What is new with inhibition of PCSK9?

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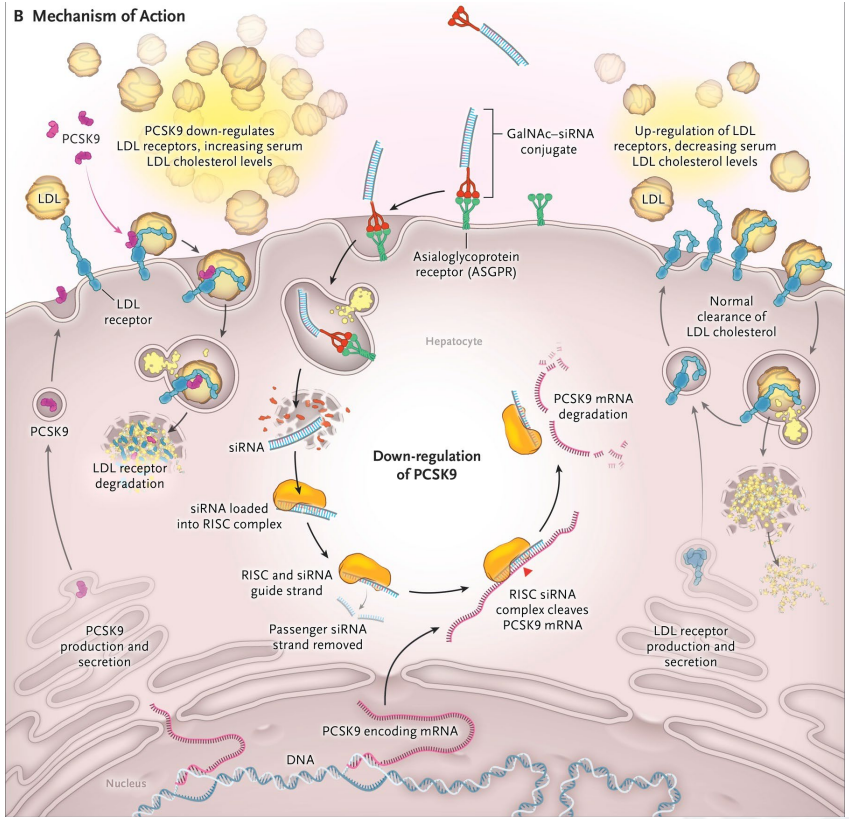
Current Therapies to Inhibit PCSK9: Monoclonal Antibodies

- Alirocumab and evolocumab initially approved in 2015
- Both lower LDL-C approximately 60%
- Given as injections either every 2 weeks or monthly
- Each agent with a large outcome trials in high-risk patients with significant reduction in MACE of approximately 15%, both relatively short-term studies

Inclisiran – siRNA targeting PCSK9
Mechanism of action



Khvorova | *NEJM* 2017

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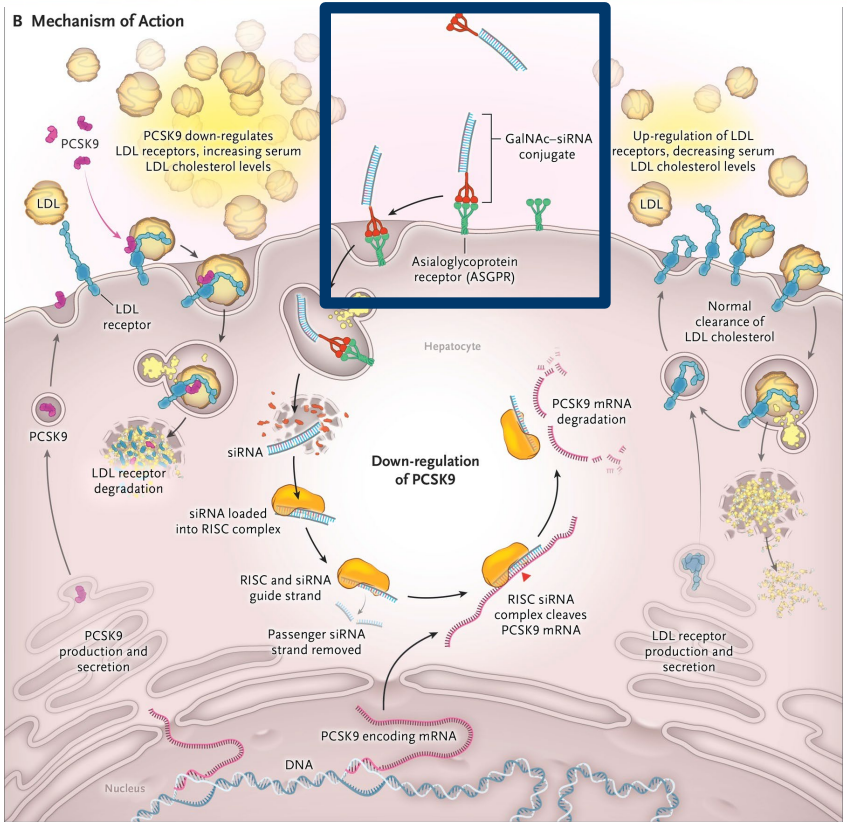

