Inclisiran and the ORION clinical development programme

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Inclisiran and the ORION Project

Derick Raal

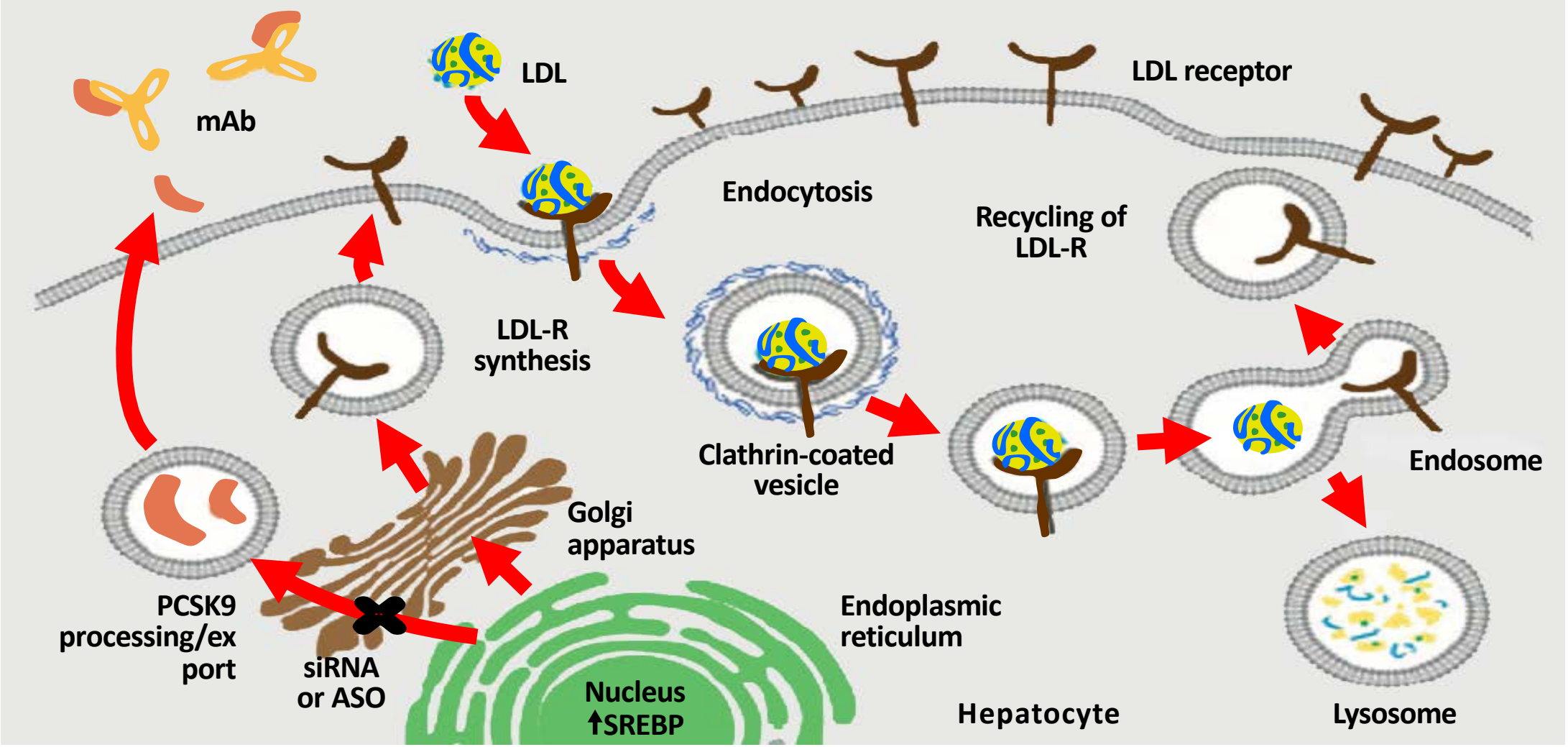
FCP(SA), FRCP, FRCPC, Cert Endo, MMED, PHD

Head, Division of Endocrinology & Metabolism

Director, Carbohydrate and Lipid Metabolism Research Unit

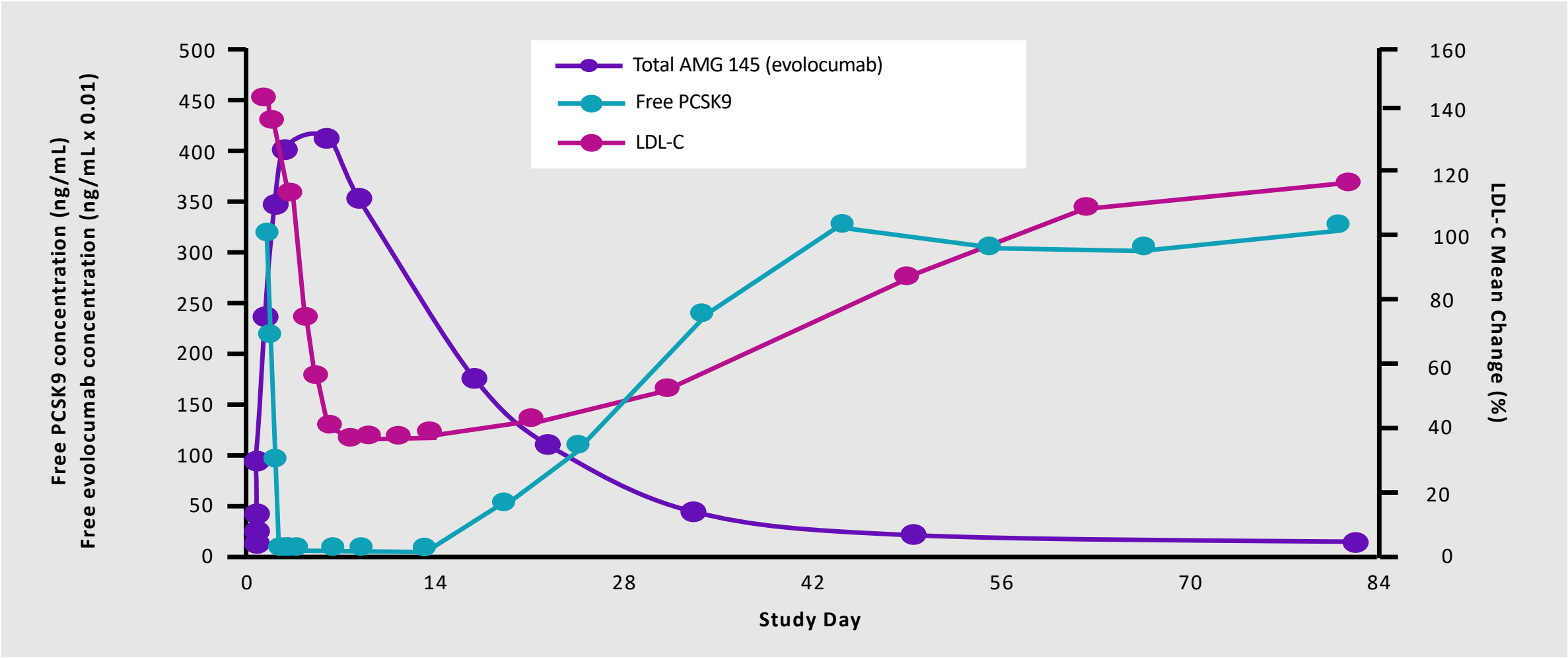
Faculty of Health Sciences, University of the Witwatersrand

Catabolism of LDL, the role of PCSK9 antibody to PCSK9



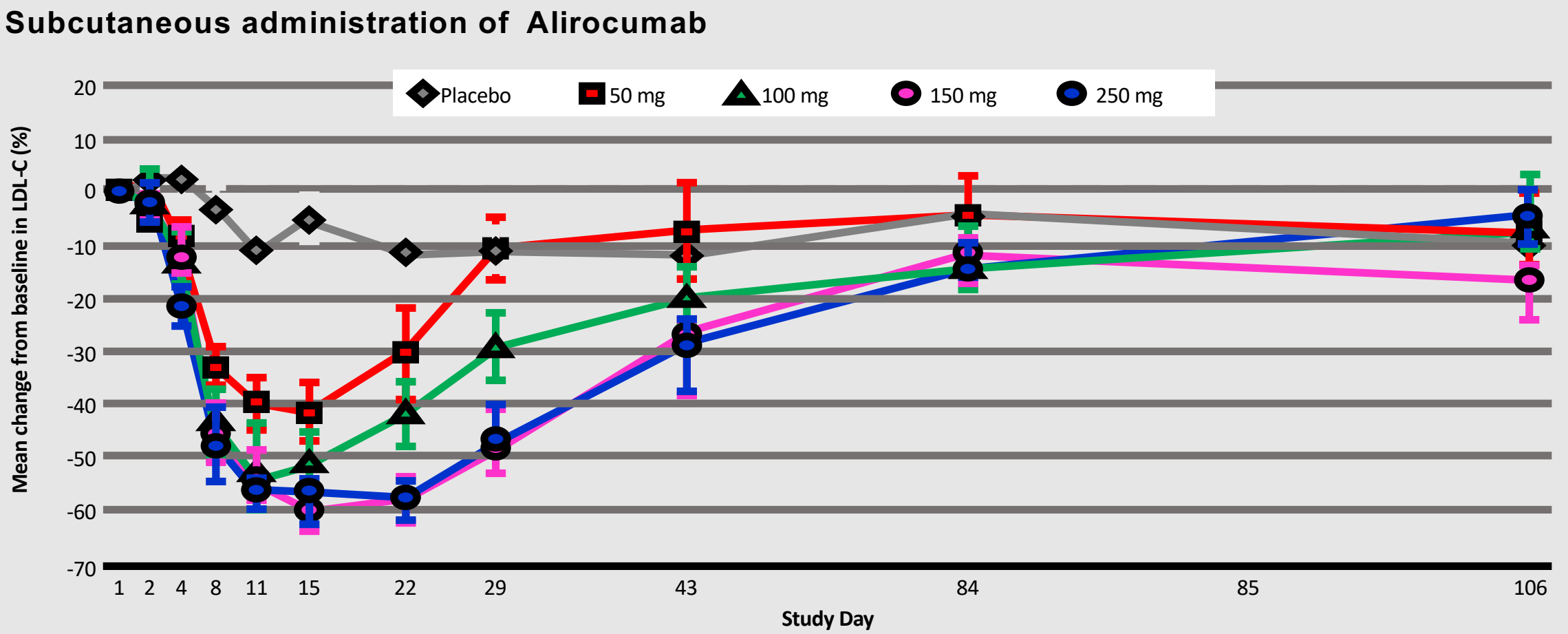
modified from Hovingh G K, et al. *Eur Heart J* 2013;34:962-71

Pharmacokinetics of PCSK9 monoclonal antibody therapy



Stein EA & Raal FJ Annu. Rev. Med. 2014. 65:417–31.

