ORION-1

Primary efficacy & safety outcomes

LDL-C reduction from 6 to 9 months following single or second injections of inclisiran, a novel siRNA compound

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On behalf of the ORION-1 investigators

Background
Major progress is being made in ASCVD

PCSK9 inhibition is now a validated target for reducing LDL-C and ASCVD[1]

PCSK9 mAb therapy requires 12-26 injections per year

Adherence data with PCSK9 mAbs show no substantial improvement over statins[2]

Poor adherence and LDL-C variability are associated with poor outcomes[3]

These limitations are most relevant in high risk patients with high LDL-C

1. Sabatine M et al NEJM 2017
2. Hines D et al ACC 2017 abstract #1203-313
3. Bangalore S et al JACC 2015;65:1539-48

Rationale and objective
Inclisiran: a novel agent to address unmet needs

Harnessing RNAi offers an alternative treatment for PCSK9 and LDL-C[1]

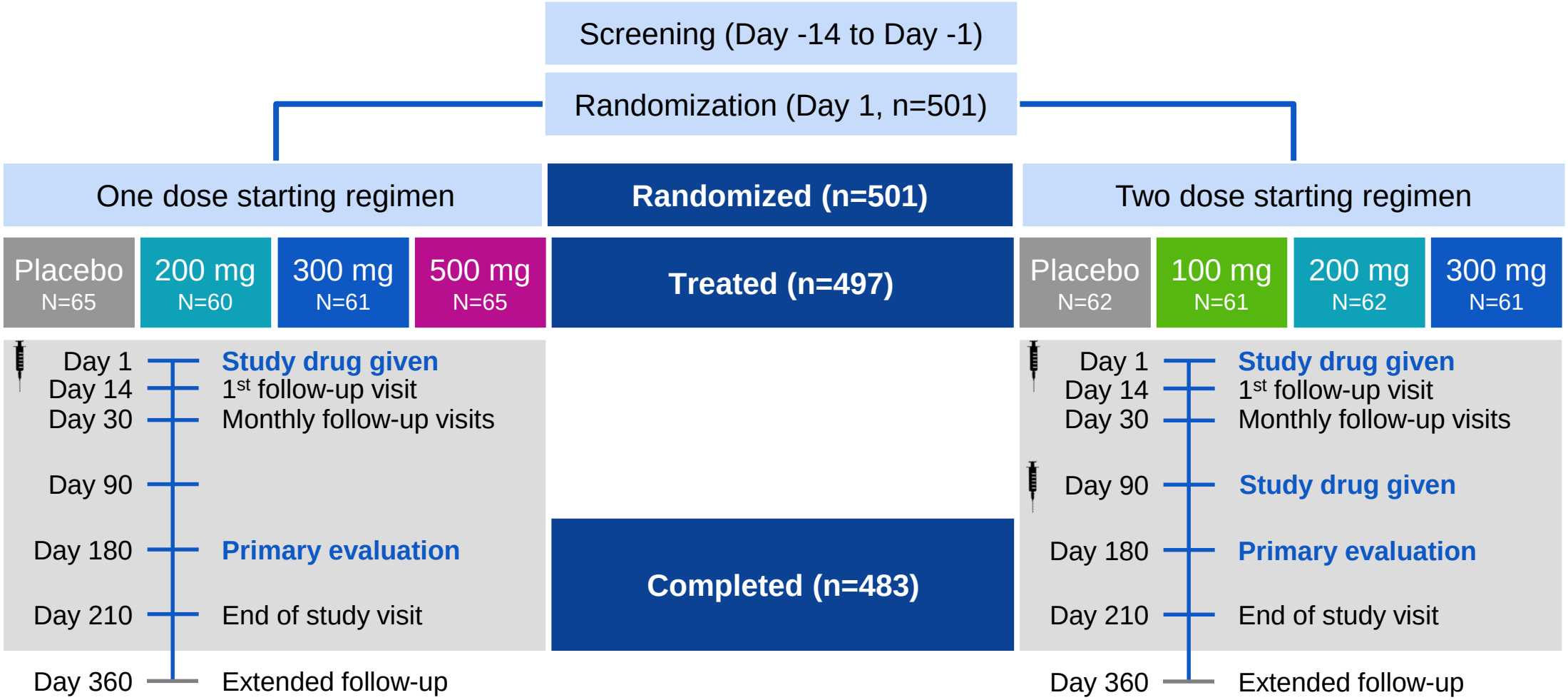
- Inclisiran, a synthetic siRNA molecule, inhibits PCSK9 synthesis in the liver[2]
- In Phase I, 300 mg inclisiran lowered LDL-C 50-60% for 84 days (n=69)[3]