1. Delivered to hepatocytes
GalNAc / ASPGR

Khvorova | *NEJM* 2017

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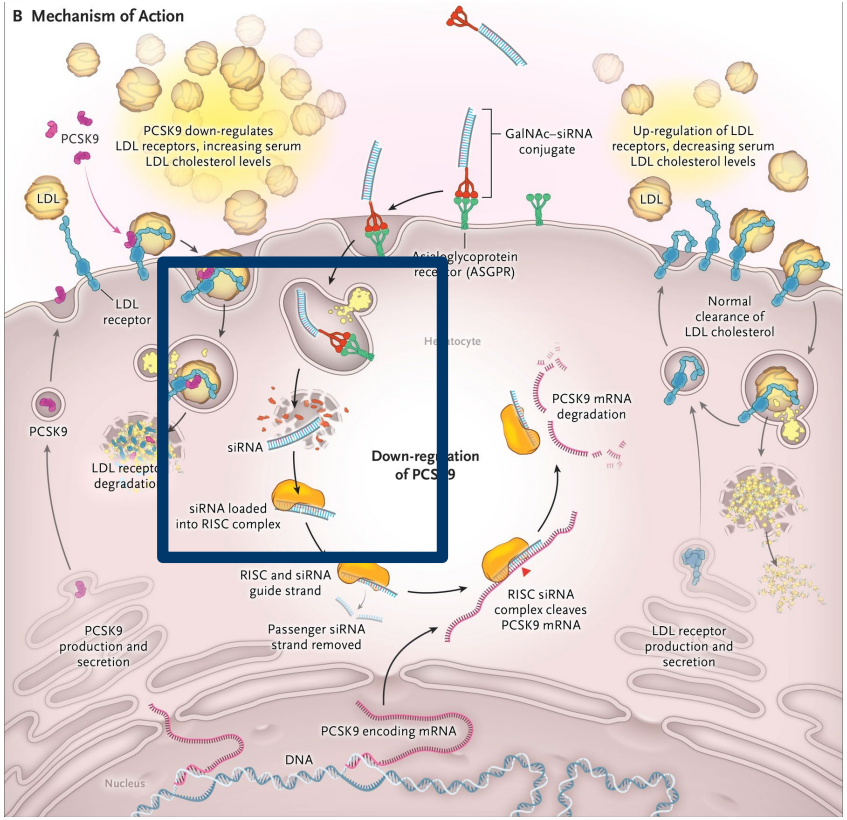