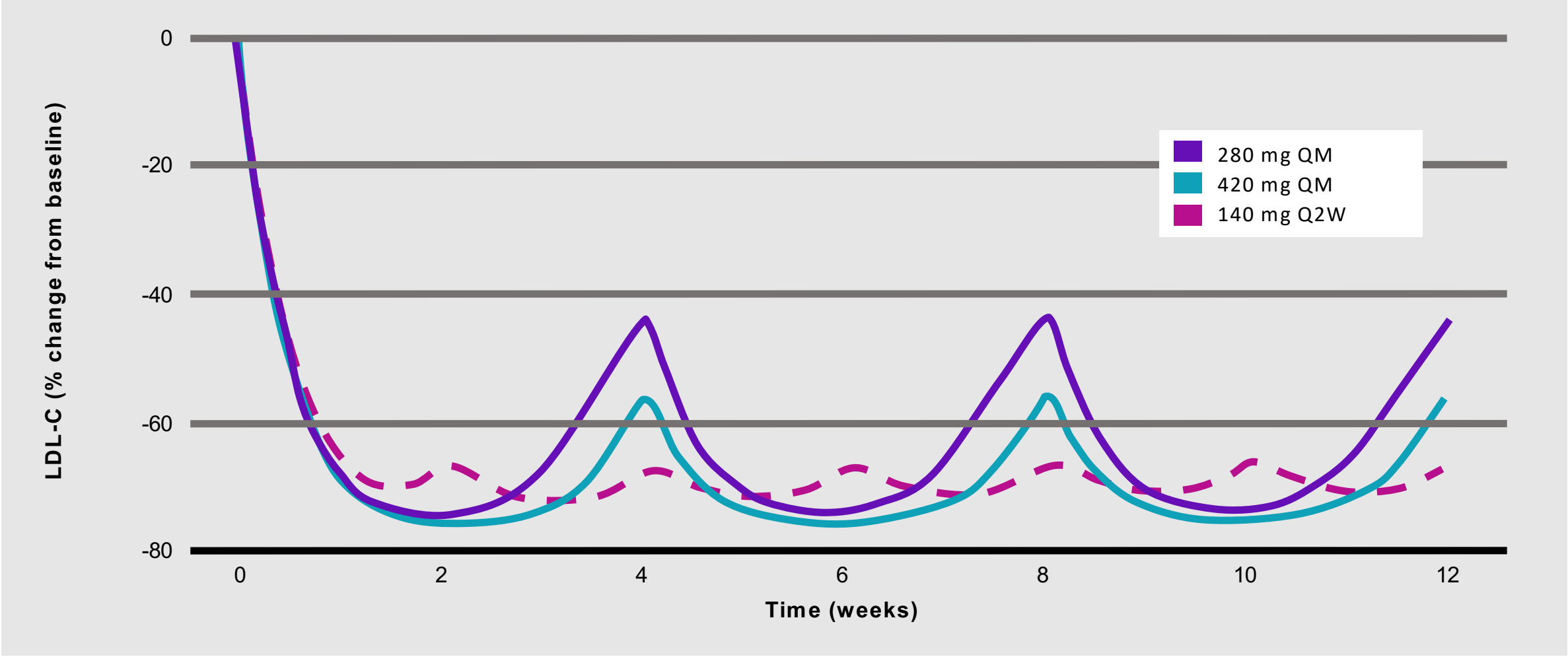
Reduction in LDL-C values among healthy volunteers in single-dose studies



Stein E. *N Engl J Med* 2012;366:1108-18

Stein E. *N Engl J Med* 2012;366:1108-18

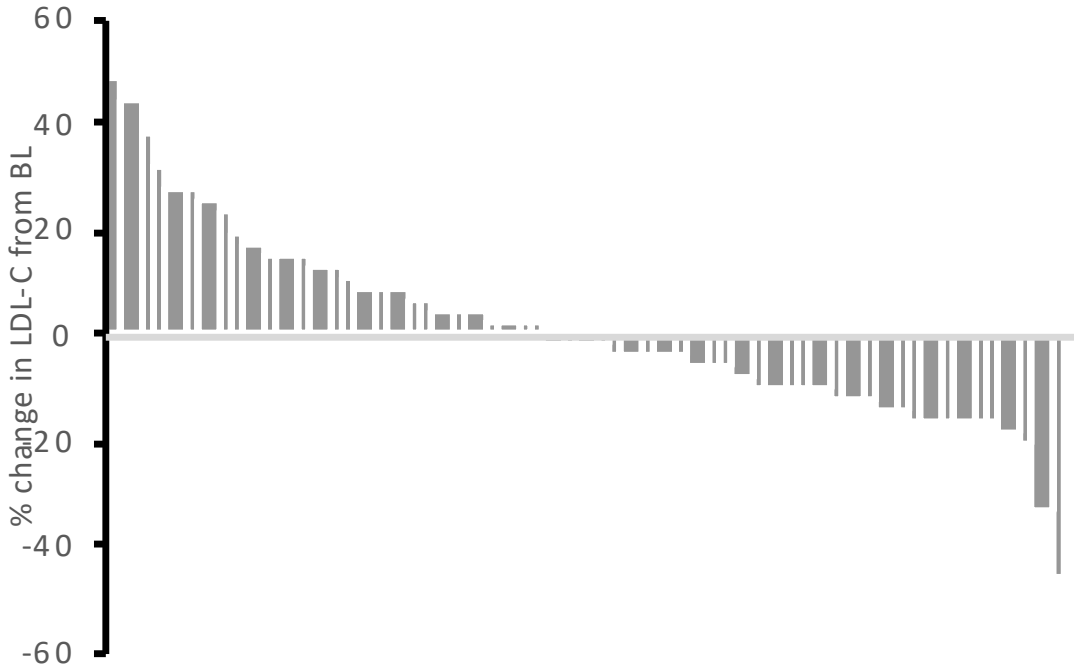
Model predicted time course of LDL-C after multiple evolocumab doses



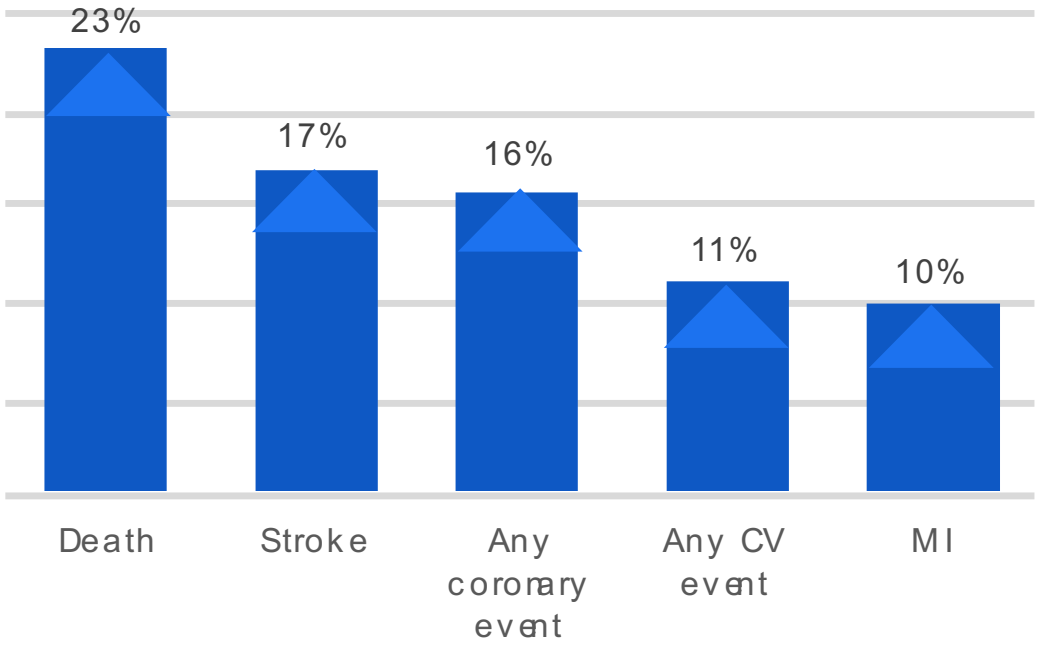
Gibbs et al. *J Clin Pharm*. 2017;57:616

Unmet need
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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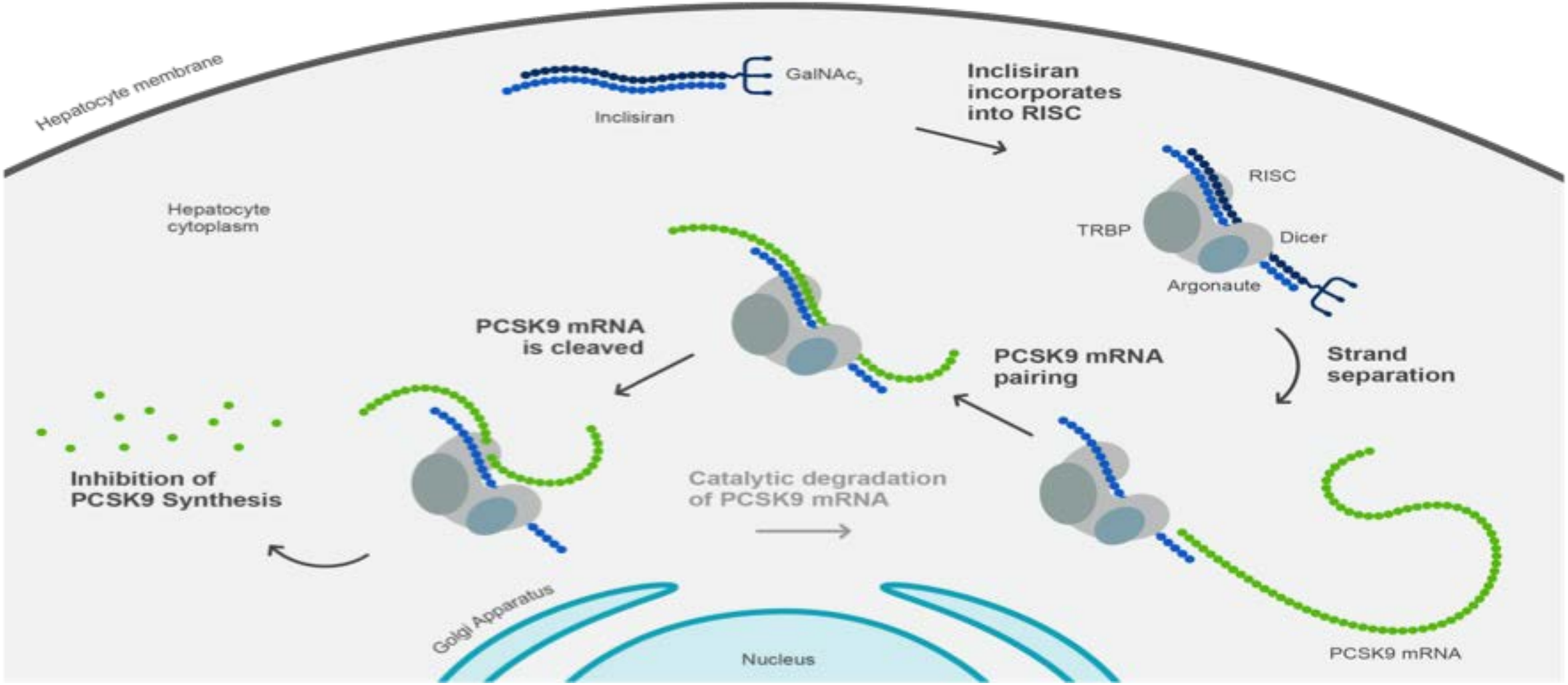
Small interfering RNA (siRNA) targeted to PCSK9