Objective of ORION-1

- Evaluate optimal dosing regimens in patients with elevated LDL-C and high CV risk

1. Wittrup A & Lieberman J Nature Rev Gen 2015;16: 543-52
2. Fitzgerald K et al. Lancet 2013;9911:60-8
3. Fitzgerald K et al. N Engl J Med 2017;376 (1):41-51

Methods
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: Adverse events similar to placebo

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	46	(70.8)	140	(75.3)	50	(80.6)	142	(77.2)
Serious	3	(4.6)	17	(9.1)	6	(9.7)	24	(13.0)
Severe	2	(3.1)	11	(5.9)	7	(11.3)	19	(10.3)
Related	12	(18.5)	39	(21.0)	18	(29.0)	51	(27.7)
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

Safety
No safety concerns: Liver and muscle enzymes

No LFT elevations related to drug

- Transient transaminase increases - no differences between randomized groups
  - 0.8% placebo
  - 0.8% inclisiran

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 deaths[1] >100 days beyond injection and clearly 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)

Safety
No safety concerns: Other relevant parameters

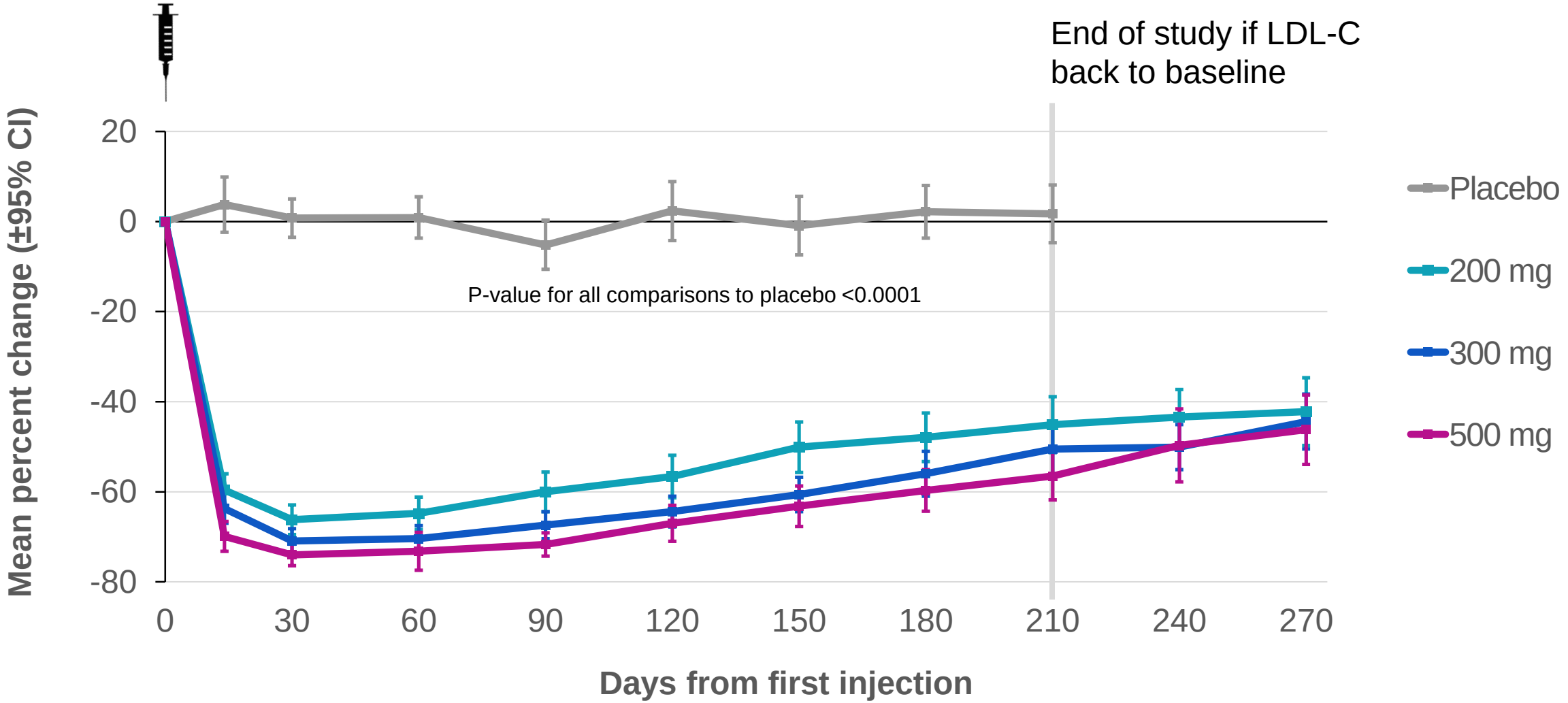
No thrombocytopenia

No neuropathy

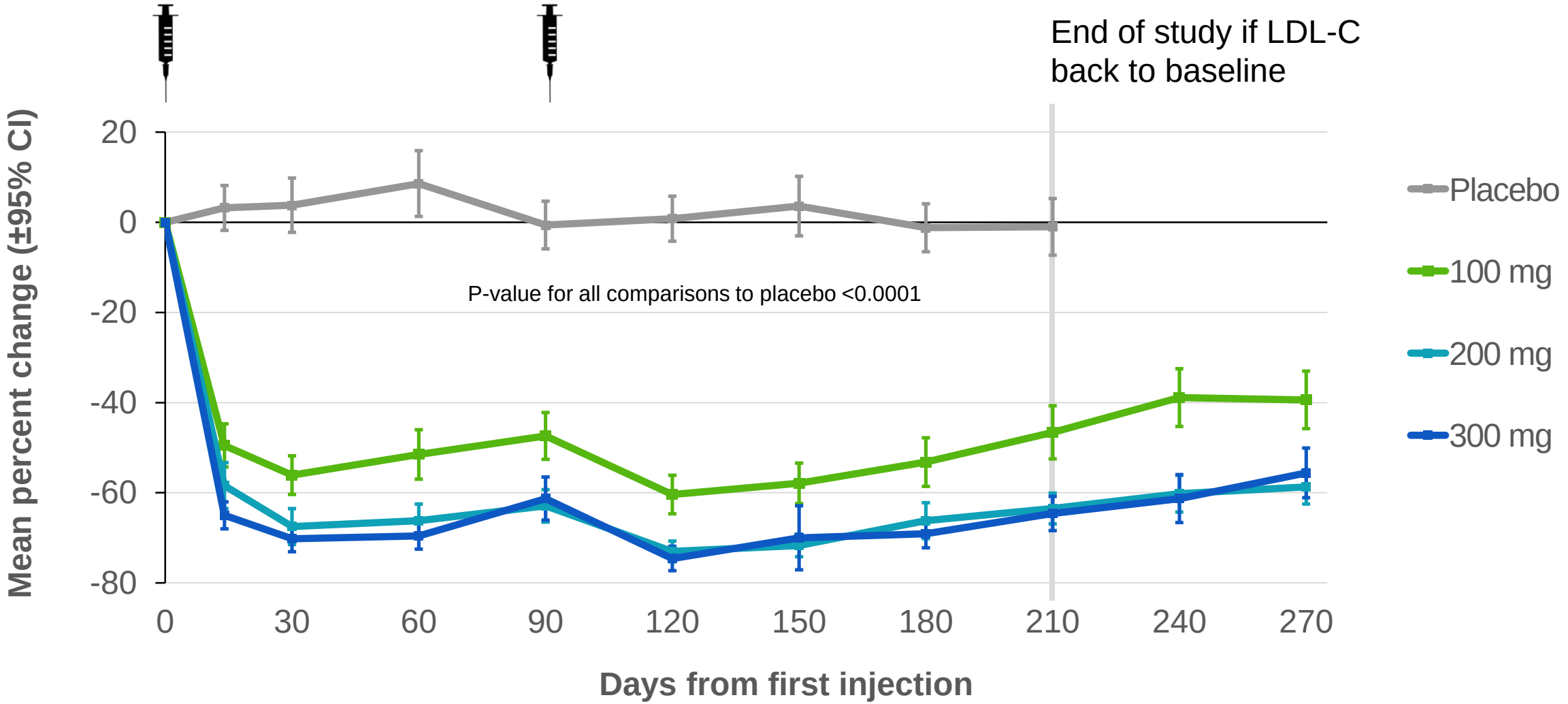
No immunogenicity (no anti-drug antibodies)