1. Delivered to hepatocytes GalNAc / ASPGR
2. Guide strand delivers to RISC

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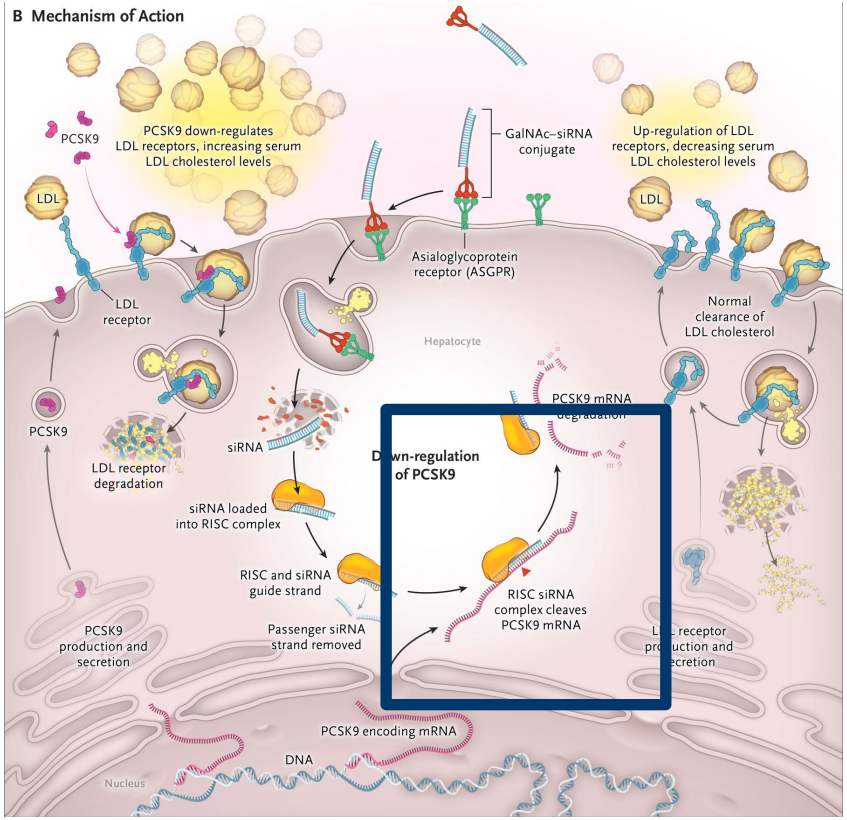
Inclisiran – siRNA targeting PCSK9
Mechanism of action



1. Delivered to hepatocytes GalNAc / ASPGR
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3. RISC-siRNA cleaves PCSK9 mRNA degraded

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Inclisiran – siRNA targeting PCSK9
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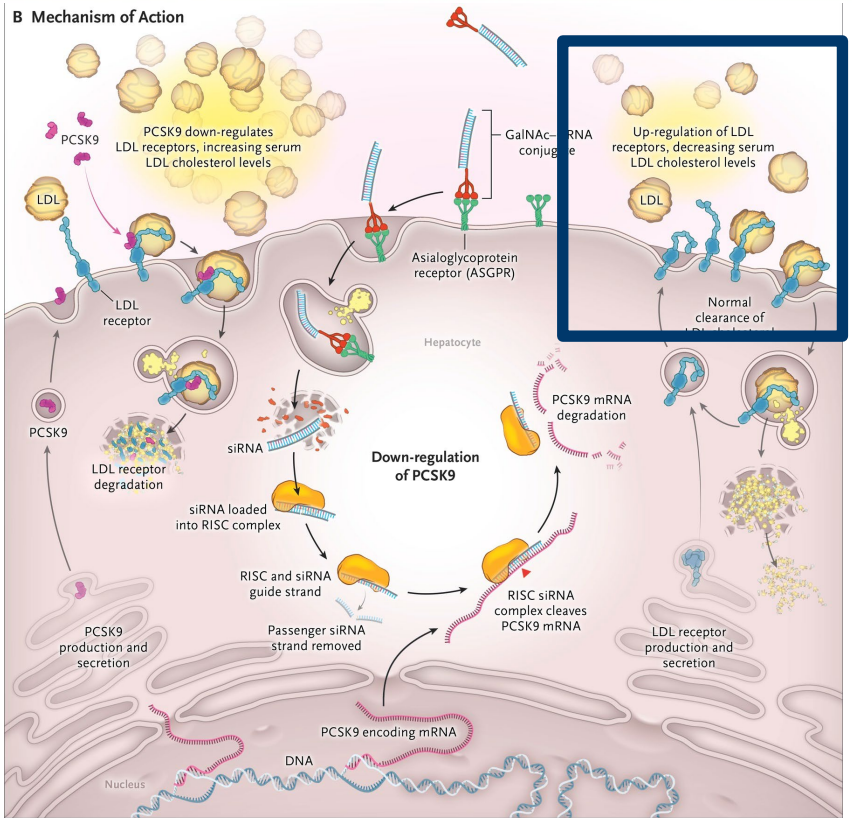