Mechanism of action



RISC = RNA induced silencing complex

Whitehead et al. *Nat Rev Drug Discov* 2009;8:129-38

GalNAc-siRNA conjugates facilitate rapid hepatic uptake

Background

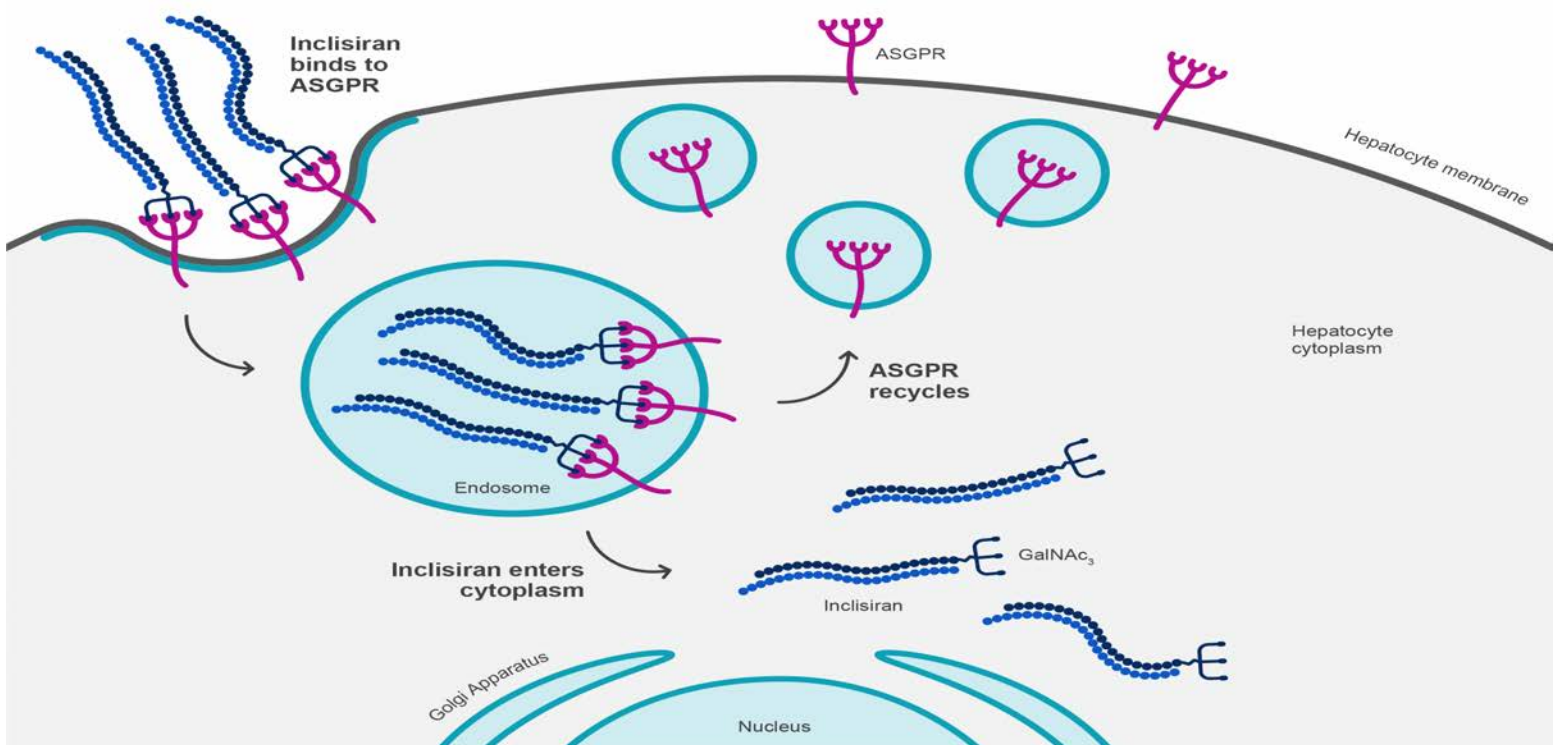
Inclisiran:

siRNA conjugated to N-acetylgalactosamine

Subcutaneous administration

Targeted delivery to hepatocytes

Third generation with enhanced stablilisation chemistry



Asialoglycoprotein receptor (ASGPR):

Highly expressed in hepatocytes only.

High rate of uptake

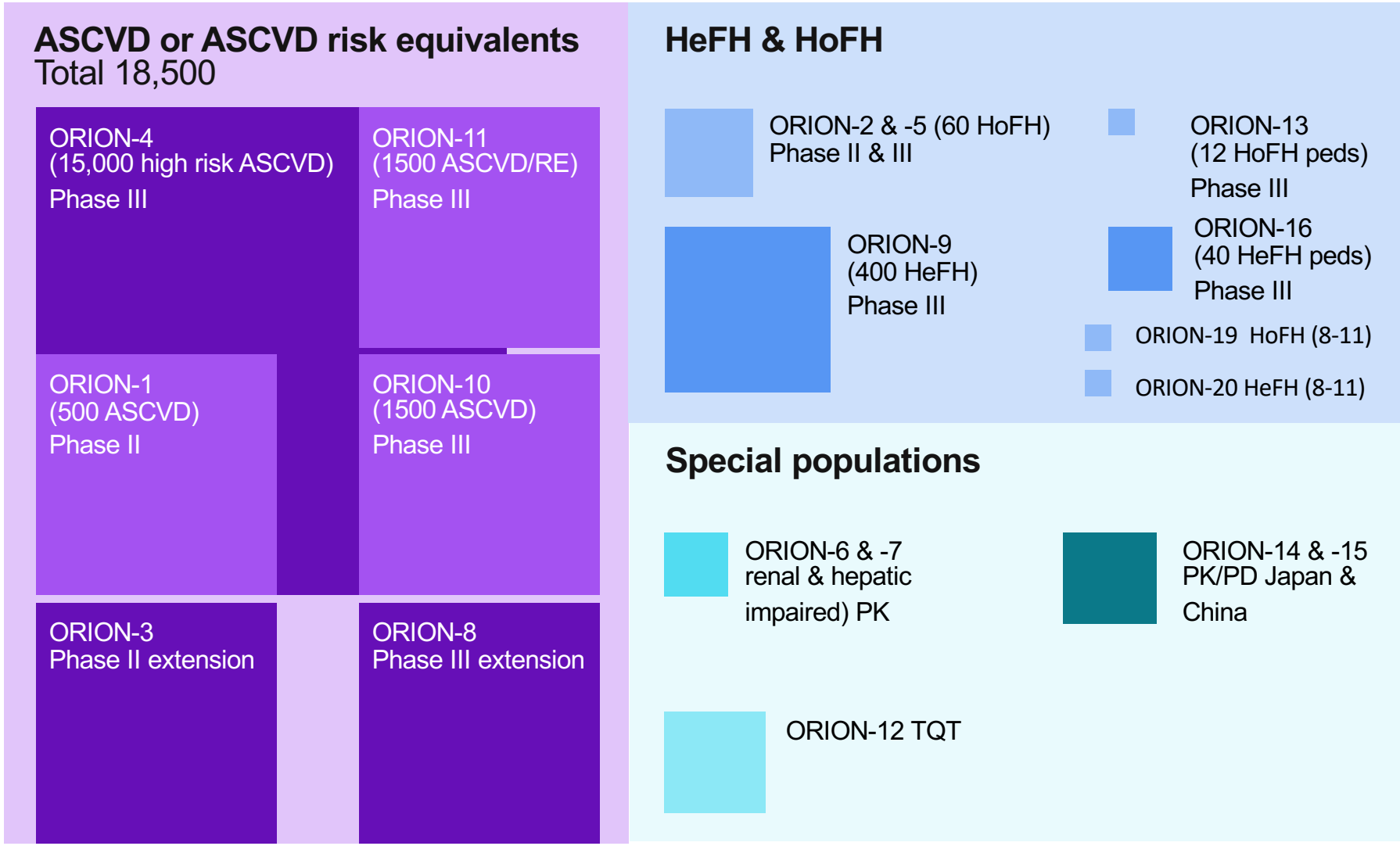
Clinical & regulatory strategy

ORION Program

Study Rationale and Designs

ORION clinical development program overview

Clinical & regulatory strategy



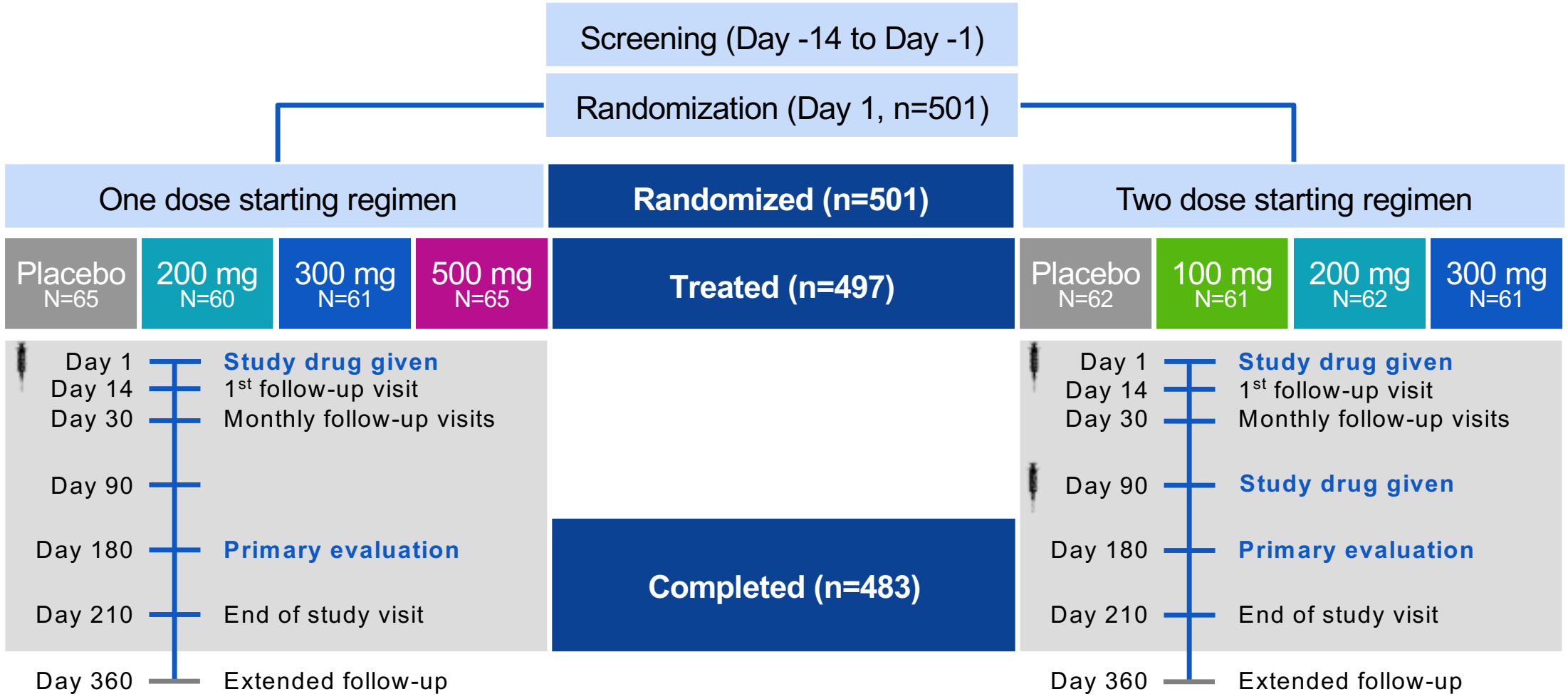
ORION development program through ORION-12