No pro-inflammatory symptoms or elevated markers

Efficacy: One dose starting regimen
Clamped PCSK9 knockdown



Efficacy: Two dose starting regimen
Clamped PCSK9 knockdown



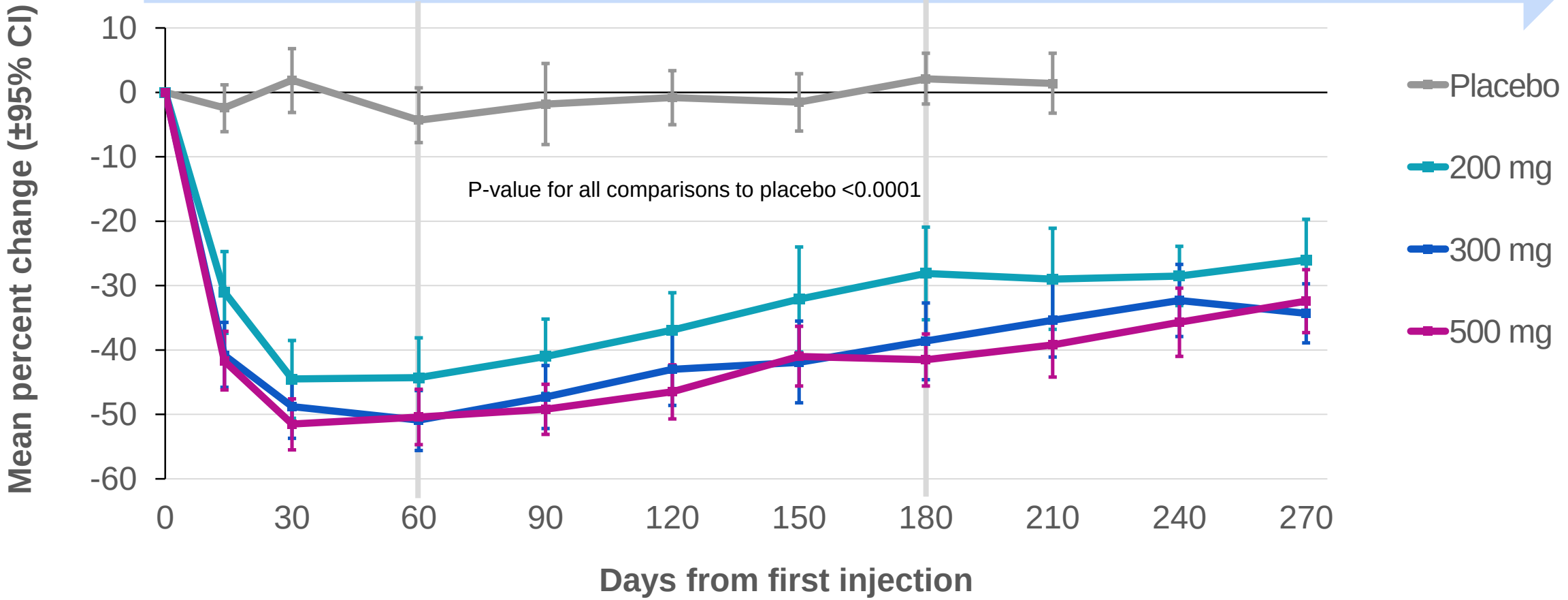