1. Delivered to hepatocytes GalNAc / ASPGR
2. Guide strand delivers to RISC
3. RISC-siRNA cleaves PCSK9 mRNA degraded
4. Increased LDLR density dec circulating LDL

Khvorova | *NEJM* 2017

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

Patients[1,2]

HeFH, ASCVD, and / or risk-equivalent patients

Age ≥18 years

High-intensity statin

LDL-C

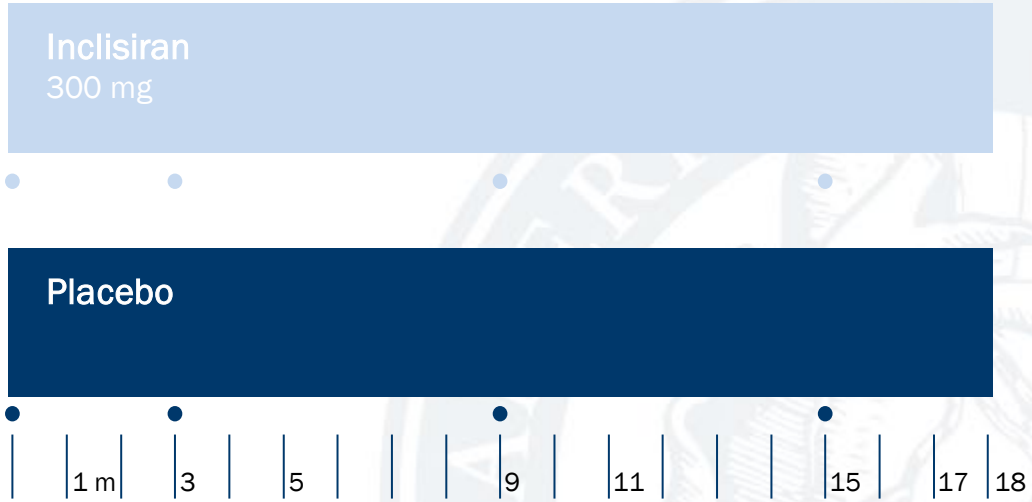
>70 mg/dL, or

>100 mg/dL (risk equivalent, HeFH)

Randomize 1:1

Visits

18-month duration[1,2]



1. Raal FJ et al. *N Engl J Med* 2020;382(16):1520-30; 2. Ray KK et al. *N Engl J Med* 2020;382(16):1507-19

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Entry criteria

ORION-9[1]	ORION-10[2]	ORION-11[2]
▪ HeFH[a] ▪ Stable on a low-fat diet ▪ LDL-C ≥100 mg/dL	▪ ASCVD (CHD, CVD, PAD) ▪ LDL-C ≥70 mg/dL	▪ ASCVD (CHD, CVD, PAD) ▪ ASCVD risk equivalents – Type 2 diabetes – 10-year risk ≥20% – HeFH[a] ▪ LDL-C ≥70 mg/dL

Maximally tolerated statin therapy (or documented intolerance), with or without ezetimibe

CVD, cardiovascular disease; CHD, chronic heart disease; HeFH, heterozygous familial hypercholesterolemia; PAD, peripheral arterial disease

[a]Diagnosed by genetic testing and / or Simon Broome criteria

1. Raal FJ et al. *N Engl J Med* 2020;382(16):1520-30; 2. Ray KK et al. *N Engl J Med* 2020;382(16):1507-19

Common end points of ORION-9, -10, -11 studies

Primary end point[1,2]

- 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 end points[1,2]