Clinical & regulatory strategy

	Trials	Relevant endpoints	Patients selected (number)	Expected start time
Pivotal trials	**ORION-4**	Cardiovascular M&M (Phase III)	HRASCVD or ASCVD RE (N=15,000)	Q2 2018
	ORION-5	LDL-C lowering (Phase III)	HoFH (N=60)	Q2/3 2018
	ORION-9	LDL-C lowering (Phase III)	HeFH (N=400)	Ongoing
	ORION-10	LDL-C lowering (US) (Phase III)	ASCVD (N=1,500)	Ongoing
	ORION-11	LDL-C lowering (EU) (Phase III)	ASCVD or ASCVD RE (N=1,500)	Ongoing
Extension trials	**ORION-3**	LDL-C lowering (extension of ORION-1)	ASCVD or ASCVD RE or HeFH (N=490)	Ongoing
	ORION-8	LDL-C lowering (extension of ORION -9, -10, -11)	ASCVD, ASCVD risk equivalent, HeFH (N=3,460)	Q4 2019
Supportive trials	**ORION-1**	LDL-C lowering (Phase II)	ASCVD or ASCVD RE or HeFH (N=501)	Completed
	ORION-2	LDL-C lowering (Phase II)	HoFH (N=10)	Ongoing
Special populations studies	**ORION-6**	Pharmacokinetics	Hepatic impairment (N=24-32)	Q2 2018
	ORION-7	Pharmacokinetics	Renal impairment (N=31)	Ongoing
	ORION-12	TQT	Healthy volunteers (N=200)	Q1/2 2018

ORION-1
Long-Term Efficacy & Safety

Methods
Trial design



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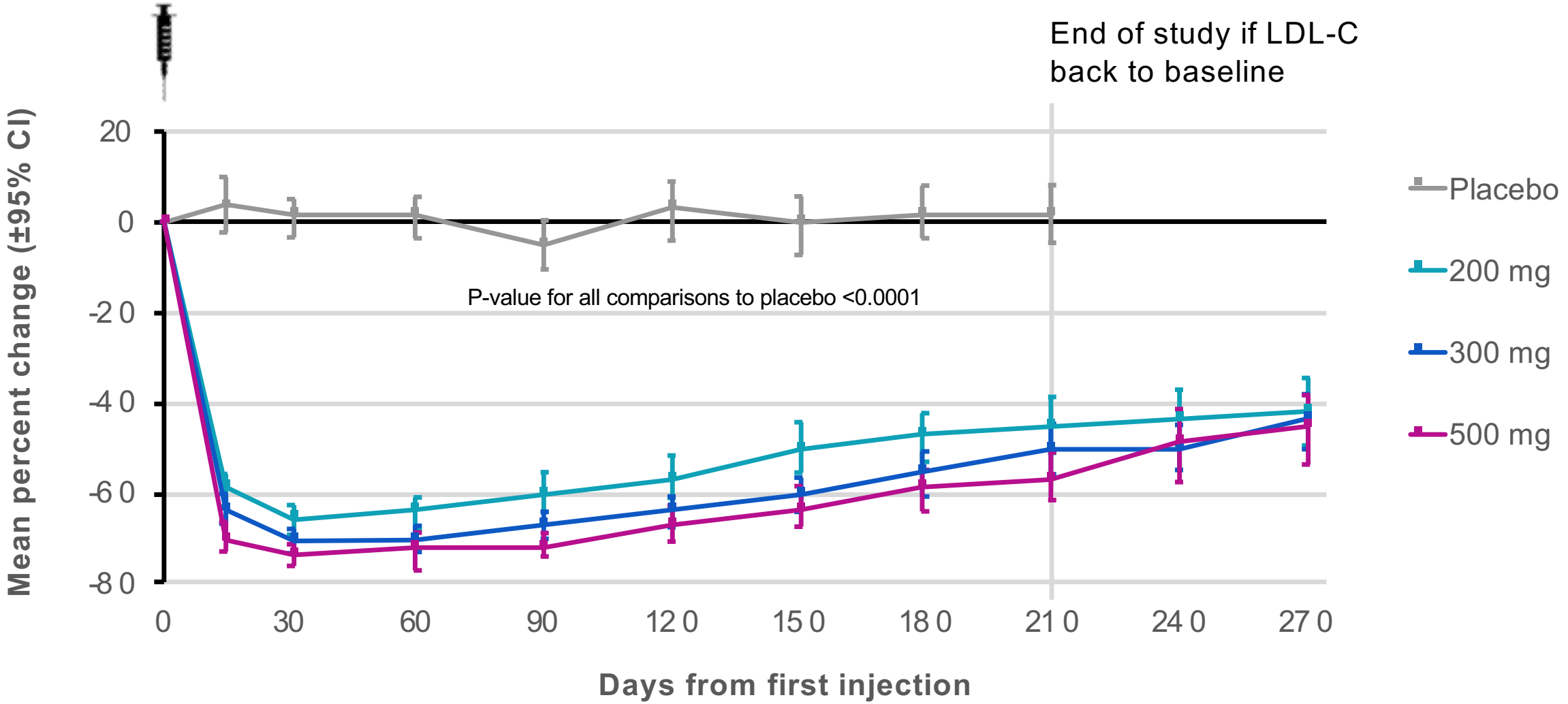
Efficacy: One dose starting regimen
Clamped PCSK9 knockdown



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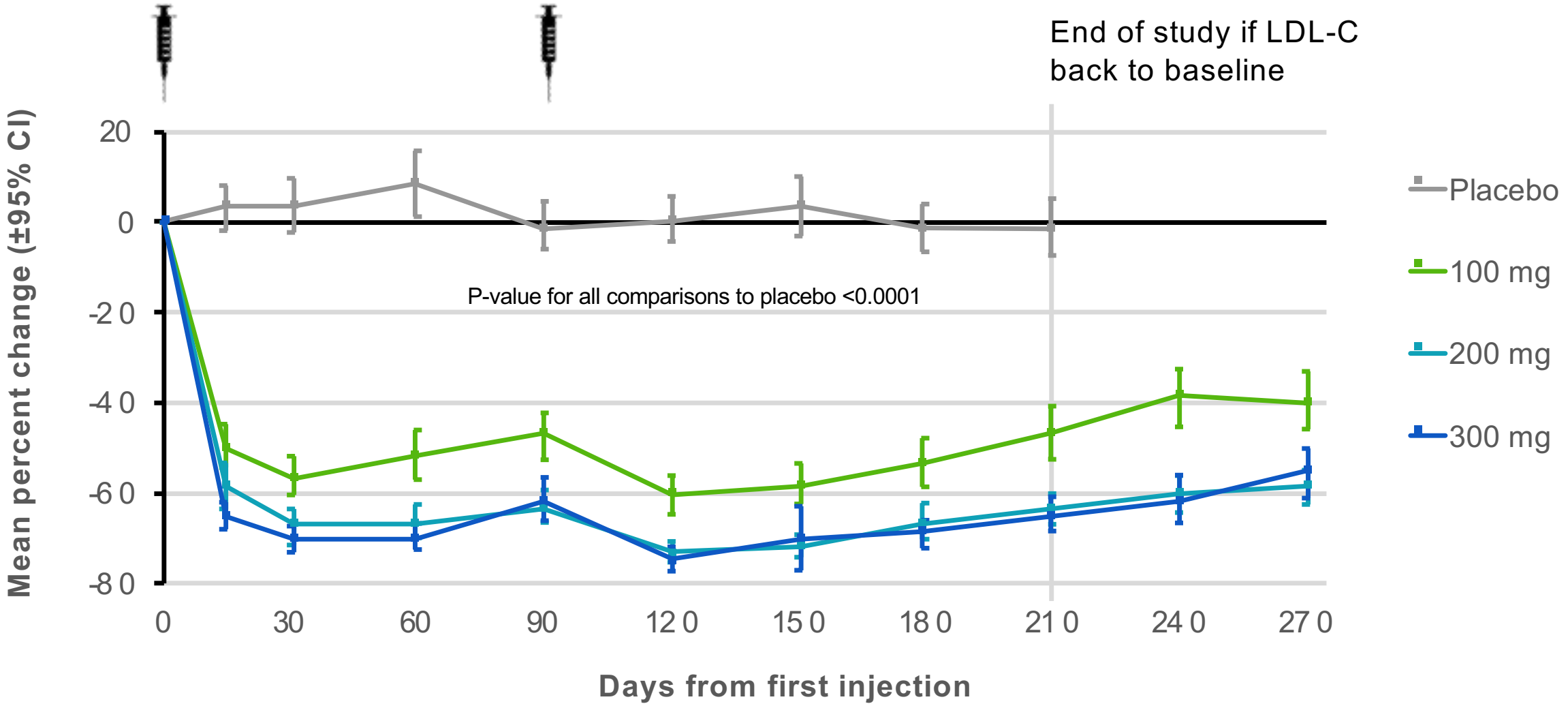
Efficacy: Two dose starting regimen
Clamped PCSK9 knockdown