Efficacy: One dose starting regimen

Robust, sustained LDL-C reductions – 300 mg optimal

300 mg
50.9% reduction

300 mg
38.4% reduction

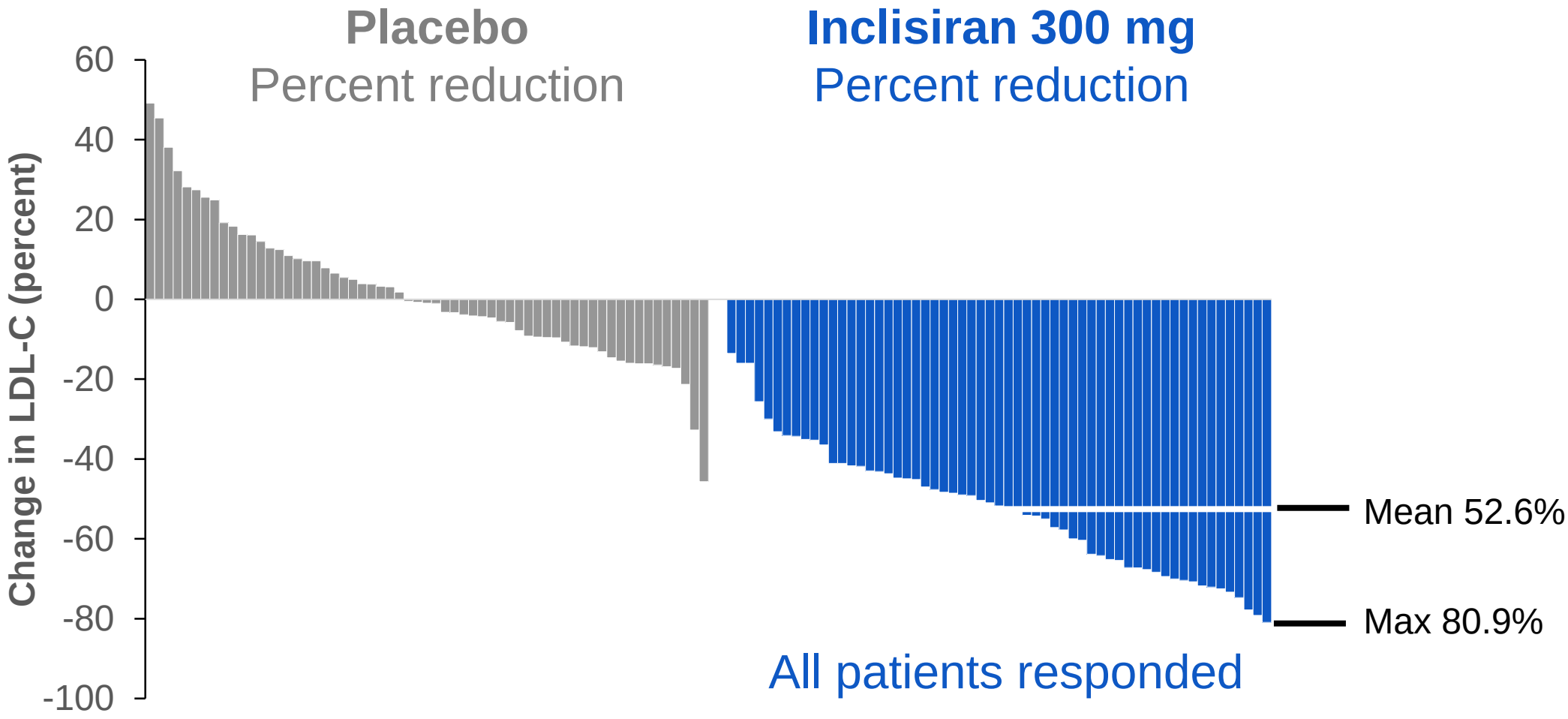
9 months time adjusted mean 41% reduction