- 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

HDL-C, high-density lipoprotein cholesterol

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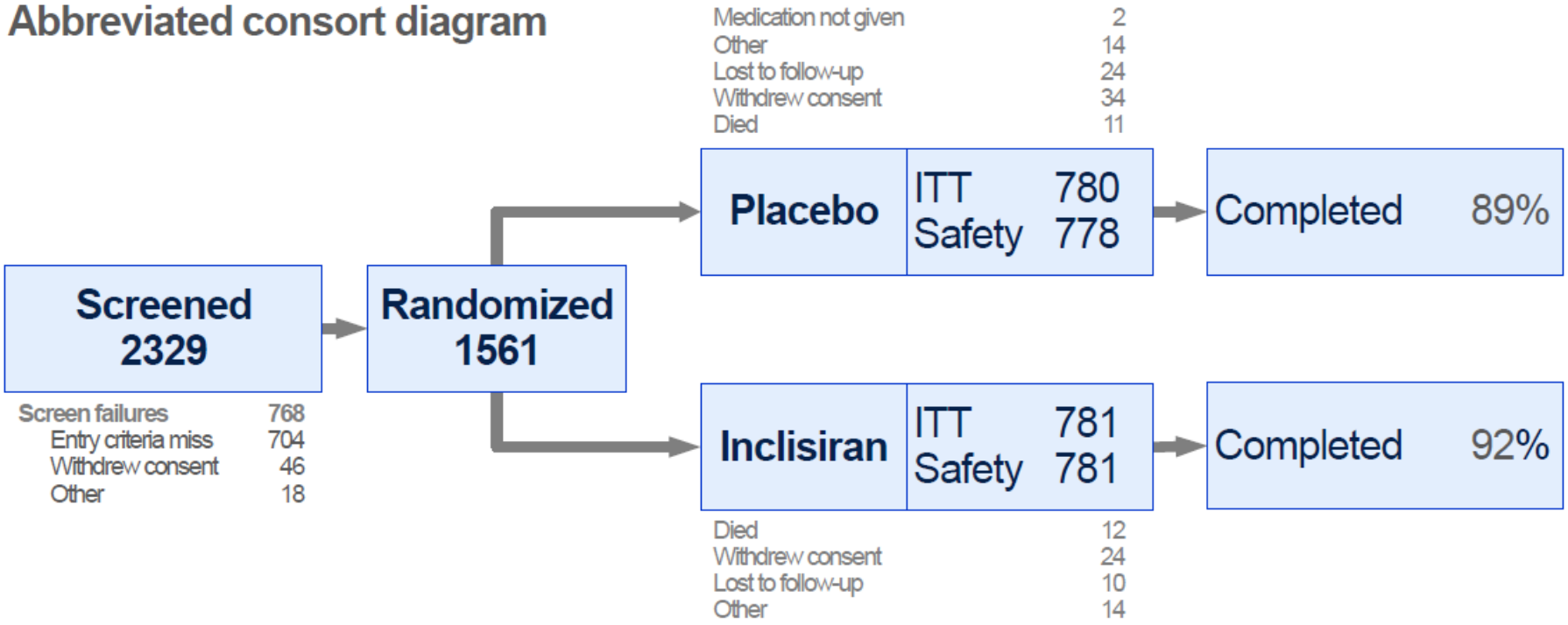
ORION-10: Patient disposition

High proportion of patients completed the study

Abbreviated consort diagram



Safety population comprises any subject given any study medication

Ray KK et al. *N Engl J Med* 2020;382:1507-19

ORION-10: Patients

Representative high risk cohort balanced by randomization

Patient characteristic	Placebo	Inclisiran
ITT population[1]	N = 780	N = 781
Age median (range) - years	66 (39-89)	67 (35-90)
Male gender	548 (70%)	535 (69%)
Diabetes	331 (42%)	371 (48%)
Heterozygous familial hypercholesterolemia	69 (9%)	68 (9%)
Lipid management treatment	730 (94%)	748 (96%)
Statins	692 (89%)	701 (90%)
Of which high intensity statins given	**546 (79%)**	**538 (77%)**
Ezetimibe use	74 (9%)	80 (10%)
Baseline LDL-C mg/dL (SD)	105 (37)	105 (40)