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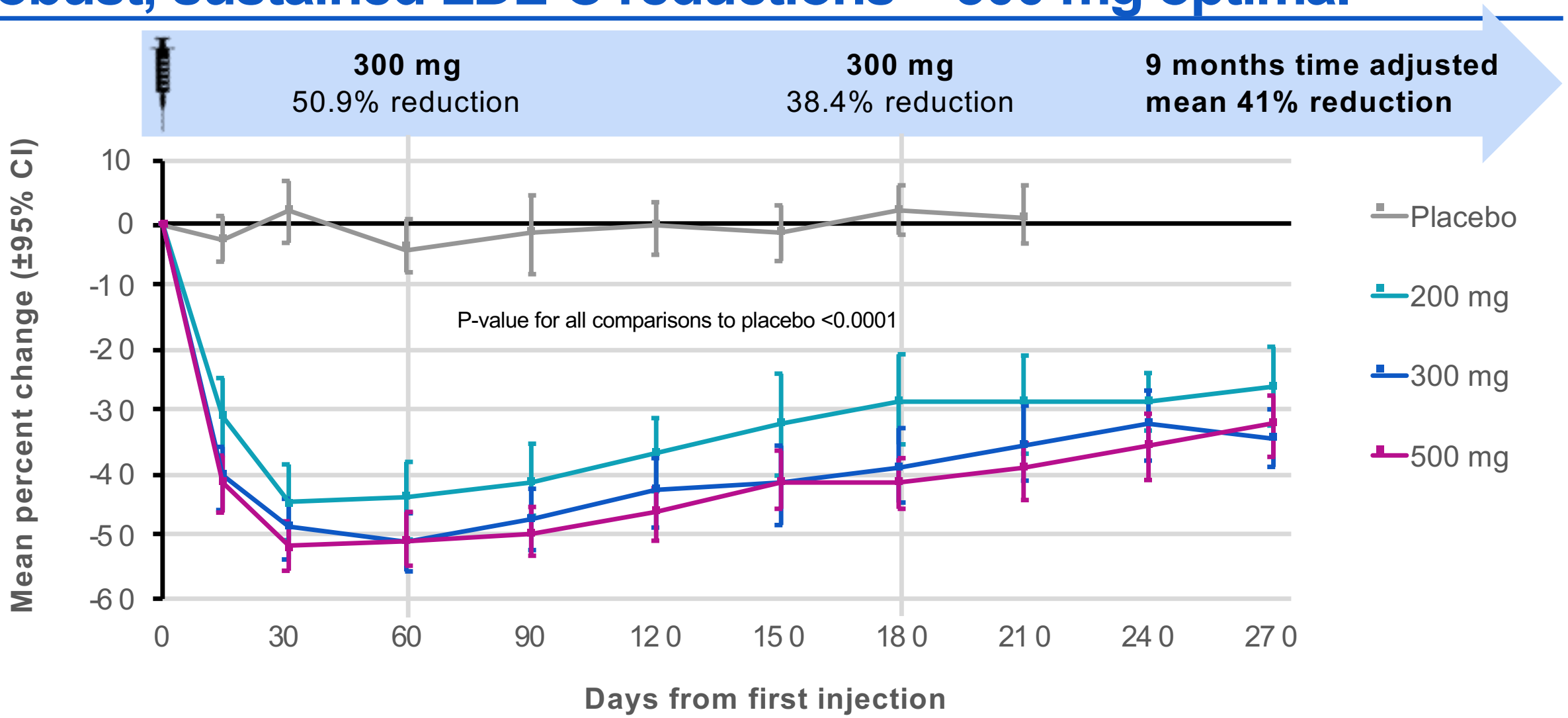
Efficacy: One dose starting regimen

Robust, sustained LDL-C reductions – 300 mg optimal



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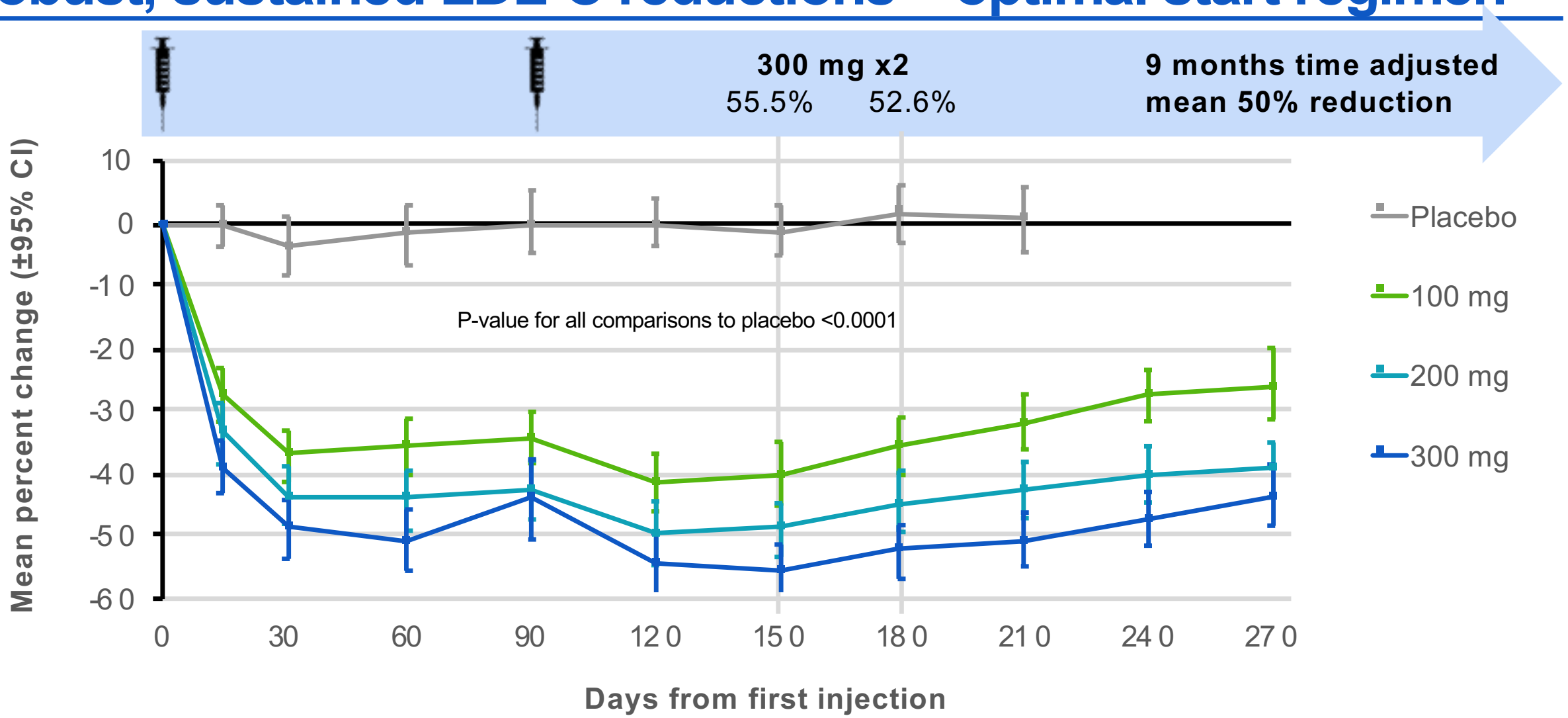
Efficacy: Two dose starting regimen

Robust, sustained LDL-C reductions – optimal start regimen



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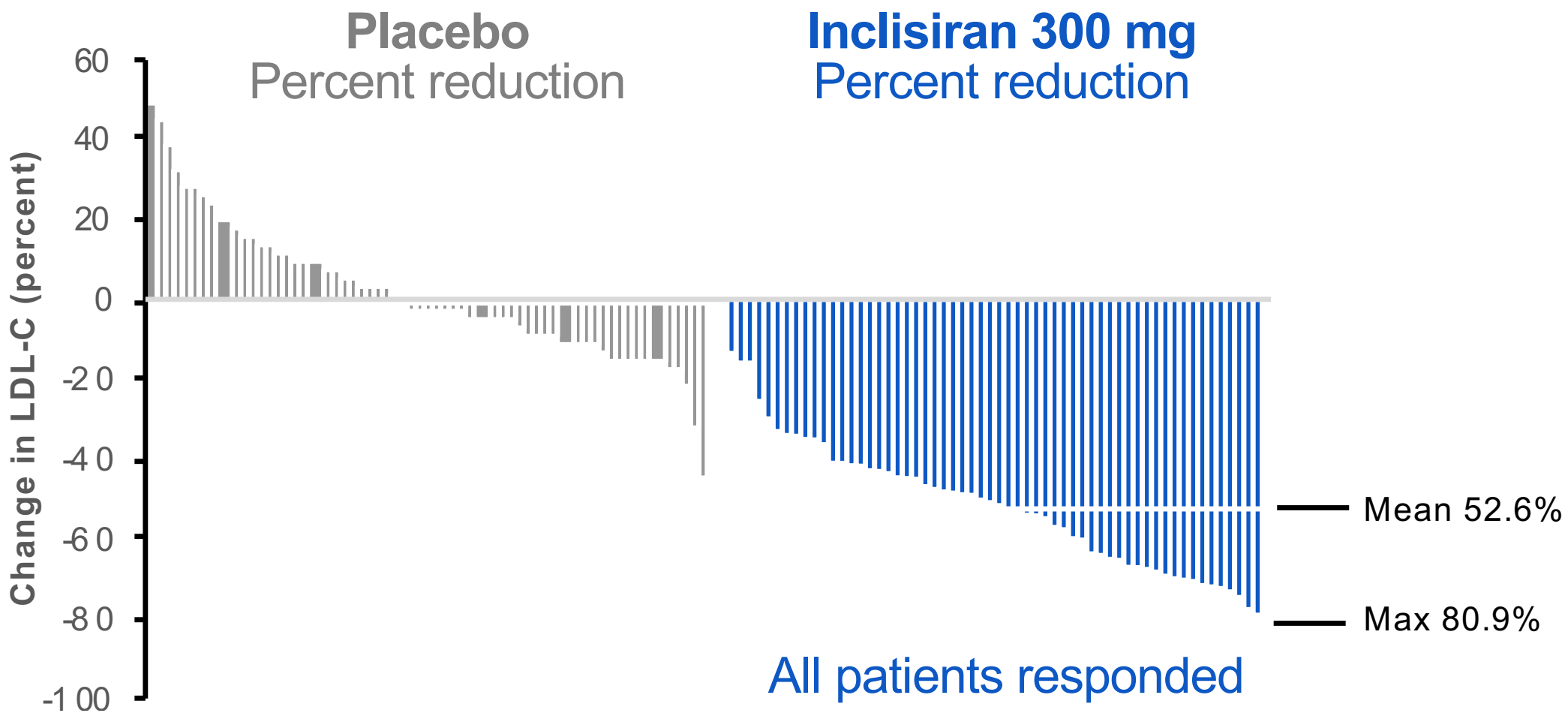
Efficacy: Two dose starting regimen

