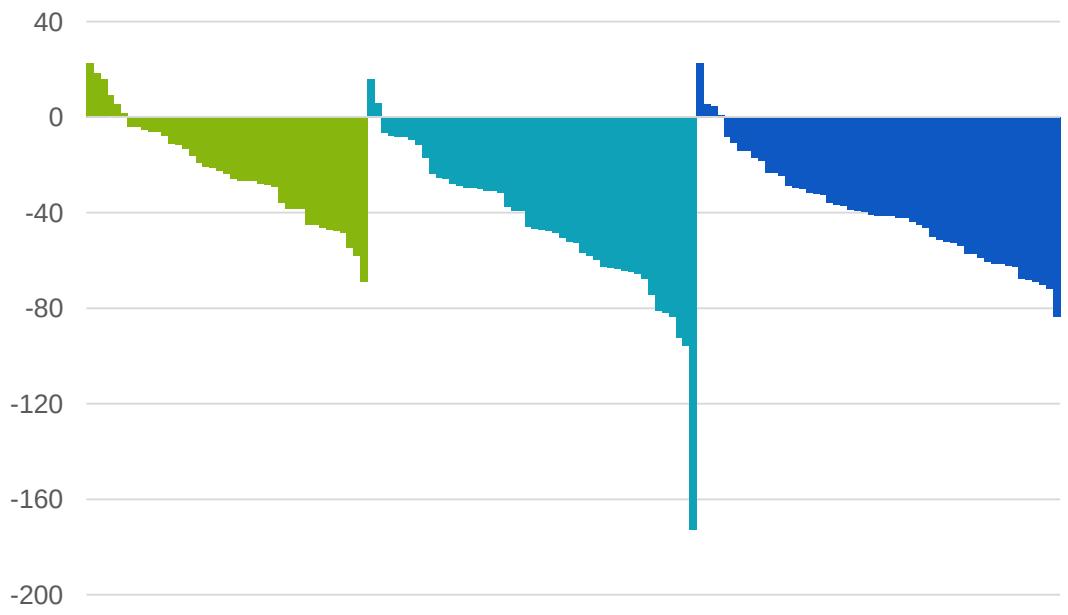
One dose starting regimen (N = 112)

200 mg N = 30 | 300mg N = 38 | 500 mg N = 44



Two dose starting regimen (N = 142)

100 mg N = 41 | 200 mg N = 48 | 300 mg N = 53



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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)

Backup

Safety
No safety concerns in follow up to Day 360

Safety population	One dose starting regimen				Two dose starting regimen			
	Placebo		**Inclisiran**		**Placebo**		**Inclisiran**	
	N=65		N=186		N=62		N=184	
	n	(%)	n	(%)	n	(%)	n	(%)
Any TEAE	51	(78.5)	155	(81.3)	51	(82.3)	153	(83.2)
Serious	3	(4.6)	30	(16.1)	7	(11.3)	31	(16.8)
Severe	2	(3.1)	18	(9.7)	7	(11.3)	22	(12.0)
Related	12	(18.5)	39	(21.0)	19	(30.6)	52	(28.3)
AE discontinuation	0		0		1	(1.6)	1	(0.5)
Injection site reaction	0		7	(3.8)	0		12	(6.5)

TEAEs (treatment emergent adverse events) - similar incidence placebo vs inclisiran:
One dose starting regimen: Nasopharyngitis, myalgia, back pain, cough, arthralgia, headache
Two dose starting regimen: Myalgia, headache, diarrhea, nasopharyngitis, arthralgia, back pain