1. All patients who were randomized. analyzed according to randomization 2. SD is standard deviation

Ray KK et al. *N Engl J Med* 2020;382:1507-19

ORION-10: Efficacy

Highly significant lowering of LDL-C relative to placebo

Treatment group	N (ITT)	Percent change LDL-C			
		Mean at day 510		Time-averaged day 90 - 540	
		Observed	Imputed[1]	Observed	Imputed[2]
Placebo	780	+ 1	+ 1	+ 3	+ 3
Inclisiran	781	- 56	- 51	- 53	- 51
Difference (1º endpoint)		**- 58**	**- 52**	**- 56**	**- 54**
P-value		<0.00001		<0.00001	

1. A wash-out model was used to account for missing data
2. A pattern mixed model was used to account for missing data

Ray KK et al. *N Engl J Med* 2020;382:1507-19

ORION-10: Safety and tolerability

Injection site AEs infrequent, mostly mild and transient

Injection site TEAEs Safety population[1]	Placebo N = 778		Inclisiran N = 781		Δ
Protocol-defined event	**7**	**(0.9%)**	**20**	**(2.6%)**	**1.7%**
(Reaction, erythema, rash, pruritus, hypersensitivity)					
Mild	7	(0.9%)	13	(1.7%)	0.8%
Moderate	0		7	(0.8%)	0.8%
Severe	0		0		
Persistent	0		0		
Injection site pain					
Vial + syringe (cycle 1+2)	3	(0.4%)	18	(2.1%)	1.7%
Pre-filled syringe (cycle 3+4)	1	(0.1%)	7	(1.0%)	0.9%

1. Safety population includes all patients who received at least 1 dose of study medication

Ray KK et al. *N Engl J Med* 2020;382:1507-19

ORION-10: Safety and tolerability

No evidence of liver, kidney, muscle or platelet toxicity

Laboratory tests Safety population[1,2]		Placebo N = 778		Inclisiran N = 781	
Liver function	ALT >3x ULN	2	(0.3%)	2	(0.3%)
	AST >3x ULN	5	(0.6%)	4	(0.5%)
	ALP >2x ULN	3	(0.4%)	5	(0.6%)
	Bilirubin >2x ULN[3]	3	(0.4%)	4	(0.5%)
Kidney function	Creatinine >2 mg/dL	30	(3.9%)	30	(3.9%)
Muscle	CK >5x ULN	8	(1.0%)	10	(1.3%)
	CK >10x ULN	2	(0.3%)	1	(0.1%)
Hematology	Platelet count <75x10^9/L	0		1	(0.1%)

1. Safety population includes all patients who received at least 1 dose of study medication
2. Patients may be counted in more than one category
3. No cases met Hy's Law

Ray KK et al. *N Engl J Med* 2020;382:1507-19

ORION-10: Safety and tolerability

No difference in serious adverse events

Serious treatment emergent adverse events Safety population[1,2]	Placebo N = 778		Inclisiran N = 781	
Patients with at least one serious TEAE	**205**	**(26.3%)**	**175**	**(22.4%)**
All cause death	11	(1.4%)	12	(1.5%)
Cardiovascular	5	(0.6%)	7	(0.9%)
Cancer	3	(0.4%)	1	(0.1%)
New, worsening or recurrent malignancy	26	(3.3%)	26	(3.3%)
TEAEs leading to drug discontinuation	**17**	**(2.2%)**	**19**	**(2.4%)**