Individual patient responses (%) at day 180



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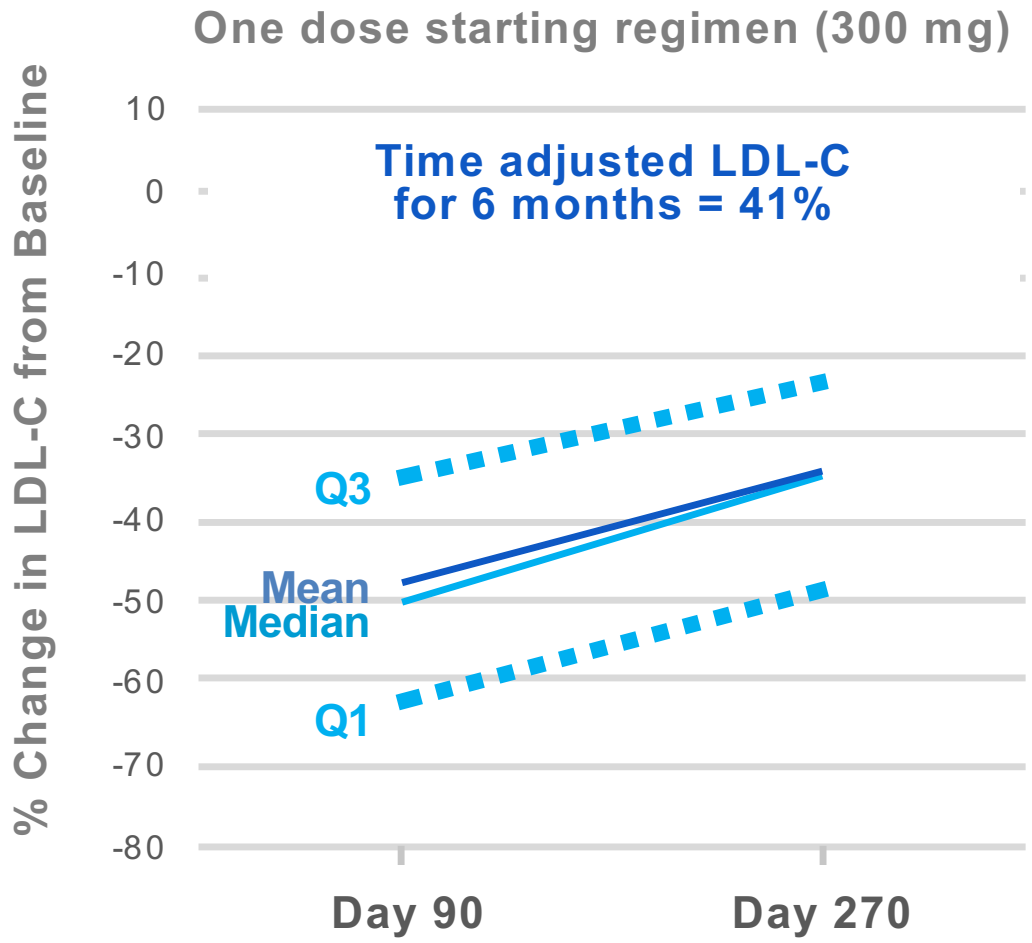
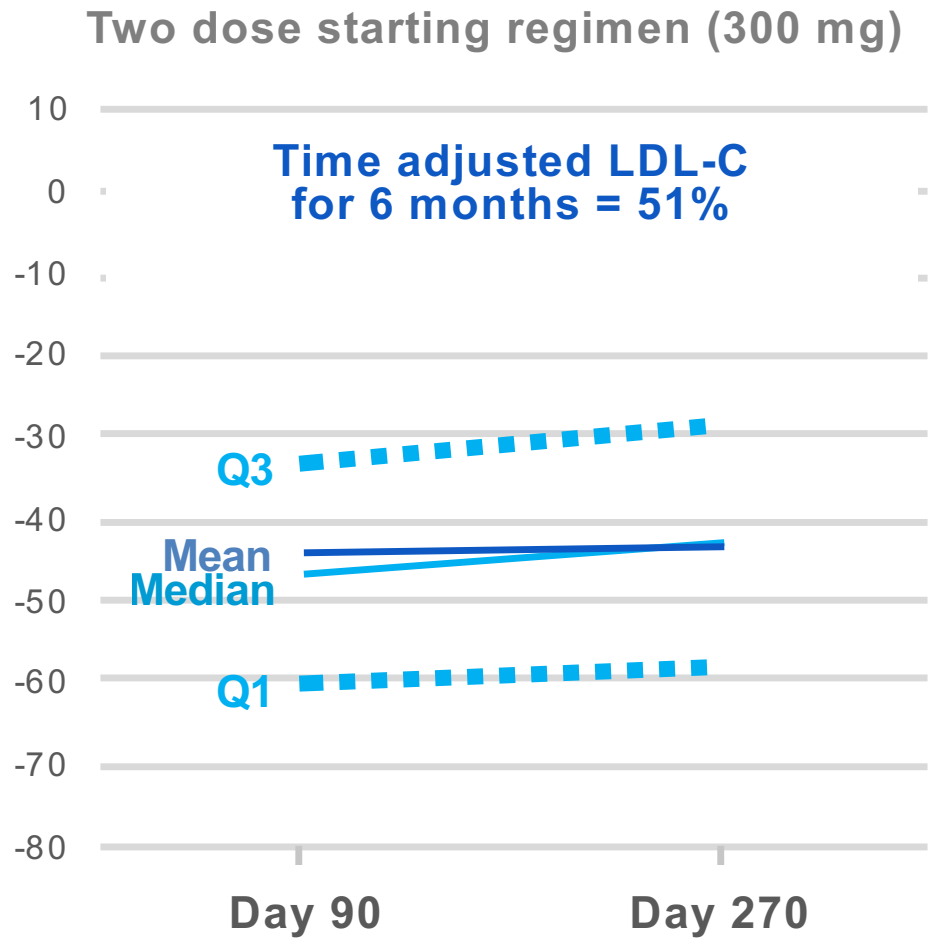
Inclisiran dose 300mg sc Day 1, 90, 270 and 6-monthly
Sustained >50% reduction in LDL-C for 6-months





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Summary
Two 300 mg starting dose regimen for inclisiran selected

No safety concerns

Optimal dosage 300 mg given twice as starting regimen

- 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)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

Kausik K. Ray, M.D., Ulf Landmesser, M.D., Lawrence A. Leiter, M.D., David Kallend, M.D., Robert Dufour, M.D., Mahir Karakas, M.D., Tim Hall, M.D., Roland P.T. Troquay, M.D., Traci Turner, M.D., Frank L.J. Visseren, M.D., Peter Wijngaard, Ph.D., R. Scott Wright, M.D., and John J.P. Kastelein, M.D., Ph.D.

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The ORION Phase III Program
ORION-2, -3, -5, -7, -9, -10, -11

ORION: Phase III trials

Pivotal Phase III studies to support LDL-C lowering labeling

Study	Sites	Main inclusion criteria	Patients
ORION-11	EU, SA	ASCVD (LDL-C >70mg/dL) and risk equivalent patients (LDL-C >100 mg/dL)	1,500
ORION-10	US	ASCVD (LDL-C >70 mg/dL)	1,500
ORION-9	US, EU, SA	Heterozygous FH	400
ORION-5	US, EU, SA	Homozygous FH	60
			3,460

ORION: Phase III trials

Design of the ORION-9, -10, -11 studies

Patients

HeFH, ASCVD and/or risk equivalent patients

Age ≥18 years

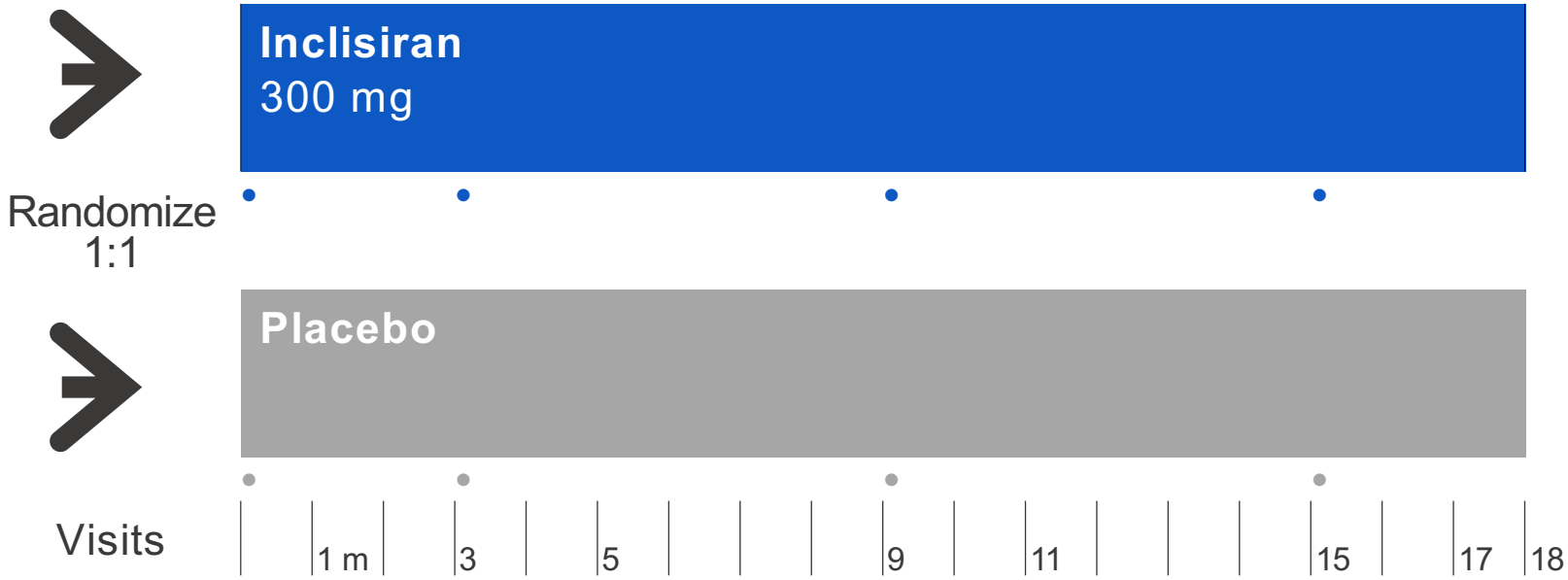
High intensity statin

LDL-C

>70 mg/dL, or

>100 mg/dL (RE, HeFH)

18 month duration



ORION-9, ORION-10 and ORION-11
Common inclusion criteria

Clinical & regulatory strategy

ORION-9	ORION-10	ORION-11
Male or female subjects ≥ 18 years of age	Male or female subjects ≥ 18 years of age	Male or female subjects ≥ 18 years of age
History of HeFH with a diagnosis of HeFH by genetic testing; and/or a documented history of untreated LDL-C of > 4.9 mmol/L (>190 mg/dL), and a family history of FH, elevated cholesterol or early heart disease may indicate FH	History of ASCVD (CHD, CVD or PAD*)	History of ASCVD (CHD, CVD or PAD*) or ASCVD-risk equivalents (type 2 diabetes, familial hypercholesterolemia, and including subjects whose 10-year risk of a CV event assessed by Framingham Risk Score or equivalent has a target LDL C of < 2.6 mmol/L (< 100 mg/dL).
Stable on a low-fat diet (e.g., NCEP)	N/A	N/A
Serum LDL-C ≥ 2.6 mmol/L (≥ 100 mg/dL) at screening	Serum LDL-C ≥ 1.8 mmol/L (≥ 70 mg/dL) at screening	Serum LDL-C ≥ 1.8 mmol/L (≥70 mg/dL) for ASCVD subjects or ≥ 2.6 mmol/L (≥ 100 mg/dL) for ASCVD-risk equivalent subjects at screening

* Coronary heart disease (CHD), Cerebrovascular disease (CVD); Peripheral arterial disease (PAD) [Protocol Appendix A]

ORION-9, ORION-10 and ORION-11
Inclusion criteria identical for all studies

Clinical & regulatory strategy

Elevated triglyceride at screening

Mild and Moderate renal impairment

Maximum tolerated statin and other LLTs

Stable lipid-lower therapies for ≥ 30 days before screening with no planned medication or dose change during study participation

Subjects must be willing and able to give informed consent

ORION-9, ORION-10 and ORION-11
Exclusion criteria identical for all studies

Clinical & regulatory strategy

Exclusion criteria are similar to those used in many lipid lowering trials for the last 20 years and reflect the lack of restrictions required for subjects on inclisiran