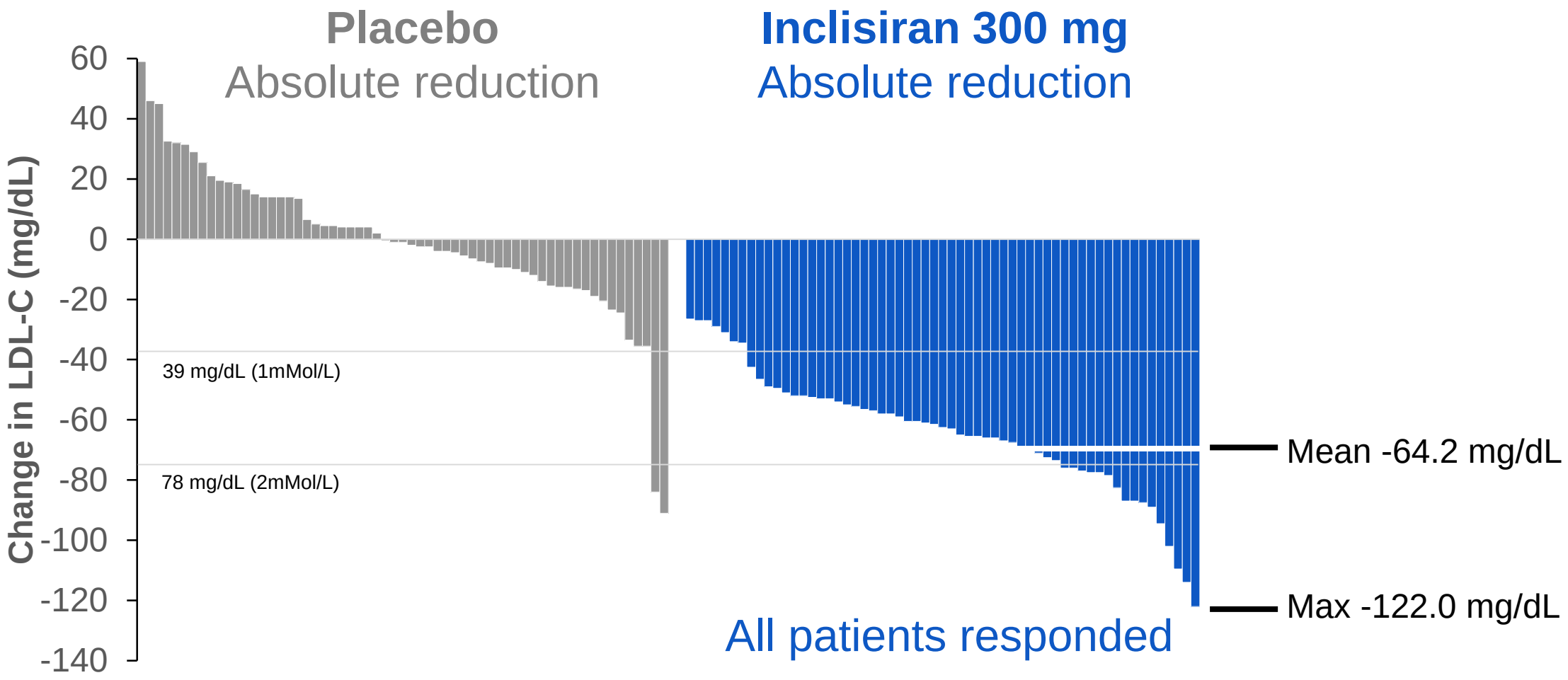
Efficacy: Two dose starting regimen

Robust, sustained LDL-C reductions – optimal start regimen

Efficacy: Two dose starting regimen
Individual patient responses (%) at day 180



Efficacy: Two dose starting regimen
Individual patient responses (mg/dL) at day 180



Conclusions
Two 300 mg starting dose regimen for inclisiran selected

No safety concerns

Optimal dosage 300 mg given twice as starting regimen then Q6 monthly

- All patients responded with significant LDL-C lowering
- At 6 months, mean LDL-C↓ of 52.6% (64 mg/dL), and up to 81% (122 mg/dL)

Unique attributes of inclisiran address multiple unmet needs

- LDL-C variability within individuals is practically eliminated
- Injection burden reduced substantially
- Sustained effect between infrequent injections
- Opportunity to improve patient adherence

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Implications
Inclisiran will move into phase III trials

In an ORION-1-like population, inclisiran 300 mg delivers sustained LDL-C lowering of 60-65 mg/dL

In a CVOT, this is likely to confer substantial reductions in MACE

ORION-4 will study CV outcomes with inclisiran in high risk primary and secondary prevention patients with average LDL-C ~130 mg/dL

Online publication
New England Journal of Medicine, 17th March 2017