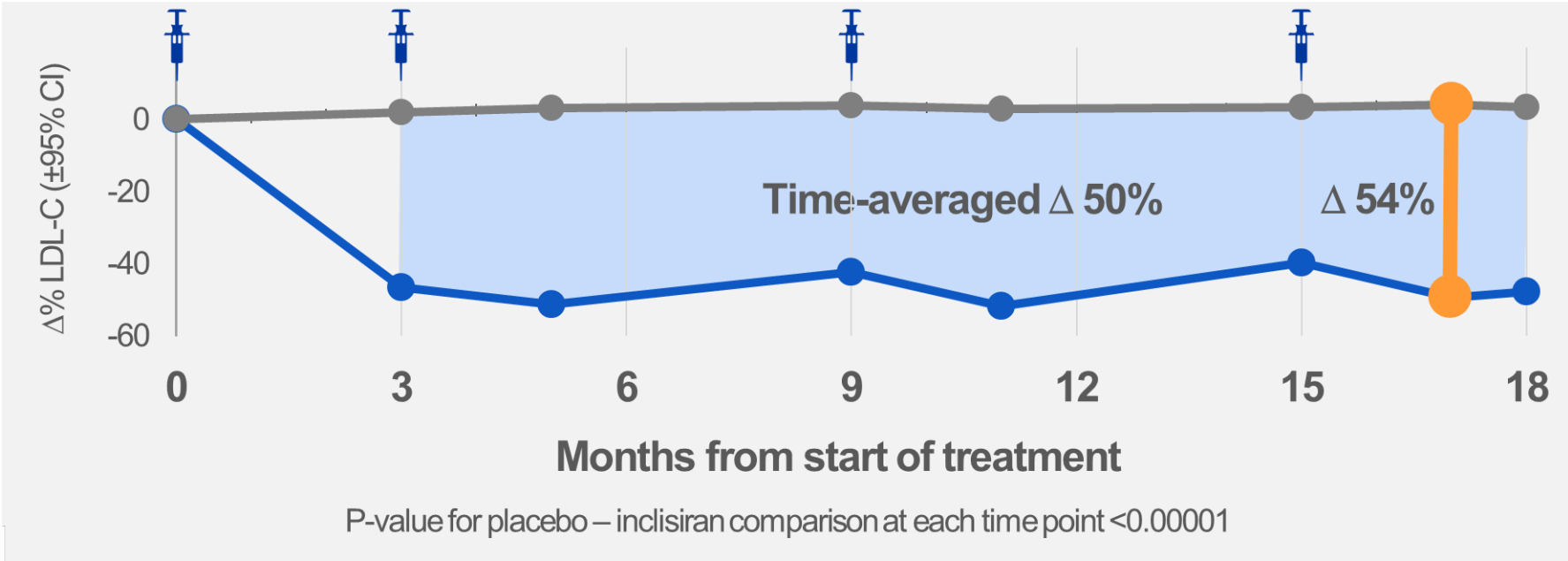
1. Safety population includes all patients who received at least 1 dose of study medication 2. Patients may be counted in more than one category

Ray KK et al. *N Engl J Med* 2020;382:1507-19

ORION-11: Efficacy

Durable, potent and consistent effect over 18 months

Percent change in LDL-C over time – observed values ITT patients



1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

Ray KK et al. *N Engl J Med* 2020;382:1507-19

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ORION-11: Safety and tolerability

No difference in serious adverse events

Serious TEAEs Safety population[1,2]	Placebo N = 804		Inclisiran N = 811	
Patients with at least one serious TEAE	181	(22.5%)	181	(22.3%)
All cause death	15	(1.9%)	14	(1.7%)
Cardiovascular	10	(1.2%)	9	(1.1%)
Cancer	3	(0.4%)	3	(0.4%)
New, worsening or recurrent malignancy	20	(2.5%)	16	(2.0%)

1. Safety population includes all patients who received at least 1 dose of study medication
2. Patients may be counted in more than one category