- Significant medical conditions that will affect the subject participation of the interpretation of the results
- Major adverse cardiovascular event within 3 months prior to randomization
- Uncontrolled blood pressure
- Active liver disease
- Pregnant or women of child bearing potential not using contraception
- Male not using acceptable contraception
- Alcohol or drug abuse
- Patients unsuitable for a clinical trial

ORION-9, ORION-10 and ORION-11
Common study endpoints

Clinical & regulatory strategy

Primary endpoint:

- Percentage change in LDL-C from baseline to Day 510
- Time adjusted percentage change in LDL-C from baseline between Day 90 and Day 540. This is the average percentage change in LDL-C from baseline over the period between Day 90 and Day 540

Key secondary endpoints:

- Absolute change in LDL-C from baseline to Day 510
- Time adjusted absolute change in LDL-C from baseline between Day 90 and Day 540
- Percentage change from baseline to Day 510 in PCSK9, total cholesterol, ApoB, and non-HDL-C

Phase III lipid lowering trials overview

Clinical & regulatory strategy

Project	ORION-9	ORION-10	ORION-11
Protocol #	MDCO-PCS-17-03	MDCO-PCS-17-04	MDCO-PCS-17-08
Indication	HeFH (Heterozygous Familial Hypercholesterolemia)	ASCVD	ASCVD or ASCVD Risk Equivalents (RE)
Phase	Phase III	Phase III	Phase III
Total # of subjects Randomized	**482**	**1561**	**1617**
Total # of sites	54	149	73
Recruitment period	3 months	3 months	3 months
First subject in (consented)	28 NOV 2017	15 DEC 2017	27 OCT 2017
First subject randomized	12 DEC 2017	21 DEC 2017	01 NOV 2017
Last subject In (randomized)	22 FEB 2018	07 MAR 2018	29 JAN 2018
Country/site mix	Canada Czech Republic Denmark Netherlands South Africa Spain Sweden US	United States	Czech Rep Germany Hungary Netherlands Poland South Africa UK Ukraine

ORION: Phase III trials

Reassuring safety and tolerability profile emerging

DSMB review (March 2018)

- >2000 patients
- Recommended continuation of Phase III studies with no changes

Ongoing review of blinded data (3,660 patients)

- Very low incidence of reported mild, transient skin reactions
- No reports of LFT or other significant lab abnormalities

ORION-2: Phase II HoFH

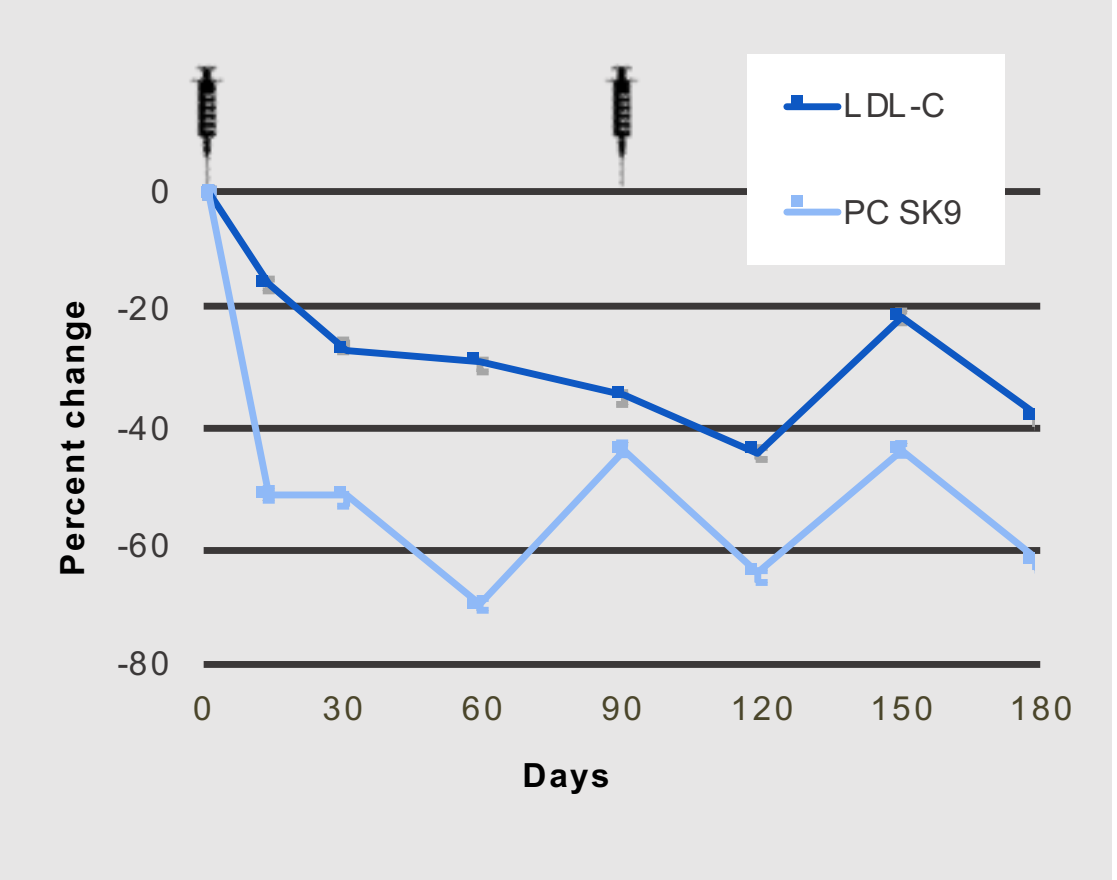
Robust, durable effects in homozygous familial hypercholesterolemia

Asp227Glu/Asp227Glu variant

Absolute LDL-C reduction

- 184 mg/dL at day 60
- 276 mg/dL at day 120
- 242 mg/dL at day 180

Standard dose



ORION-5: Phase III HoFH

Design of a 6-month duration efficacy study

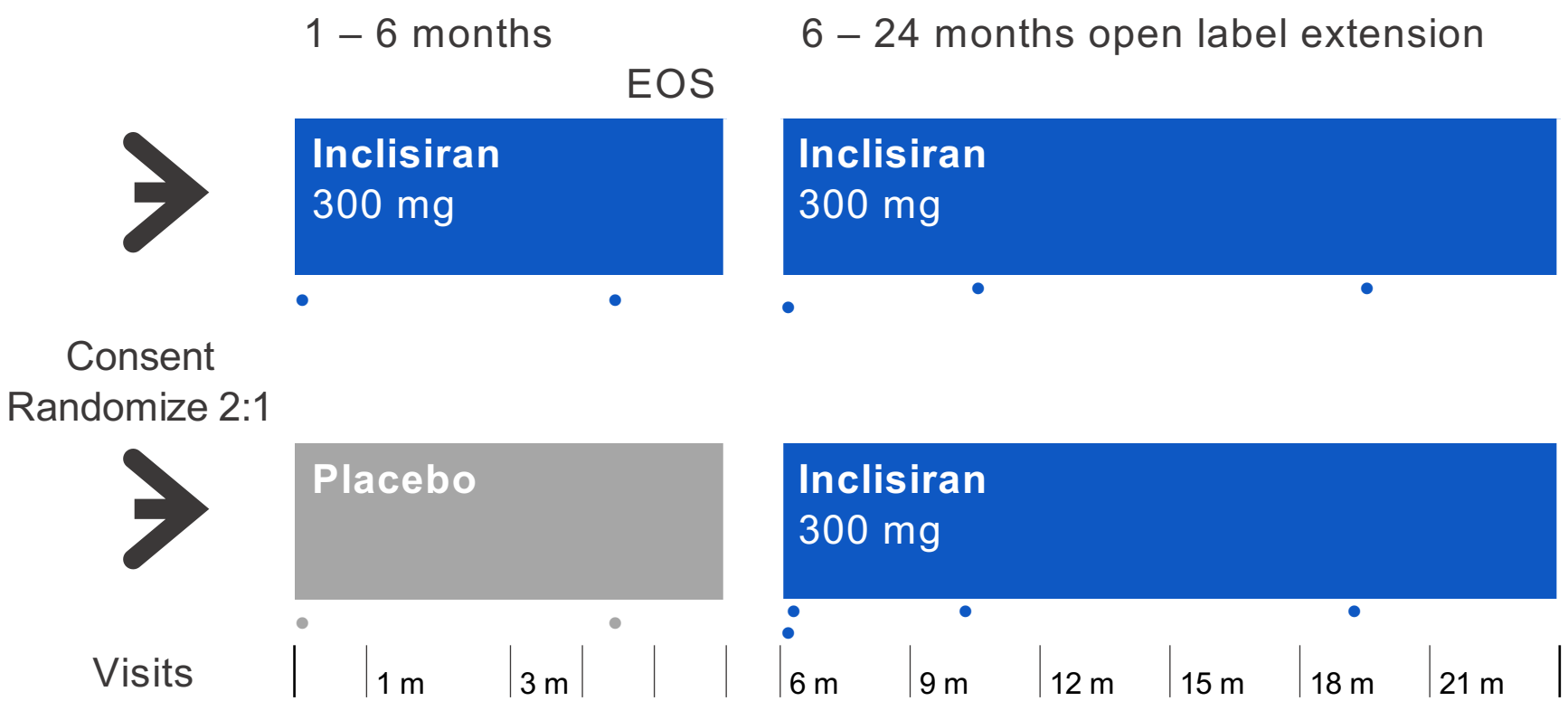
Starts 2H 2018 – not on critical path to NDA, separate pediatric program

Patients

Homozygous FH
Genetic confirmation

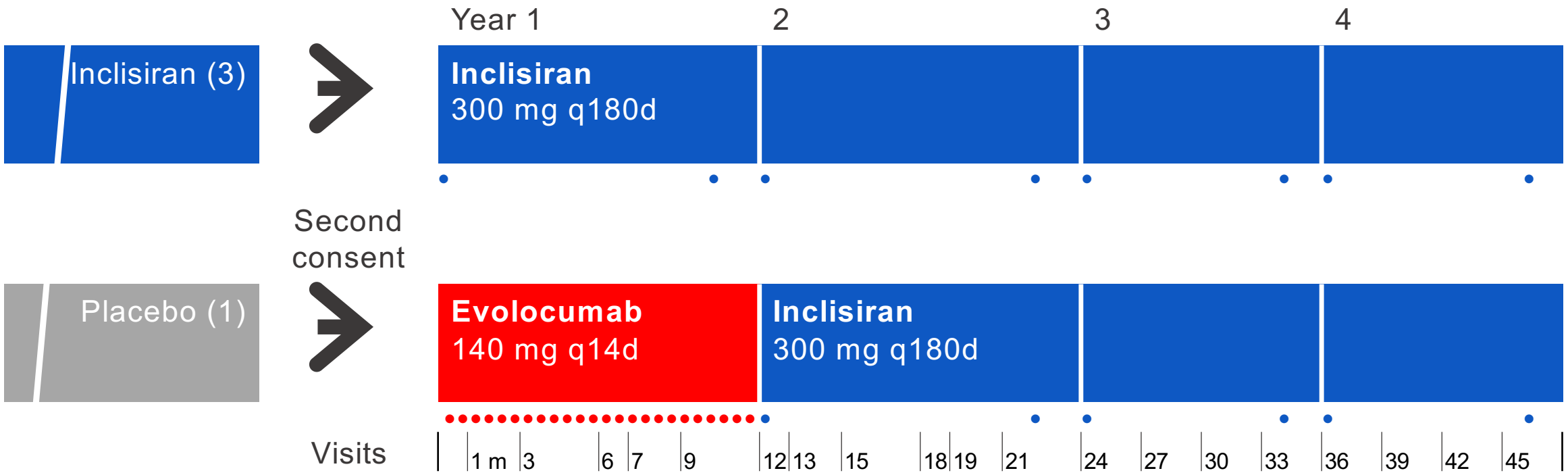
Rx
High dose statin
Ezetimibe
(Plasmapheresis)

ORION-5 anticipated design



ORION-3: Head-to-head versus Repatha®

Assess switching, comparative efficacy, safety and patient preference



ORION-3: Head-to-head versus Repatha®

Safety profile similar to evolocumab

Interim safety data (18 April 2018 – 290 inclisiran and 92 evolocumab)

- No difference in safety profile between groups
- No other safety signals

Patient reported outcomes and efficacy data in 2019

ORION-7: Renal function

Renal function does not effect safety or efficacy – no dose adjustment

Renal function group	Calc. creat. clearance	ORION-3		
		0-48 hours	Day 2-60	Day 60-180
Mild (N=8)	60-89 mL/min	PK-PD Safety	PD Safety	LDL-C Safety
Moderate (N=8)	30-59 mL/min			
Severe (N=7)	15-29 mL/min			
Normal (N=8)	≥90 mL/min			

ORION-7: Renal function

Renal function does not effect safety or efficacy – no dose adjustment

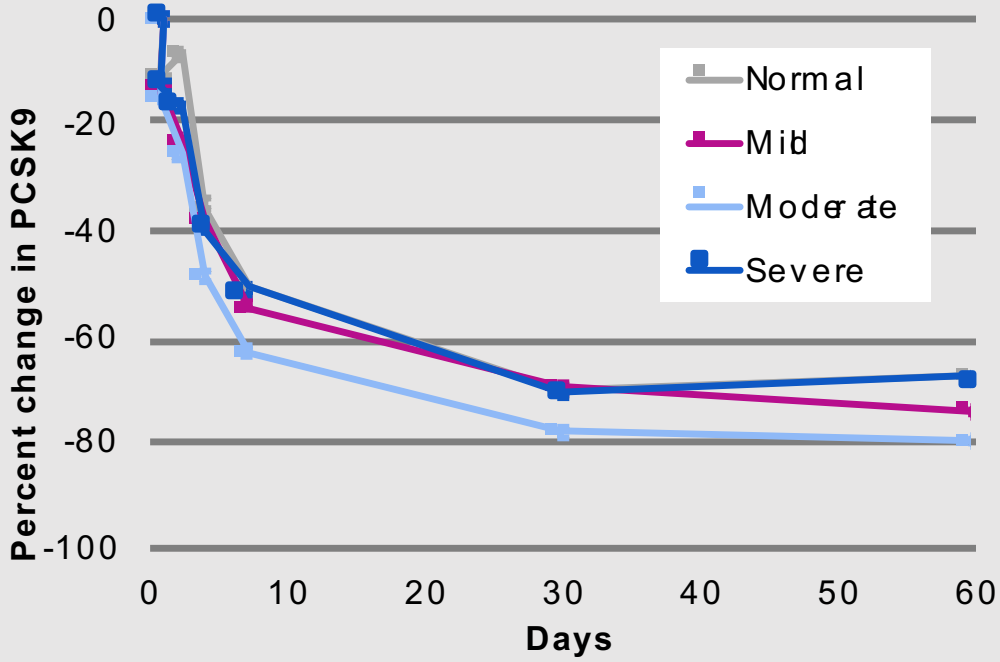
Plasma PK over the first 48 hours

Exposure ^ with renal dysfunction – as anticipated

Inclisiran not detectable in any group after 48 hours

Group	Cmax ng/mL	AUC h*ng/mL
Normal	421	7,600
Mild	987	11,800
Moderate	897	13,433
Severe	1,756	19,214

PD effects on PCSK9 not significantly different



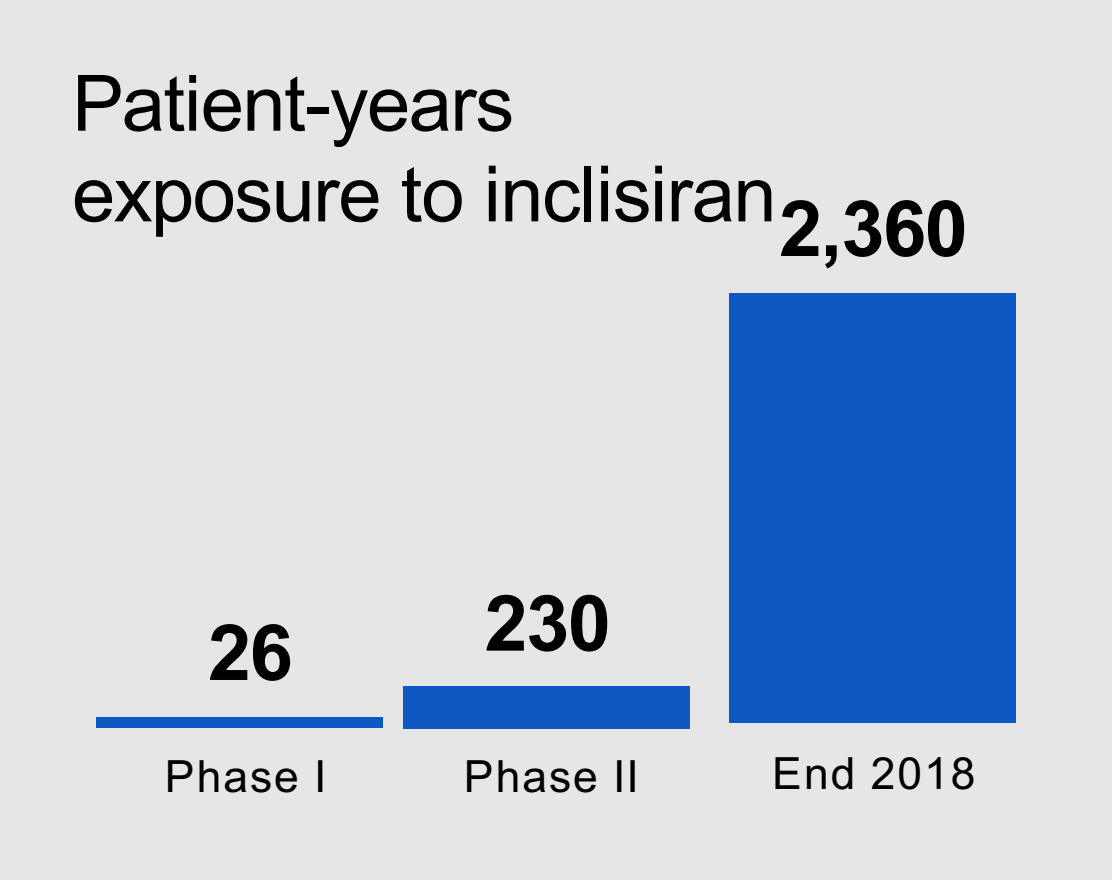
Inclisiran clinical trials program

During 2018, safety data expected to increase 10-fold

Rapid accumulation of safety data

10-fold increase during 2018

- 1,700 with 3 doses
- 290 with 4 – 5 doses

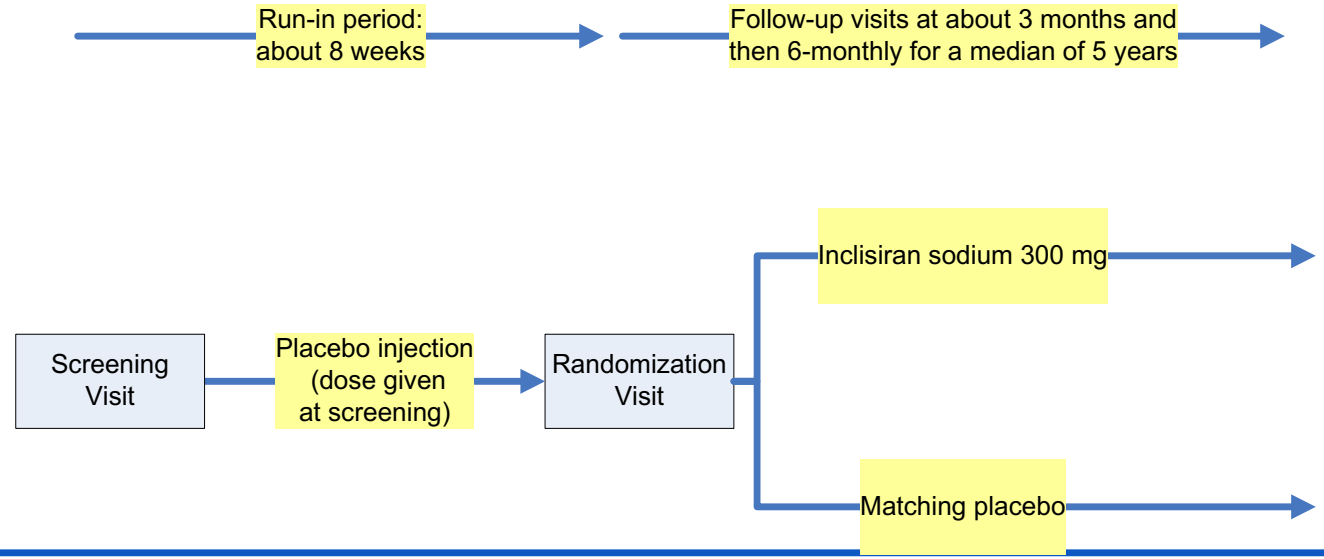


ORION-4
Long term cardiovascular outcomes study

Clinical & regulatory strategy

Study Aims

- To assess the effect of inclisiran on major cardiovascular events
- The study will randomize ≥15,000 participants aged ≥55 years with pre-existing cardiovascular disease between inclisiran sodium 300 mg and matching placebo for a median of about 5 years.



ORION-4
Long term cardiovascular outcomes study

Clinical & regulatory strategy

Primary endpoint:

Composite of major adverse cardiovascular events (MACE), defined as:

Coronary (CHD) death;

Myocardial infarction;

Fatal or non-fatal ischaemic stroke; or

Urgent coronary revascularization procedure

Secondary endpoints:

Composite outcome of CHD death or myocardial infarction

Cardiovascular death

Conclusions

PCSK9 Inhibitor therapy with Inclisiran

Inhibition of PCSK9 with Inclisiran is a very promising, and potentially the simplest and most effective, approach to further reducing LDL-C, the cause of atherosclerosis

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

Phase II and the ongoing phase III studies have shown robust long term efficacy with no safety issues