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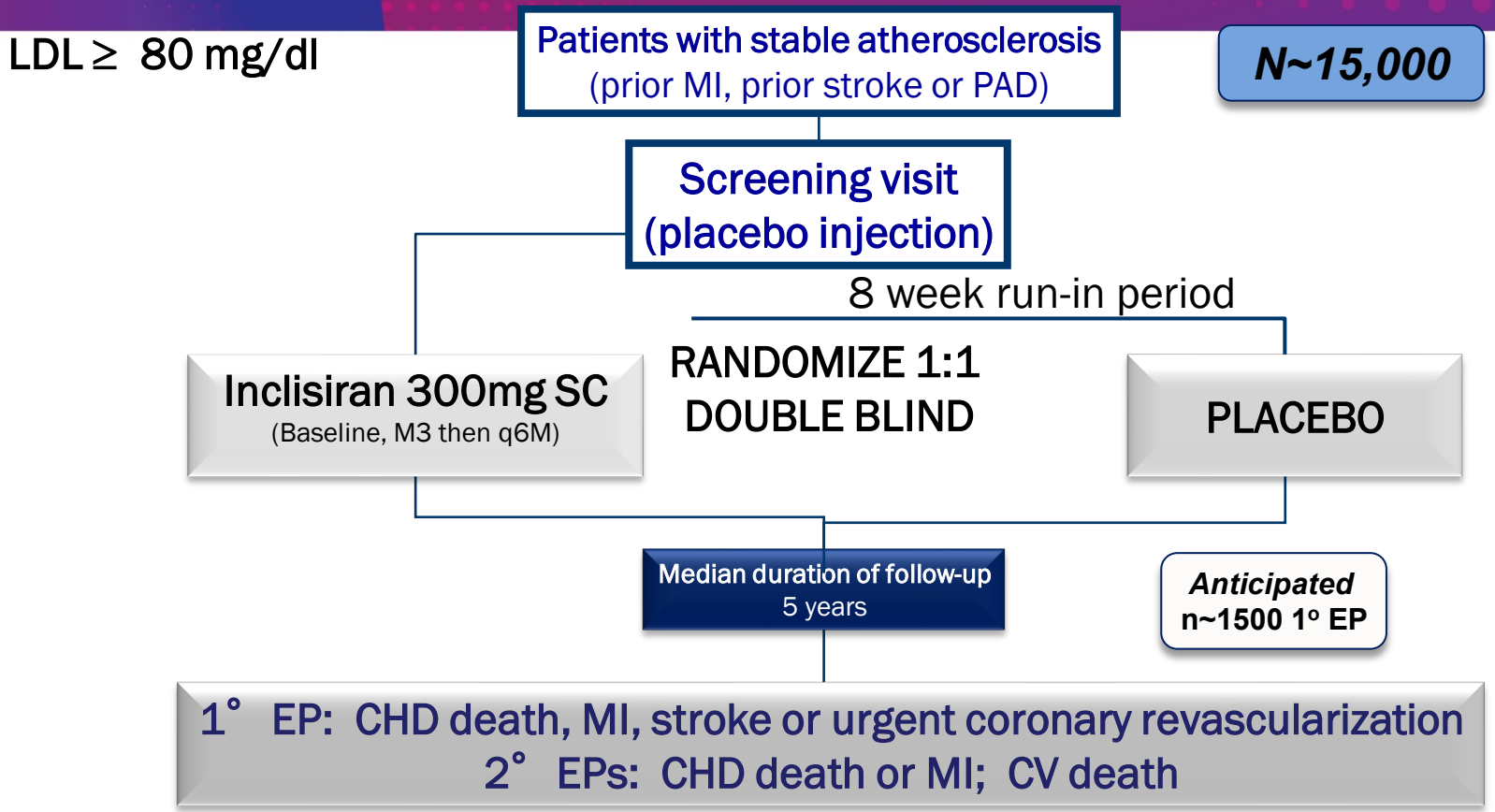
Inclisiran – ORION clinical development program
ORION-4 CV Outcomes Trial, results ~2024



Summary

- Inclisiran emerged from Phase 2 with a “one size fits all” dosing regimen:
  - 300 mg SC dose on Day 1, 90, then every 180 days
  - Applicable to all patient populations and subgroups
- Consistent and durable efficacy
- No safety signals observed to date in a broad range of patient groups
- More than 3500 patients followed up to 450 days to date and more than 3000 patient-years of exposure to inclisiran across the ORION Program
- Large outcomes trial ongoing

Summary

ADHERENCE: The greatest challenge in prevention treating asymptomatic conditions such as lipids

Could inclisiran improve adherence and lead to a disruptive technology that changes the way preventive cardiology is practiced?